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Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: Scoping Review

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Abstract

Background: The SARS-CoV-2 pandemic has brought substantial strain on hospitals worldwide; however, although the success of China's COVID-19 strategy has been attributed to the achievements of the government, public health officials, and the attitudes of the public, the resilience shown by China's hospitals appears to have been a critical factor in their successful response to the pandemic.

Objective: This paper aims to determine the key findings, recommendations, and lessons learned in terms of hospital resilience during the pandemic; analyze the quality and limitations of research in this field at present; and contribute to the evaluation of the Chinese response to the COVID-19 outbreak, building on a growing literature on the role of hospital resilience in crisis situations.

Methods: We conducted a scoping review of evidence on the resilience of hospitals in China during the COVID-19 crisis in the first half of 2020. Two online databases (the China National Knowledge Infrastructure and World Health Organization databases) were used to identify papers meeting the eligibility criteria. After extracting the data, we present an information synthesis using a resilience framework. Articles were included in the review if they were peer-reviewed studies published between December 2019 and July 2020 in English or Chinese and included empirical results pertaining to the resilience of Chinese hospitals in the COVID-19 pandemic.

Results: From the publications meeting the criteria (n=59), we found that substantial research was rapidly produced in the first half of 2020 and described numerous strategies used to improve hospital resilience, particularly in three key areas: human resources;

management and communication; and security, hygiene, and planning. Our search revealed a focus on interventions related to training, health care worker well-being, eHealth/telemedicine, and workplace organization, while other areas such as hospital financing, information systems, and health care infrastructure were less well represented in the literature. We also noted that the literature was dominated by descriptive case studies, often lacking consideration of methodological limitations, and that there was a lack of both highly focused research on specific interventions and holistic research that attempted to unite the topics within a resilience framework.

Conclusions: We identified a number of lessons learned regarding how China's hospitals have demonstrated resilience when confronted with the SARS-CoV-2 pandemic. Strategies involving interprovincial reinforcements, online platforms and technological interventions, and meticulous personal protective equipment use and disinfection, combined with the creation of new interdisciplinary teams and management strategies, reflect a proactive hospital response to the pandemic, with high levels of redundancy. Research on Chinese hospitals would benefit from a greater range of analyses to draw more nuanced and contextualized lessons from the responses to the crisis.

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KEYWORDS

COVID-19; pandemic; SARS-CoV-2; health care; hospitals; health care strategy; hospital resilience; interventions; crisis response; crisis preparedness; public health

Introduction

Since the emergence of the initial outbreak in Wuhan, the SARS-CoV-2 pandemic has created serious problems for hospital resilience globally [1], with overoccupation of intensive care unit beds [2], overworking of medical staff while treating patients with COVID-19 [3], and an inability to provide other essential services [4]. In addition to the challenges of meeting increased capacity needs, health care systems and hospitals have had to prepare for and minimize the risk of nosocomial infection, which has often required major infrastructure and organizational changes [5].

The response of hospitals in China to the pandemic in early 2020, particularly the situation in Wuhan, has been well publicized. As Wuhan was the source of the first major documented nosocomial outbreak, many feared that hospitals in the city and elsewhere in China would struggle to cope with the shock of the pandemic [6]. However, hospital strategies were part of a concerted national effort, including a strict lockdown in Wuhan and forceful restrictions on movement and association, that allowed case numbers to become negligible by late March. The final patient with COVID-19 associated with the initial outbreak in Wuhan was finally discharged on June 5, 2020 [7]. Although China maintained certain restrictions throughout 2020, experienced other minor outbreaks, and suffered economic losses in the first half of the year, the country's response has generally been viewed as a success story [8].

Defined as a system that can adapt its functioning to absorb a shock and, if necessary, transform to recover from adverse events, resilience has become an increasingly common concept within international health and development literature [9]. However, the concept is used less frequently when considering hospital and health system issues in the Chinese context. For example, in a scoping review examining resilience in disaster health management, health infrastructure safety, disaster preparedness, and medical response capability in China, Zhong et al [10] found that the topic was poorly covered in the Chinese context in both English- and Chinese-language literature.

Research by the same authors [11] led to the development of a quantitative conceptual framework of hospital disaster resilience that highlights the role of hospital resilience in the first severe acute respiratory syndrome pandemic in 2003, and a related study [12], based on questionnaires addressed to tertiary hospitals across Shandong province, identified four key factors that reflected the overall levels of disaster resilience (hospital safety, disaster management mechanisms, disaster resources, and disaster medical care capability) and compared the extent to which hospitals in the region met these criteria. They found that there was substantial variability within the province under study (Shandong) based on the type and location of hospitals. Although some elements of resilience were commonly achieved (38/41, 93% of hospitals had infectious disease surveillance), others were only managed by certain hospitals (eg, only 5/41, 12% of hospitals were able to surge staff capacity).

This literature must be reconsidered in the light of the recent SARS-CoV-2 outbreak, where the resilience of China's hospitals has been challenged by a more severe health crisis. Although the success of China's strategy has been attributed to achievements of the government, public health officials, and the attitudes of the public [8], the specific role of hospital resilience in this strategy is less documented. We have therefore conducted a scoping review to identify and synthesize the literature regarding the resilience of China's hospitals in the context of the COVID-19 pandemic during the first wave and to draw lessons from these experiences to better inform and improve responses to the current pandemic and to future crises.

Methods

Rationale

As part of a multidisciplinary team, and with the support of two external librarians, we chose a scoping review to enable us to synthesize, with rigor and in a relatively short period of time, the state of knowledge regarding our research question, to clarify the concept of hospital resilience in the literature, and to identify and analyze relevant knowledge gaps [13]. A scoping review was preferred to a full systematic review as our goal was to

provide, from a broad search, rapid information for public decision makers, stakeholders, and researchers regarding insights into hospital resilience in China. We conducted our review based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology specific to scoping reviews, which is largely based on the methodological framework of Arksey and O'Malley [14].

Protocol and Registration

In June 2020, we designed a protocol in advance of the study and published it on protocols.io [15].

Relevant Literature Identification

We conducted a systematic search using two different strategies to select appropriate academic literature from each context.

For the English-language literature, we have based our research on a collection of articles related to the COVID-19 pandemic published on the World Health Organization (WHO) website [16]. These articles were collected from the following databases: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO COVID-19 website, Centers for Disease Control and Prevention (CDC) COVID-19 website, China CDC Weekly, Eurosurveillance, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The search terms included the following keywords, comprising the three concepts: (1) China; (2) health care systems, hospitals, and professionals; and (3) resilience. English-language search terms (see Multimedia Appendix 1) and the search methods were checked by a professional librarian affiliated with the Centre Population et Développement. We searched for relevant Chinese-language articles on the database China National Knowledge Infrastructure (CNKI) using the search terms found in Multimedia Appendix 2. The request in Chinese was designed in consultation with a Chinese-speaking librarian from the Bibliothèque universitaire des langues et civilisations in Paris.

To limit the results to peer-reviewed journals, we limited the search on CNKI to five subcategories: those included in the *Science Citation Index*, the *Engineering Index*, the Beidahexin (Beijing University Core Journal Database), the Chinese Social Science Citation Index, and the Chinese Social Science Database.

The selection of evidence sources was conducted following an extended iterative process, confirming that there was complete overlap of articles with searches on other platforms (eg, Wanfang, Google Scholar, PubMed, or CDC website).

Data Extraction Process

The following information was extracted from each of the selected articles: title, authors, publication type, type of resilience, whether resilience was explicitly referred to, the hospital dimension, main objectives of the article, a slightly adapted Mixed-Methods Appraisal Tool (MMAT) evaluation, a simple representation of the results, limitations and main findings, recommendations by the authors, and some subjective notes by the reviewers. The MMAT was adapted to better capture single case studies [15].

Study Selection

Articles were included in the review if they were published between December 2019 and July 2020, were published in English or Chinese, focused on the resilience of Chinese hospitals in the COVID-19 pandemic, included empirical results, included accessible full articles, and were not considered gray literature (eg, press articles, letters, or editorials). Two reviewers (anonymous) used the software Rayyan [17] to select the papers using a two-stage review process.

Reasons for Exclusion

Articles were initially excluded based on reading the titles and abstracts, and then, for remaining articles, the full paper was evaluated. If an included article was identified as concentrating on public health systems, hospitals, or health care professionals, it was classified as such and only included in the study if it pertained to hospital resilience. *Public health system resilience* refers to elements that reflect broader choices made by the health system, such as media, supply chains, and nonpharmaceutical interventions; *hospital resilience* refers to choices made by and within individual hospitals; and *health care professional resilience* refers to the individual and group resilience of health care staff, such as psychological issues, physical injuries, or exhaustion experienced by staff. There was a significant amount of overlap; therefore, many studies were identified as belonging to more than one category (see Multimedia Appendix 3).

Critical Appraisal of Individual Sources of Evidence

Two authors (JS and RH) used MAXQDA 2020 (VERBI Software), a qualitative data analysis tool, to code the data using a coding tree consisting of 7 larger categories, including governance, human resources, professional values, finance, security, planning and management, communication, background (pre-existing policies), and two other coding categories to map methods (including methodological limitations) and the dimensions included in our conceptual framework. A separate category for professional opinions, recommendations, and other cited articles was included to facilitate the synthesis. The quality of studies was not evaluated although we did include information on the type of study design, data collection methods, potential limitations, a summary of the results, main findings, and recommendations given within the articles (Multimedia Appendix 3).

Data Synthesis and the Conceptual Framework

Results from the Chinese and English articles were initially synthesized separately by JS and RH, respectively; then, the two syntheses were combined by all authors. We synthesized the literature according to the Ridde et al [18] definition of health care system resilience: "the capacities of dimensions/components of a health system faced with shocks, challenges/stress or destabilizing chronic tensions (unexpected or expected, sudden or insidious, internal or external to the system), to absorb, adapt and/or transform in order to maintain and/or improve access (for all) to comprehensive, relevant and

quality health care and services without pushing patients into poverty."

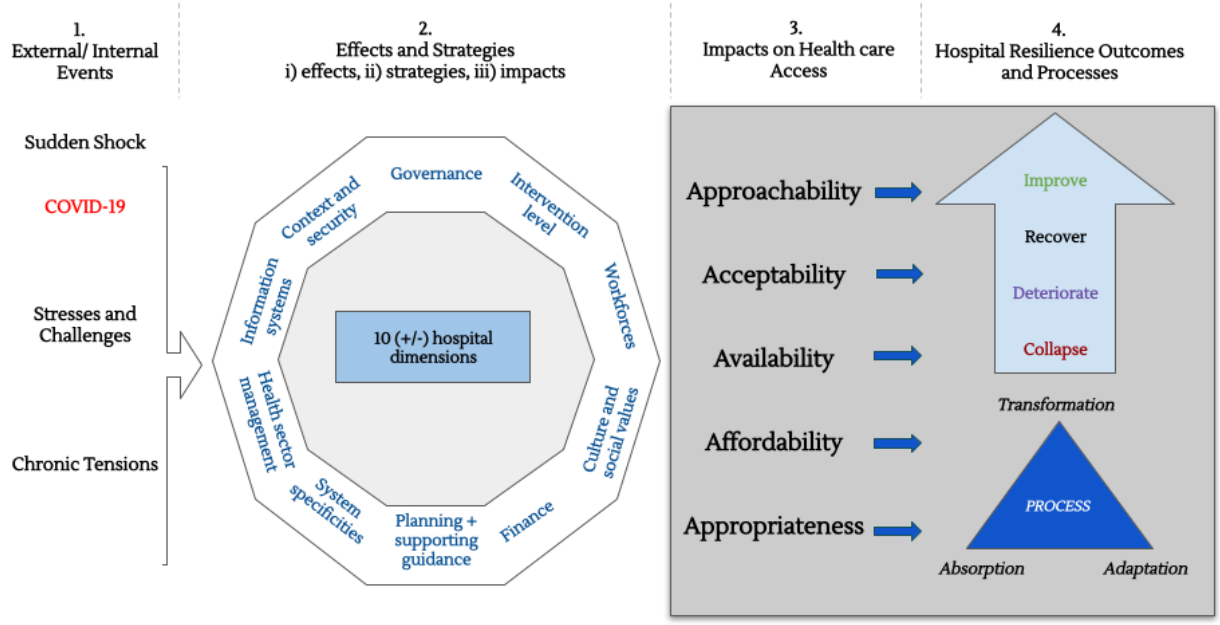
The synthesis of the articles was performed in terms of context, strategy, and impact. First, we explain the context in which a specific strategy is adopted, including the events in question and the effects of the pandemic experienced by the hospital in question. We then provide a synthesis of the strategies used, giving examples if necessary. Finally, we note the impacts of these strategies on health care access, which can theoretically be positive, negative, or neutral. The causality attributed to certain interventions is examined cautiously in the Discussion section. The right side of this resilience framework (Figure 1, parts 3 and 4) is not used in the evidence synthesis but will be examined briefly in the Discussion section.

This framework also helps us to address the question of how hospitals anticipate or react to crises. The *effect-strategy-impact* stage can illustrate different configurations:

- A reaction: When all three factors are present (an effect is felt, a strategy is adopted, and this strategy has positive or negative impacts)
- Anticipation: When strategies have an impact before a shock or are preventing a shock
- Inaction: When a shock has negative effects, but there are no strategies in place to react to this

The framework identified 10 conceptual dimensions of health systems: governance, intervention level, workforce, culture and social values, finance, planning and supported guidance, systems specificities, health sector management, information systems, context, and security, which we integrate into three larger categories with which to perform the synthesis: (1) human resources, (2) management and communication, and (3) the hygiene-security-planning nexus.

Figure 1. Resilience framework.



Results

Overview

As shown in Figure 2, we obtained 888 articles in Chinese and 5031 in English.

We identified 236 studies that met the criteria regarding resilience in general, of which 59 studies, 26 in English and 33 in Chinese, met the criteria for inclusion in the hospital-focused study; Figure 2 shows the process of study inclusion in this scoping review. We mapped the distribution of study design according to region, type of study, category of hospital, and language (Multimedia Appendix 4).

The geographical distribution of the papers is described in Figure 3; the studies were based on research undertaken at a diverse array of hospitals and settings. Only 2 articles were based on national surveys and therefore not focused on a single hospital. Understandably, the most represented geographical location with 14 papers of 59 (24%) was Wuhan in Hubei Province, with Sichuan Province in second place (n=8, 14%), followed by Guangdong (n=7, 12%) and Shanghai (n=5, 9%). A total of 50 (85%) studies were focused on tertiary A hospitals, the highest-ranked large hospitals in the country; 8 (14%) studies included various hospitals, including secondary hospitals, while only 1 study targeted primary health care providers.

Our analysis revealed that 94% (n=56) of the articles were explicitly identified as peer-reviewed articles, with 1 review article, 1 commentary article, and 1 short report. In terms of methodology, the studies were dominated by single case studies using mixed methods (n=30, 51%) and descriptive quantitative studies (n=22, 37%). There were 4 (7%) qualitative studies, 2

(3%) studies using other mixed methods, and 1 randomized study. The dimensions of hospital resilience most commonly referred to were health sector management (n=44), context and security (n=47), intervention level (n=8), planning and support (n=29), system specifics (n=8), information systems (n=8), workforce (n=31), and cultural and social values (n=4). Other dimensions such as governance and finance were not covered in the selected articles.

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. CN: Chinese; EN: English.

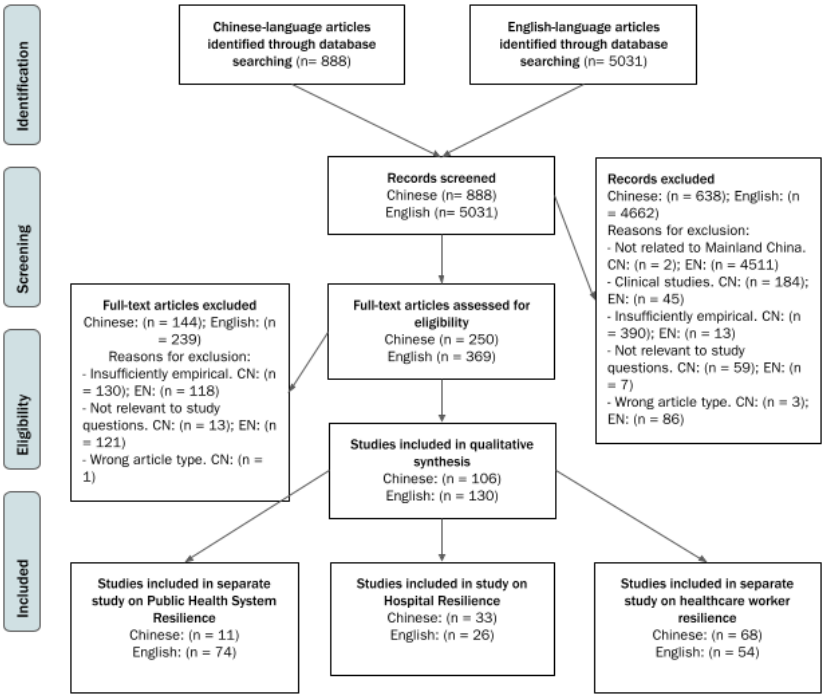
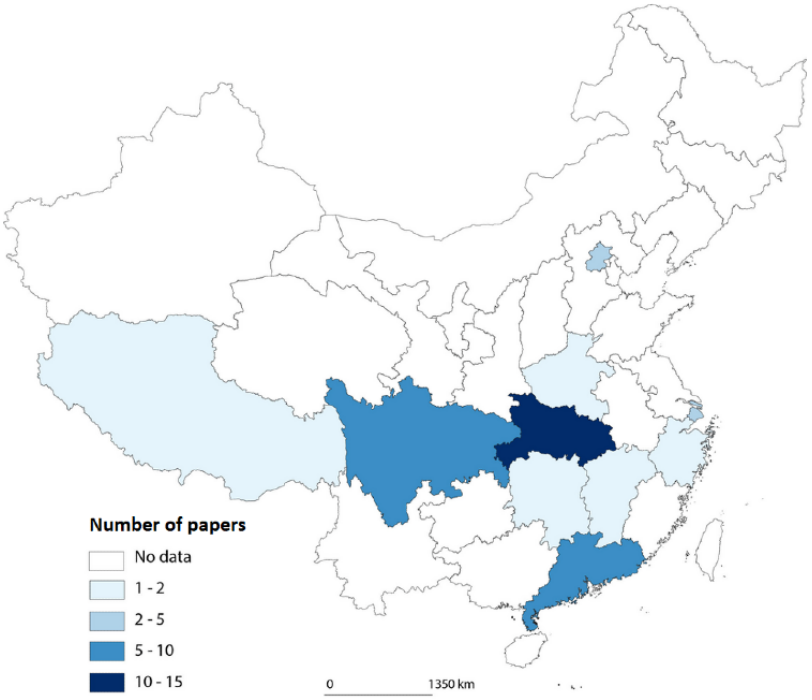


Figure 3. Geographical distribution of papers.



In terms of MMAT criteria, 85% (n=50) of articles contained clear questions and objectives, and addressed them appropriately. Quantitative studies adhered to the MMAT criteria to mixed degrees: the sampling strategies were often not made explicit (n=4) and many studies used some form of convenience sampling (n=5) due to accessibility and need for timeliness given the crisis context. It was often unclear whether the study was representative of the population (n=8), and in some articles (n=6), there appeared to be some overrepresentation of certain groups within the population (women and nurses in particular).

All quantitative articles were deemed to have used appropriate measurement tools, and only 9% (n=2) of the quantitative articles did not specifically mention response rates. Similarly, 7% (n=2) of the mixed methods articles were considered to have used an unclear methodology, and 17% (n=5) were identified as not integrating qualitative and quantitative data in a relevant manner. Only 36% (n=11) of articles explicitly considered limitations of the study methodology.

Studies published in Chinese were more likely to be case studies (n=21, 62%) compared to studies published in English (n=7, 27%). Chinese-language studies were also less likely to consider limitations of the methods used, with 71% (n=24) not mentioning any limitations, as opposed to 23% (n=6) of the English-language papers. Our MMAT evaluation determined that the papers published in English conformed more closely to the MMAT framework than those in Chinese.

We identified 10 different categories in which strategies to address the pandemic were used and 29 specific strategies recommended by the articles (Multimedia Appendix 5), with a description of the strategies involved and in which studies these strategies were mentioned.

Multimedia Appendix 5 illustrates that a number of different strategies were identified in the scoping review procedure, and the results of these are explored in the following synthesis.

Human Resources

Reinforcements

After the initial outbreak of COVID-19 in Wuhan, the Chinese authorities made the decision to send personnel reinforcements from all over the country to Hubei Province to fight the epidemic. Wuhan is medically well equipped (9.25 hospital beds per 1000 inhabitants in 2018) and has 110,000 health professionals, including 40,000 medical practitioners and 54,434 nurses [19], but at the end of January 2020, reinforcements were nevertheless sent from all over the country. A total of 42,000 new health workers arrived in Hubei Province, including 35,000 arriving in the city of Wuhan, remaining in the area for between 18 and 50 days [20]. The implementation of a rapid response mechanism to the pandemic thus required the rapid integration of external reinforcements, as well as adaptation to the local hospital environment and management style [21]. Several articles reported the strategies implemented by hospitals to facilitate the integration of reinforcements and improve work efficiency [22,23].

- Strategy 1: Standardization of nursing procedures. In one hospital in Wuhan, the 27 nurses in a ward dedicated to patients with COVID-19 had all come from different departments (eg, infectiology and cardiology) from six different hospitals in Sichuan Province. These nurses had different experiences, skills, and habits; therefore, to facilitate collaboration and improve work efficiency, the management of this hospital introduced a new work system, standardizing nursing procedures and responsibilities of each staff member [24].
- Strategy 2: Creation of backup teams. This involved forming a team composed of staff members and external reinforcements in preparation for increased staff demand in COVID-19 infection wards and to compensate for a reduction in staff numbers due to infection. These teams were often formed strategically; for example, Jinyintan Hospital in Wuhan deliberately split nursing teams into teams comprising of backup (nonlocal) nurses and local nurses, experienced nurses and newly graduated nurses, and intensive care unit nurses and nonintensive care unit nurses to share experience, skills, and awareness of procedure [25].
- Strategy 3: Delineating the responsibilities of each staff member. Many hospitals instituted measures such as checklist interventions [26], training, and management strategies to ensure that the roles and responsibilities of all staff, especially transdisciplinary nurses and new staff, were clearly defined and that staff were aware of any changes. These new responsibilities included recording electrocardiogram results, organizing ward supplies, and observing critical patients [27]. Training interventions involved training on protective measures and the operation of medical equipment. As the backup nurses were not familiar with emergency equipment and instruments, hospitals set up a series of training programs to help the nurses understand the operation of various pieces of equipment [24].

Impacts

The articles reported many positive outcomes as a result of these interventions, including how the efforts helped facilitate the integration of reinforcements into the service and deliver quality care efficiently while maintaining the mental and psychological health of reinforcement staff [21,25]. For example, Feng et al [24] described how, between January 27 and March 15, 2020, as a result of the close collaboration between local nurses and backup nurses, 84 of 97 (87%) patients with COVID-19 admitted to the hospital were discharged, and the hospital only had one fatality. Care and psychological support offered to both backup and local nurses was timely, with none of their nurses reporting any severe psychological problems. Additionally, as Liu et al [27] note, reinforcement staff experienced negligible levels of infection, likely due to strict adherence to procedures, ample access to personal protective equipment (PPE), and special accommodations away from their families and other potential sources of infection.

eHealth, Telemedicine, and Use of Technology

Context

Due to the contagiousness of SARS-CoV-2, new ways of caring for patients were implemented to reduce the risk of contamination. Family visits were restricted, and the loneliness of inpatients became a substantial challenge requiring hospital staff to pay more attention to the mental health of patients. To prevent and control the spread of the virus and to avoid cross-contamination, some departments closed their ambulance services and stopped receiving patients, while lockdown and the accompanying transport control measures made it difficult for non–COVID-19 patients to travel and receive treatment [28]. Due to these disruptions, many patients receiving radiotherapy, chemotherapy, or dialysis could not be treated in a timely manner [29].

To continue providing health care to the community and fulfill their obligations to patients, hospitals had to use other methods to provide care; therefore, a common element examined in the chosen studies was the use of telemedicine interventions. Telemedicine interventions serve the role of allowing patients to receive medical appointments, services, and treatment without having to visit a hospital; preparing and screening patients before they arrive at the hospital to facilitate their entry into the hospital and avoid contamination; monitoring patients with COVID-19 in home quarantine; and using human resources more efficiently. Additionally, mobile and digital technology was used by hospitals across China in a range of other ways to increase efficiency and reduce person-to-person contacts [30].

- Strategy 1: Use of online services for psychological issues in the population. A hospital in Chengdu implemented a multitiered intervention program, with online media, free hotline consultation, and targeted online video interventions provided to citizens with psychological problems, with crisis intervention provided on site [31,32].
- Strategy 2: Development of online screening mechanism for potential patients. A range of strategies were suggested to provide web-based consultations, appointments, prescription services and drug delivery, and other services, as a complement to in-person hospital services. For example, in a qualitative study of patients' experiences with online services offered to non–COVID-19 patients, one patient reported: "Use of mobile apps in this pandemic is very important. You can pay, register, and view results on your mobile phone. You don't need to queue up at the outpatient clinic, and you can chat with a doctor online after you get home, so it's far more secure" [33].
- Strategy 3: Using online platforms to monitor patients with COVID-19. A number of articles described a process of offering e-counselling support to patients who were struggling with the physical and psychological effects of the disease [34]. In addition to providing a greater monitoring and awareness of the individual patients, this intervention also allowed the staff to collect data to use in the improvement of in-hospital treatment [35-37].
- Strategy 4: Developing and using onsite information technology services and infrastructure. The use of nonmedical technology to improve hospital services, such as using app-based QR Codes (a machine-readable optical label, similar to a barcode) to share information and using robots for certain tasks to avoid person-to-person contact, was expanded during the pandemic [30,38].

Impacts

Telemedicine interventions were reported as an effective substitute or complement to onsite health care [35-37] and were also cited as being popular and time-saving among the majority of users [32]. The introduction of teleconsultations also reduced the difficulties of patients with chronic illnesses regarding the management and purchase of medicines [28]. Furthermore, the implementation of eHealth interventions allowed staff to address the needs of a higher number of patients while also helping to spread understanding regarding the virus risks and public health knowledge [39].

Organization of Work and Health Care Worker Well-being

Context

At the beginning of the epidemic, medical personnel experienced panic and fear due to insufficient knowledge of the epidemiological characteristics of the virus and the need for protection, and many experienced a temporary shortage of medical supplies [40]. The problems of work overload were also highlighted in many papers, particularly the problems associated with new unfamiliar tasks for which nurses had not been specially trained [41], high work intensity [42], disrupted circadian rhythms, and restrictions and challenges of protective clothing.

These factors intensified workload pressures and led to anxiety, insomnia, depression, pain, symptoms of posttraumatic stress disorder, and grief. Furthermore, a higher workload led to worse hygiene behavior, such as reduced adherence to handwashing guidelines [32]. As 1 article explains:

> *high risk of professional exposure, the intense workload, the sharing of the patients' anxiety, a feeling of helplessness while struggling to treat severely ill patients and many other factors can lead to high levels of psychological pressure, low confidence in one's own work and depression among nurses, which affects their quality of work and their physical and mental health [24]*

- Strategy 1: Readjustment of health care staff schedules. For health care staff who had direct contact with patients with COVID-19, a 4- to 6-hour schedule was implemented by a number of hospitals. Protection protocols in Chinese hospitals were extremely strict, especially for health care workers who were working directly with patients with COVID-19. Once PPE was applied, it was required that the wearer avoid all potential contamination risks, including physiological needs: eating, drinking, and using toilet [43]. The hospital thus reorganized the timetable of the staff, accounting for the physical needs of the staff, the efficient use of single-use protective material, and the needs of the patients. For example, in Jinyintan hospital (Wuhan, Hubei), three systems were successively implemented as early as December 2019: shifts of 4, 5, and 6 hours were tested, and after surveying staff perceptions of the three shifts, the hospital adopted the 5-hour per day system [25]. Another hospital in Wuhan implemented 6 shifts per day with a 4-hour rotation to allow nurses the time to take care of their physiological needs [23].
- Strategy 2: Increased flexibility of working hours according to the number and condition of inpatients. During the peak period of patient admissions, the number of staff was increased to provide an appropriate nurse-to-patient ratio, which is essential to ensure that patients receive appropriate care and that the workload of caregivers or staff remains reasonable. For example, in a hospital in Wuhan, each nurse was responsible for 6 to 8 patients [23]. The hospitals also used backup teams while using shorter shifts and appropriate working hours to reduce risks associated with workload, including lowered quality of work, medical

errors, and increased rates of nosocomial transmission [25,32,41].

- Strategy 3: Providing material and psychological support to the staff. As well as ensuring provision of essential supplies, several hospitals provided high-nutrition meals to support staff and boost their immunity. Many strategies were used to provide psychological support, either through colleagues, health professionals, or specialized psychologists [44]. For example, a maternity ward in Tongji Hospital (Wuhan) established a WeChat group, "to promote scientific articles on mental health, to understand...problems in the life and work of the medical staff and subsequently to provide help and support...A psychological consultation platform was also established to provide medical staff a channel to vent their negative emotions and to offer psychological interventions when needed" [35].

Impact

These strategies improved working conditions for health care workers and quality of care for patients. A number of articles [45,46] highlighted that use of shorter shifts and appropriate working hours could be effective strategies to deal with mental health needs, work quality, and hygiene requirements. Furthermore, a flexible work schedule also meant that staff members were less affected by fatigue and stress. For example, in Tongji hospital in Wuhan, 97% (n=63) of the staff members were satisfied with the schedule of 5 hours per day, compared to 59% (n=37) satisfaction with the previous schedule of 6 hours per day [25].

Management and Communication

Emergency Team and Nursing Management

Context

After the COVID-19 outbreak in Wuhan, China, human resources were rapidly reorganized within hospitals, between hospitals, and throughout the country. Transdisciplinary nurses without specific expertise in infectious diseases were brought in to support COVID-19 wards [3], backup teams were introduced, and frontline nurses had major changes in their responsibilities. However, many issues arose from this reorganization, such as nurses lacking understanding about their specific responsibilities [39]. Several strategies in management were used to increase the effectiveness of medical staff under these new circumstances:

- Strategy 1: Creation of new teams. Soon after the epidemic was declared, many new teams were created, such as the nursing technical support team, comprised largely of head nurses from different departments [45], and the emergency management and sensing control team, with a focus on procuring new information about the virus, and establishing an emergency management plan [22].
- Strategy 2: Implementation of a plan-do-check-act (PDCA) cycle, a management tool. This consisted of a repeated four-stage model for continuous improvement in quality management [46]. In terms of human resource management, this included 3 relevant components: defining the staff's role and responsibilities, establishing a clear staffing structure and changing the shift handover modes, and testing and verification of procedures, such as evaluating nursing staff with questionnaires.
- Strategy 3: Implementation of regular training for health care workers. Given the speed of SARS-CoV-2 spread, health care staff required rapid training to properly apply the protection protocols and needed continuous information regarding the evolution of knowledge about the virus. In addition, reinforcements who were unfamiliar with the workplace also needed to familiarize themselves with their new colleagues and the work environment. Many hospitals in our study implemented a dual training system including online training and face-to-face training on topics such as "COVID-19 hospital infection prevention and control, hospital air purification management specifications, medical institution disinfection technical specifications, and personal protection requirements for disinfection and isolation" [41] was undertaken to improve care and reduce the risks of contamination between colleagues. The training content included the following elements: the characteristics of the service and the environment, spatial planning and reorganization, disinfection measures and knowledge of protection protocols, work procedures, and the use of medical equipment. As well as training, WeChat groups were established to communicate up-to-date information on the progression of the pandemic and knowledge of treatment options [30].

Impacts

Several articles quantitatively measured the effectiveness of different aspects of management interventions, finding that they succeeded in making staff aware of their roles and responsibilities, as well as clarifying the staffing structure and handover procedures [22,27]. Through training interventions and communication facilitated by the WeChat groups, frontline caregivers developed a better knowledge of the virus, which helped to alleviate their anxiety and fear [21,47], and they were better able to apply the protection protocols [48]. A quantitative study focusing solely on a training intervention on COVID-19 knowledge and training techniques provides an example of this, finding strong positive effects of the intervention on employee knowledge [40] and concluding that interactive simulation training is complementary to didactic teaching. In a hospital in Beijing, 7 days after the implementation of the standardized training program for 1125 medical staff, scores in a test on the prevention and control of nosocomial infection rose from an average of 69 of 100 to 88 of 100. The correct answers by supervisors rose from an average of 83 of 100 to 92 of 100 (n=309), while the proportion of staff members wearing surgical masks increased from 86% to 93%, and the proportion of adherence to hand hygiene protocols increased from 92% to 96% (n=1630) [41]. In Chen et al [46] the PDCA team identified the problem of poorly defined responsibilities, noting that, although 12% (n=4) of a small nursing team initially lacked awareness of their responsibilities, this was reduced to 0% following a training intervention.

Communication and Information

Context

During the early stages of the outbreak, as knowledge of the virus rapidly evolved and the number of patients in the hospital increased daily, hospitals were required to react immediately to the situation and readjust strategies accordingly, whether in terms of protection protocol, patient care, or organization of work. The situation was more complex in hospitals with external reinforcement from other provinces because, according to one article, "each medical team has its own process and philosophy of care, the only way to provide quality care to patients is to coordinate and standardize and homogenize care" [47]. Quickly and accurately conveying expert information and the response plan to staff at all levels became a serious challenge for various medical institutions. In this situation, fluid communication between the different parties involved (government, hospital, carers, patients and families, etc) was essential.

- Strategy 1: Implementation of regular meetings between the different team members for daily briefings. For example, in Tongji Hospital in Wuhan where national medical aid teams served in a "whole-system-takeover model," nursing department staffers worked in partnership to establish a range of measures including smoothing communication channels through daily meetings. According to one author: "In the early stages, we held daily nursing council meetings to shorten the adjustment period and standardize the work in order to shift from a 'wartime state' to a daily routine" [5].
- Strategy 2: Promotion of the use of new information and communication technologies to aid communication between colleagues. Use of communication platforms, usually WeChat groups, and occasionally telephone exchanges, was identified in a number of articles. In Tongji Hospital, to provide an effective communication and information mechanism, a WeChat group with all the nursing staff was set up to enable communication at any time. In addition, the hospital set up a daily nursing information system: the progress of nursing work as well as problems encountered in the quality control of care were analyzed and then sent to everyone in image/text form [5].
- Strategy 3: Promotion of the use of visual materials to better convey information to health care staff. This involved the use of physical signs such as multicolored arrows indicating the different hospital zones and posters of protection protocols displayed in different zones [21].

Impact

Some evidence in the articles indicates that the aforementioned communication measures were effective in improving the psychological health and efficiency of health care workers. In the People's Hospital of Wuhan University, 1 week after a *visual management* communications intervention was implemented, the time taken to obtain materials was shortened, the satisfaction rate of medical staff improved, and nursing quality increased [21]. Moreover, regular updates on the state of scientific understanding of the virus and informing the staff promptly about key information using the framework of *what we know*, *what we don't know yet*, *what we have* (in the hospital), *what we don't have* (in the hospital), and *what we are doing* was seen as particularly effective, both in relieving the anxiety of health care workers and improving the effectiveness of protection measures [41,47,48].

Security, Hygiene, and Planning

As well as analyzing the number of infected staff, a large number of articles in the scoping review examined the reasons for infection of health care workers and presented hospital strategies to reduce the risk of nosocomial infections.

Protection Protocols (Change and Application of Protocols)

Context

The issue of contamination risk is one of the most frequently discussed topics in the articles and relates to many dimensions of hospital resilience, such as human resources, management, communications, and information. The risk of nosocomial infection was extremely high in Wuhan, especially in the early phase of the outbreak. One study found that 84.5% (1426/1688) infected health personnel believed that their infection had been acquired in the hospital wards [49]. To reduce the contamination risk as much as possible, Chinese hospitals implemented strict protocols for hospital admissions, discharge procedures, PPE, and the application of social distancing rules.

- Strategy 1: Strict management of hospital space. Access to the hospital analyzed in Lu et al [50] was closely controlled in terms of body temperature and mask wearing. Patients with a temperature over 37.5 °C or showing respiratory symptoms were redirected to the fever ward or the emergency department.
- Strategy 2: Focus on environmental contamination with routine disinfection. In the COVID-19 unit, strict measures were applied regarding the disinfection of medical instruments (stethoscopes, thermometers, etc). This was described in detail in 1 article, which explained how floors, tables, chairs, and diagnostic and treatment beds were wiped and disinfected regularly with 1000 mg/L of chlorine disinfectant and that this behavior was regularly monitored [29].
- Strategy 3: Encouraging health care workers to apply personal equipment protocols appropriately, according to their role and their level of contact with patients with COVID-19. To help staff to properly apply the protocols, hospitals proposed regular training for staff and the establishment of a 24-hour supervisor position to verify the appropriate application of protocols when entering and leaving the buffer zone. Hospitals often introduced comprehensive management plans involving screening, personnel management, disinfection and hygiene procedures, and training and supervision of employees, as well as PPE supply chains.
- Strategy 4: Restricting family visits to avoid patient-family contact. Family visits were restricted, as they increased the risk for nosocomial transmission; however, many hospitals implemented a video visit system to facilitate exchanges between patients and their families. One article quoted a staff member: "For people who come to the hospital to visit

patients, the warden enables the video visit with an iPad connected to the nurses' iPad at the patient's bedside, which enables exchange with the visitors" [51].

Impact

Only a few articles evaluated the impact of these strategies on infection rates, with most concluding that no medical staff member was contaminated by SARS-CoV-2 during this period. With regards to PPE use, a regression analysis in self-reported compliance with security protocols [32] found two seemingly contradictory findings: although staff in high-risk departments have higher rates of compliance with security protocols, further contact with at-risk patients had a negative effect on compliance. The research did not capture information to determine whether this was due to resource shortages, human deficiency, high workload, or other factors, but reducing workload through reinforcements, ensuring resource supply and increased training is recommended as an intervention. In terms of environmental contamination, 1 article [52] found the highest rates of environmental contamination in the isolation ward for pregnant women, even when compared to the fever clinic. It was hypothesized that this was due to the differences in ventilation and the number of visitors. This article also found that hand sanitizer dispensers and used gloves were greater sources of contamination than eye protection or face shields.

Personal Protective Equipment

Context

In the response to the COVID-19 outbreak, the supply of PPE was a substantial challenge globally. This problem was also present in China, where several regions had a shortage of PPE and disinfection products [40]. Hospitals were required to adjust the variety and quantity of protective materials in a timely manner to find an ideal balance between the level of equipment consumption and storage capacity, which was essential to ensure continuity of care.

- Strategy 1: Implementation of an inventory register for important materials while standardizing the process of managing and using these materials. In many hospitals, a physical security team leader was put in charge of recording the real-time use of equipment and strictly controlling the receipt and distribution of materials [35].
- Strategy 2: Avoiding overconsumption and waste of materials. The presence of the hygiene team and the supervisor in the application of caregiver protocols was to make sure that staff wore PPE correctly and avoided PPE overuse [53]. In another hospital, when restocking materials, it was not permitted to mix materials with different expiry dates to ensure that different materials were used in order of expiry dates, from oldest to newest, to avoid waste [21].
- Strategy 3: Decrease in the protection level for the provision of certain non–COVID-19 services in view of the shortage of medical resources. Some studies examined decreased protection measures to identify the minimal level of protection needed in different hospital areas. For example, a study in the Huaxi Hospital of Sichuan University suggested that the staff in non–COVID-19 intensive care units did not need to wear full body protective overalls, thus saving on PPE [54].

Impacts

Overconsumption of PPE was a common problem in hospitals, particularly in the early and midstages of the outbreak. However, according to surveys from a hospital in Shenyang, the aforementioned strategies contributed to the optimization of PPE and disinfection supplies, allocating based on needs and stock while ensuring that frontline personnel were well protected [40]. The Huaxi Hospital of Sichuan University applied these protective protocols to its pediatric intensive care unit, finding that health care professionals (91 people) and household members (5 people) in contact with COVID-19–positive patients wore only masks and did not wear the full protective suit required by some institutions, yet there were no infections in the ward [54], suggesting that lighter PPE could be sufficiently effective.

Reorganization of Services

Context

During the outbreak, hospitals had to reorganize their services to both increase capacity and reduce the risk of contamination. The changes in infrastructure, hospital procedure, and protocols in Chinese hospitals involved substantial changes. For example, a hospital in Wuhan revised 32 items on its regular hospital procedures to transform a general hospital into a designated COVID-19 treatment hospital [45], and a number of case studies were written on particular changes in procedure and ward renovation [37].

- Strategy 1: Transformation of non–COVID-19 hospital areas into specialized COVID-19 wards. Many hospitals lacked a negative pressure chamber to provide a buffer zone; therefore, many large non–COVID-19 hospital areas were required to be transformed into specialized COVID-19 wards to accommodate the growing number of patients with COVID-19 [53].
- Strategy 2: Reorganization of space. In designated COVID-19 hospitals, necessary infrastructure changes were implemented, which included setting up fever tents, ward renovation, unidirectional channels for patients, and converting sections of the hospital for patients with COVID-19. These were done to minimize contact between infected and uninfected individuals, reduce patient flow throughout the hospital, and maximize the shared space available to patients with COVID-19. Another example is the creation of the "three zones and two passages" system (Chinese: 三区两通道) that included a contaminated zone, potentially contaminated zone, and a clean zone, as well as two separate passages for medical staff and patients.
- Strategy 3: Reorganization of inpatient rooms. Certain hospitals decided to convert double rooms into single rooms, whereas for hospitals that were forced to put several patients in the same room, a distance of more than 1 meter between beds was maintained.

Impacts

The impacts of these strategies were not examined in detail in the included studies. Gao et al [55] claimed that their

management strategy contributed to effective prevention of virus spread in the endoscopy center in Sichuan; however, none of the articles claimed to provide strong evidence of the effectiveness of a given intervention.

Discussion

Summary of Evidence

In this scoping review, we identified 59 studies that addressed resilience in hospital settings across China in the context of the initial SARS-CoV-2 outbreak in the first half of 2020. Our findings indicate a wealth of research describing certain strategies used to improve hospital resilience, particularly those concerning human resources: management, communication, security, hygiene, and planning. We found that much attention was focused on training, health care worker well-being interventions, eHealth and other technology-related interventions, and work organization interventions, while training and management interventions were also subject to more rigorous quantitative analysis. Some themes, such as information systems and reinforcements, were mentioned in a small number of studies and lacked rigorous analysis, while others, such as hospital financing and the development of new health care infrastructure, were neglected in the literature despite being mentioned explicitly in Chinese official policy papers [56]. Most importantly, our findings also represented a paucity of rigorous research focusing on the effectiveness of interventions and a lack of research attempting to unify these different elements within a resilience framework.

In terms of the "Effects—Strategies—Impacts" framework, there were some cases of inaction, anticipation, and reaction represented in the literature. Only a handful of studies examined cases of inaction; for example, Gao et al [49] analyzed the reasons for personnel infections in the early stages of the outbreak. Most studies referred to actions taken in anticipation of major outbreaks in provinces with only limited spread. Some studies, especially those carried out within Wuhan, described a strong reaction to a serious ongoing outbreak.

The majority of the included studies provided details on the effects and strategies with an appropriate methodology, whether quantitative, qualitative, or mixed. However, few studies performed any kind of systematic analysis to evaluate the impacts of these strategies and were more descriptive in nature. The goal of a large portion of the studies was to share knowledge as quickly as possible, but the lack of rigorous analyses provides issues in identifying effective strategies. An important characteristic in the interpretation of a strategy or a specific intervention was that most studies were written by health care workers working directly in a given hospital during the outbreak. Participation by health care workers in the process of knowledge creation can be an invaluable tool, demonstrating what Alexander et al [57] have identified as "reflexivity on action," and enabling the creation of a "collective space for health professionals to reflect on and improve their practices." However, this process could also represent a bias that can bring into question the neutrality of the scientific research process, especially as many articles, particularly those in Chinese, did not consider the methodological limitations.

Similarly, as China's research and medical communities are not independent from politics [20], political factors may have played a role in the choice of papers written and published, potentially neglecting those that found negative results. These two factors, politics and the predominance of health care workers, as opposed to professional researchers as authors, may also have limited the scope of articles concerning resilience issues such as finance or power structures, which can be sensitive and politicized. Many of the articles that examined hospital strategies to address health care worker health issues emphasized the physical and mental health of nurses while often neglecting the issues faced by other health care providers, including doctors. One possible reason for this phenomenon is that doctors may have more difficulty discussing problems encountered in work and sharing mental health concerns with colleagues [58]. Similarly, gender issues and potential inequalities were not discussed in the selected papers. Despite significant gender gaps existing in health care professions—men being overrepresented in senior health care roles and underrepresented in nursing staff—this was not considered in the selected articles. This suggests that a "gender blindness," the systemic failure to acknowledge gender differences in health [59], may be present in the case of Chinese hospitals.

These papers also highlighted how some processes undertaken during the pandemic attempted to increase health care access in ways that could potentially lead to a positive transformation process (as mentioned in the resilience framework). For example, articles focusing on eHealth and *internet hospital* interventions [39] mentioned ways that the transition to telemedicine provoked by the SARS-CoV-2 pandemic could be used to make health care more approachable and affordable, and improve availability to vulnerable groups across the country. Further research is needed to examine whether these resilience processes could lead to improved access to health care in China's hospitals following the pandemic.

Recommendations for Health Care Practitioners and Managers

There are a number of recommendations offered to health care practitioners within the articles (Multimedia Appendix 5). Improving patient awareness of online services enabled patients to better respond to these public health emergencies and reduced unnecessary round trips between home and hospital [41,50]. Artificial intelligence and internet technologies can be used for online self-assessment systems, robots can be used in guiding patients and delivering medicines within the hospital, and QR Codes can be used for collecting patient and visitor information [46]. Studies also found that China's advanced use of technology has a crucial role in many elements of a resilience framework, including training, knowledge management, and transfer and information systems. However, it is important to note that these recommendations were not substantiated by rigorous evidence. For example, Yan et al [30] provide a descriptive examination of information system strategies used by China's most reputable hospitals and offer recommendations without any demonstration of evidence to support the recommendations. In terms of nursing management, clear role recognition is seen as an important prerequisite for better practice. Nurses in 1 article [3] criticized the ambiguity of the roles given to over half of transdisciplinary

nurses, suggesting that "more detailed role classification, clearer role definitions and job descriptions, and appropriate suggestions for expanded responsibilities would be effective methods to alleviate role ambiguity and improve work efficiency." Other articles suggested that role ambiguity can be remedied with fairly simple interventions, such as a PDCA cycle to improve standardized nursing management in an intensive care unit ward [46].

With articles that analyzed the impact of training interventions, both more traditional and online training interventions were associated with positive effects on knowledge and behavior of staff regarding safety procedures, when compared to results before the training. Online or massive open online course–based training is an appealing alternative to in-person training when infection risk reduction is a relevant concern. To build hospital resilience, articles argue that staff training for outbreak and infectious disease practices should continue in regions without ongoing outbreaks [49] and should continue after the outbreak has subsided [46]. We can conclude that the ability to provide timely, effective training interventions in response to a health care emergency is a crucial element of a resilience framework.

Infection control measures comprise a crucial element of hospital resilience and many recommendations were given, despite not always being supported by data. Li et al [32] recommended targeting certain infection control interventions in low-risk departments, as there may be higher risk to staff on other wards (eg, the maternity unit) compared to the infectious disease unit due to disparate security measures and PPE use. Many articles related to infection control and environmental contamination recommended using risk-averse strategies with multiple layers of redundancy to reduce the risk of nosocomial and health care worker infection. Xu et al [60] also recommended that medical institutions should implement ward reconstruction so that nonspecialized hospital buildings are able to meet the requirements of an infectious disease unit.

Recommendations for Researchers

The results of these studies demonstrate the degree to which China's health care system responded and adapted to the outbreak through several innovative measures. Although evidence of the effectiveness of certain interventions was not provided, the collection of studies from across hospitals in China offers strategies that, together, have likely contributed to the decrease in daily nosocomial infections from a peak of 127 new health care worker infections on January 23, 2020, to the first day with 0 new cases on March 8, 2020 [61].

Due to the short time frame, the lack of academic diversity in the research areas, political concerns, and publication bias, this scoping review highlights the need for more rigorous intervention research and evaluation, and the inclusion of multidisciplinary teams involving social science researchers and data scientists [62]. Gilson et al [63] have called for a structured research agenda to inform health policy and system responses to COVID-19, which should include resilience research in China's hospitals.

This scoping review was not intended to draw conclusions about the causality of any particular strategy; therefore, a *realist review* [64] would be a useful way of determining middle-range theories specific to the resilience of China's hospitals in the outbreak.

Our research also revealed that there are relatively few articles that have used the concept of resilience in a Chinese medical context, indicating that China's hospitals do not consider a resilience framework as part of their research. Despite increased use in academic and professional contexts, the popular concept of *health systems resilience* has not yet reached conceptual maturity [62], and according to a recent scoping review, "empirical studies fundamentally differ in the way that resilience is understood in a healthcare context" [65]. In China, the multiple possible translations for the term *resilience*—most prominently, *tanxing* (弹性), *renxing* (韧性), and *fuyuanli* (复原力)—three terms with subtly different connotations, demonstrate this lack of conceptual clarity. Further research needs to be undertaken to understand how the concept of resilience translates and is understood across cultures and academic contexts.

Another element that must be addressed is the trade-offs associated with the risk-averse strategy used in Chinese hospitals. Some studies noted that hospitals chose to implement a highly risk-averse strategy and that this did not allow them to determine what the minimal effective level of PPE use was to maintain effective protection [27], which poses problems for knowledge transfer to regions or situations with more limited capacity or resources. As Jin et al [52] notes "...(L)ack of evidence means we are using a precautionary approach which often results in our applying all available controls all the time." Future comparative work could clarify whether China's successes could be replicated without such extreme levels of personal protection or whether a highly risk-averse *zero-tolerance* policy for nosocomial infection is the optimal choice.

Financial constraints, which comprise a central aspect of health systems resilience, have also been understudied in the Chinese context. Although comparative studies have examined macro-level decisions and cost-benefit trade-offs in COVID-19 policy between countries including China [66], our study found a lack of research pertaining to financial constraints faced by Chinese hospitals and other relevant decisions at the hospital level.

Limitations

We were unable to perform a risk-of-bias test for this paper; therefore, the issues resulting from political or other biases were difficult to determine. As few of the articles were written by non-Chinese citizens or were peer reviewed by external reviewers, selection effects caused by censorship cannot be excluded.

The exclusion criteria we chose meant that we did not include gray literature in this review, but it is worth noting that media articles, social media content, and government white papers may also provide relevant sources of information that may help better understand how Chinese hospitals have sustained resilience during the SARS-CoV-2 outbreak. Additionally, we only included articles released soon after the outbreak; therefore,

articles conducted later in 2020 and in 2021 related to similar topics may have reached different conclusions [67].

Conclusion

Our scoping review demonstrates that there is a wide range of studies concerning hospital resilience in the Chinese context and that this literature helps us to understand the strategies used by the hospitals in China during the SARS-CoV-2 outbreak. The literature, both in Chinese and English, can provide important lessons on reinforcements, organization of work, eHealth, telemedicine and use of technology, health care worker well-being, emergency team and nursing management, training, communication and information, protection protocols, PPE, and reorganization of services.

Although this review demonstrates that the evidence is generally insufficient to determine the effectiveness of specific strategies, some preliminary results on the effectiveness of training interventions, technology use, and management interventions, such as checklists and the PDCA cycle management, are provided. Furthermore, the study illuminates some common characteristics that have characterized what has generally been viewed as an effective strategy against the SARS-CoV-2 outbreak [66], including risk aversion and redundancy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms for English-language search.
[XLSX File (Microsoft Excel File), 5 KB - xmed_v3i2e31272_app1.xlsx]

Multimedia Appendix 2
Chinese-language search terms.
[XLSX File (Microsoft Excel File), 6 KB - xmed_v3i2e31272_app2.xlsx]

Multimedia Appendix 3
Mixed-Methods Appraisal Tool analysis.
[XLSX File (Microsoft Excel File), 54 KB - xmed_v3i2e31272_app3.xlsx]

Multimedia Appendix 4
Description of included studies.
[XLSX File (Microsoft Excel File), 19 KB - xmed_v3i2e31272_app4.xlsx]

Multimedia Appendix 5
Hospital resilience strategies and relevant papers.
[XLSX File (Microsoft Excel File), 10 KB - xmed_v3i2e31272_app5.xlsx]

Multimedia Appendix 6
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[DOC File , 47 KB - xmed_v3i2e31272_app6.doc]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CNKI: China National Knowledge Infrastructure
MMAT: Mixed-Methods Appraisal Tool
PDCA: plan-do-check-act
PPE: personal protective equipment
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO: World Health Organization

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Review

Supporting Technologies for COVID-19 Prevention: Systemized Review

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Abstract

Background: During COVID-19, clinical and health care demands have been on the rapid rise. Major challenges that have arisen during the pandemic have included a lack of testing kits, shortages of ventilators to treat severe cases of COVID-19, and insufficient accessibility to personal protective equipment for both hospitals and the public. New technologies have been developed by scientists, researchers, and companies in response to these demands.

Objective: The primary objective of this review is to compare different supporting technologies in the subjugation of the COVID-19 spread.

Methods: In this paper, 150 news articles and scientific reports on COVID-19–related innovations during 2020-2021 were checked, screened, and shortlisted to yield a total of 23 articles for review. The keywords “COVID-19 technology,” “COVID-19 invention,” and “COVID-19 equipment” were used in a Google search to generate related news articles and scientific reports. The search was performed on February 1, 2021. These were then categorized into three sections, which are personal protective equipment (PPE), testing methods, and medical treatments. Each study was analyzed for its engineering characteristics and potential social impact on the COVID-19 pandemic.

Results: A total of 9 articles were selected for review concerning PPE. In general, the design and fabrication of PPE were moving toward the direction of additive manufacturing and intelligent information feedback while being eco-friendly. Moreover, 8 articles were selected for reviewing testing methods within the two main categories of molecular and antigen tests. All the

inventions endeavored to increase sensitivity while reducing the turnaround time. However, the inventions reported in this review paper were not sufficiently tested for their safety and efficiency. Most of the inventions are temporary solutions intended to be used only during shortages of medical resources. Finally, 6 articles were selected for the review of COVID-19 medical treatment. The major challenge identified was the uncertainty in applying novel ideas to speed up the production of ventilators.

Conclusions: The technologies developed during the COVID-19 pandemic were considered for review. In order to better respond to future pandemics, national reserves of critical medical supplies should be increased to improve preparation. This pandemic has also highlighted the need for the automation and optimization of medical manufacturing.

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KEYWORDS

COVID-19; medical treatments; personal protective equipment; testing methods

Introduction

The COVID-19 pandemic caused 260,221,634 confirmed cases and 5,185,350 deaths throughout the world based on data from the Coronavirus Resource Center at Johns Hopkins University, with cases continuing to rise [1]. During this unexpected pandemic, technologies have been developed in response to clinical and health care needs, pinpointed by health care workers. Examples include rapid SARS-CoV-2 test kits, low-cost ventilators, rapid sanitation methods, methods for reconfiguring hospital rooms into negative pressure isolation rooms, covers to block aerosol fluid from spreading to health care personnel during intubation and nebulization procedures, rapid-fabricated personal protection equipment and use of chest x-ray and computed tomography for COVID-19 diagnosis [2-6]. These types of solutions could rapidly address public health issues because they are easily scalable and feasible for adoption, especially in low- and middle-income countries that account for 75% of the world's population [7]. However, there are still issues to be addressed. For example, it has been reported that the United Kingdom's Test and Trace program is suboptimal for handling COVID-19 and its new variants [8]. Several review papers have discussed digital health technologies as a response to these issues, including artificial intelligence and big data [9-12].

In this review paper, 150 news articles and scientific reports on inventions developed to manage the COVID-19 pandemic were considered for review. From this pool of articles, technologies related to personal protection equipment, testing methods, and medical treatment were selected, resulting in a total of 23 cases for review. Each of these cases was evaluated in terms of its engineering characteristics and potential impact on the pandemic. The inventions address various problems encountered in response to COVID-19, including a lack of testing kits, the large amount of time required to obtain test results, shortages of ventilators to treat severe cases of COVID-19, insufficient accessibility to personal protective equipment (PPE) for both hospitals and the public, and the dearth of public adherence to social distancing guidelines. Some of the inventions are intended to be long-term solutions, whereas others are temporary measures. The aim of this study is to mainly focus on small to medium size supporting equipment such as facial masks and ventilators for COVID-19 prevention.

Methods

The primary objective of this review is to compare existing supporting technologies in the suppression of the COVID-19 spread.

Eligibility

We were interested in novel supporting technologies for COVID-19 prevention and treatment within the past 2 years.

Exclusion

Articles were excluded if the results were published before 2020, were not in English, were not related to the event of COVID-19, were not related to mass testing and fast diagnosis, and when there was no access to the full texts.

Searching Method

The keywords "COVID-19 technology," "COVID-19 invention," and "COVID-19 equipment" were used in a Google search to generate related news articles and scientific reports. The initial selection was based on the titles of the news articles and scientific reports, of which 150 articles were identified in early 2021. Another 50 articles were searched via ScienceDirect. Moreover, 5 previous review papers were included [13-15].

After the initial articles were selected, they were subjected to eliminating evaluations by 2 independently working reviewers. First, each news article, as well as scientific reports, were read and manually analyzed to remove any without a technology, invention, or equipment description, which resulted in a pool of 90 articles. Then, according to the inclusion criteria, the pool was further narrowed down to 40 articles.

Next, since some news articles or scientific reports included mentions of multiple technologies, inventions, or pieces of equipment, the initial source for each technology was tracked from the news article as well as for the scientific reports.

A final yield of 23 representative articles was obtained. These 23 articles were then divided into the three categories of personal protection equipment, testing methods, and medical treatment, which were reviewed in depth. The selection of the articles followed the guideline of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020, which can be seen in Multimedia Appendix 1 [16,17].

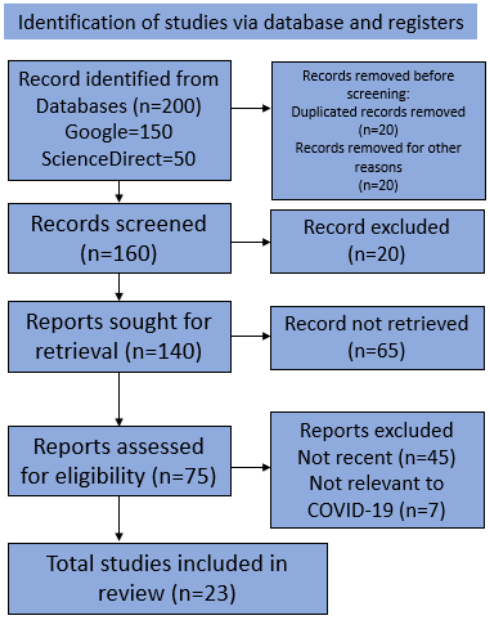
Ethics Approval

Ethics approval has not been applied as there are no human participants involved in the study.

Results

The search results are shown in Figure 1.

Figure 1. Systemized review and metanalysis flowchart.



Personal Protective Equipment

Overall, 9 articles were selected for this section. In general, the design and fabrication of PPE were moving toward the direction of additive manufacturing, intelligent information feedback, and eco-friendliness

3D-Printed Personal Protective Equipment

With the use of PPE becoming a necessity, the demand in the production of such equipment increased, especially when the pandemic resulted in a shortage of PPE globally [18]. This has led companies and research groups to search for faster and more efficient ways to streamline the production of, for example, face shields and masks for their worldwide distribution. To accommodate for the demand, 3D-printed face shields and masks were explored as an option due to their various advantages. 3D printing offers rapid prototyping to increase the speed and consistency of design and manufacturing, reduce cost, and maintain quality [19].

Rendeki et al [20] reviewed various PPE devices against various criteria, including 3D printing technology, materials and disinfection protocol, mechanical and structural comparison of materials used to construct PPE, and spectrophotometry. Three main models of PPE were examined, which where a half mask, a face protection shield, and safety goggles. The PPE was mainly manufactured using fused filament fabrication (FFF) technology with the purpose of filtering the air to reduce the risk of exposure to airborne diseases using an incorporated filter and fitting parameters to the face, providing an extra layer of protection to the eye. The authors reported that the PPEs that were examined were suitable as preventative measures both in safety, functionality, and durability, but disadvantages occurred mainly due to the potential hazards posed by FFF technology. This included lack of protection to the top of the head, high printing time and high material usage for the face shields, fitting problems causing leakage possibilities around the filter holder, weight problems for half masks, loss of peripheral viewing angles, and a reduced possibility of applying disinfection measures for the safety goggles. The authors mentioned these products were cost-effective only up to the break-even point of production at around 200-300 pieces. Hence, the production of additive manufacturing technologies using predominately FFF serves as a reliable but temporary solution for PPE production [20].

Amin et al [21] developed 3D-printed face shields using polylactic acid filaments, Velcro strips, adhesive foam, transparency film, and office supplies. The authors were able to print 100 face shields and distribute this locally to provide an easy and cost-effective solution for PPE; however, they noted that not all PPE devices would provide the same fluid barrier and air filtration as Food and Drug Administration–cleared PPE.

Belhouideg et al [22] and Swennen et al [19] explored several options with face masks to analyze printability and use. While the authors mentioned the ease in production, cost-effectiveness, and functionality, the importance of measuring the clinical effectiveness with regards to safety and the need for regulatory interventions were discussed.

Smart Personal Protective Equipment

Smart PPE offers users more information that can be used as an adjunct to further protection. It also provides information in the form of preventative measures, informing the wearer of potential risks ahead of time so that these unnecessary risks can be avoided. Other functional additions can also be included to enhance the experience of wearing such masks.

For example, Donut Robotics developed face masks that sync with a smartphone to give the user the ability to translate spoken words into text. This can be used for productivity purposes and communication and is compatible with 8 languages to accommodate a global consumer market. This may be particularly useful in a health care setting where doctors and nurses may need to communicate safely with many patients in different languages. A disadvantage may be that the translation is given in text, which may take time, and depending on the translation software used, may not be the correct translation [23].

VYZR Technologies offered a purifying shield as a response to the pandemic that provides a 360-degree seal to protect personal space on all sides. The shield has a built-in air purifying system, which is useful for filtering any pathogens, along with additional features that increase the visibility and wearability of the device. However, it was reported that the size of the shield might be inconvenient for the user and that the fan used to filter the air may be noisy [24].

Maskfone is a face mask that provides protection while allowing the user to make calls without the need to remove the mask in public. This is achieved through a built-in microphone and earphones, which reduce the inconvenience of noise pollution and ease of use. However, these masks need to be cleaned every day by changing the filter, which may be inconvenient to some users and may potentially be expensive in the long term [25].

Similarly, Airpop is a face mask that has the ability to measure breathing rate and gives alerts when it is time to change the filter. The mask is also able to track the location of the user and gives information on the quality of air and an approximate number of particles that the mask has protected the user against. These features will help track and trace those exposed to COVID-19, which has benefits of population health along with individual protection of health. However, the cost of purchasing may be significantly high and is unavailable to Android users currently [26].

Yanko Design developed a face shield with an embedded smart display that can present patients' medical information in real time. The product also offers live recording, transfer of information, and air purifying abilities. This can be beneficial in communication, learning, and convenience between medical staff to ultimately better patient health care. However, this design is currently a concept and may require some time before it comes into production [27].

Environmental-Friendly Personal Protective Equipment

With the volume of disposable masks and shields produced, particularly at the beginning of the pandemic, a surge in waste disposal occurred, with the United Kingdom being responsible for a maximum of 212.5 million mask wastes per week [28]. The focus has therefore shifted toward reusable masks, which are achieved by producing masks and shields using recycled material or from household items, making them more easily washable. Such masks and shields are inexpensive and can be mass-produced, but there are concerns over safety as these masks and shields are not medically tested and may not be airtight [29,30].

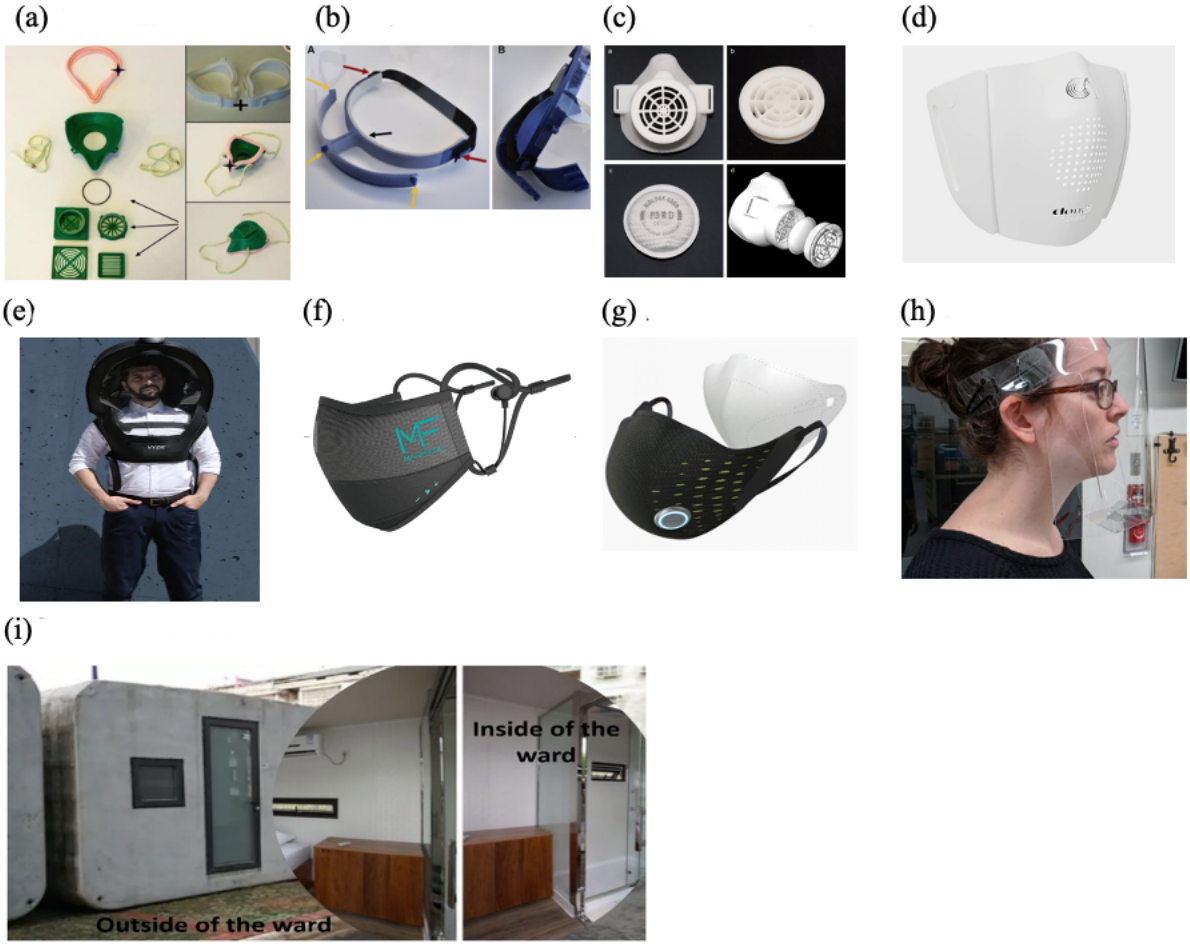
Table 1 shows some major research groups or companies that are currently working on PPEs.

Table 1. Selected papers and major contributions.

Study groups	Countries	Descriptions	Pros and cons
Amin et al, 2021 [21]	United States	3D-printed face shields	• Pros: simple; cost-effective • Cons: safety concerns with the design
Swennen et al, 2020 [19]	Belgium	3D-printed face masks	• Pros: ease in production; cost-effective; comfortable • Cons: safety concerns with the design
Belhouideg et al, 2020 [22]	Morocco	3D-printed face masks	• Pros: ease in production; cost-effective; comfortable • Cons: safety concerns with the design
Donut Robotics, 2020 [23]	Japan	Speech-transcribing face masks	• Pros: allowing for communication in different languages; allows spoken word to be transferred to text. • Cons: prolonged translation time; potential incorrect translation due to the translation software used
VYZR Technologies, 2020 [24]	Canada	Personal air-purifying shields	• Pros: 360-degree personal protection with air purifying features • Cons: large; the fan may be noisy.
Maskfone, 2021 [25]	United States	Face mask with built-in earphones	• Pros: allowing the users to make calls without taking the mask off; no muffled sounds • Cons: a filter needs to be cleaned every day; may be costly in the long term.
Airpop, 2021 [26]	United States	Smart face mask with feedback	• Pros: various features allow increased protection and prevention for the users. • Cons: expensive; unavailable to Android users currently
Yanko Design, 2020 [27]	United States	Smart display face shields	• Pros: increases communication, convenience, and learning opportunities through its features; real time display of information through the embedded screen
MIT Review, 2021 [30]	United States	Reusable face shields	• Pros: cheap; recyclable; reusable • Cons: not airtight; safety concerns

Figure 2 shows some selected equipment in the studies. As COVID-19 is spread through respiratory droplets, health care workers need more than protective equipment to reduce the infection risks when contacting patients. For people with mild symptoms of COVID-19, hospitalization may not be necessary. Instead, health care providers may recommend isolation at home to limit the further spread of the virus. Isolation may mean staying at home or in a designated space, remaining within a single, dedicated, adequately ventilated room, and preferably using a dedicated toilet [31]. However, this may not always be feasible since many people live with their families, where they may have to share a toilet and other communal spaces.

Figure 2. Selected equipment used in the studies: (a) 3D-printed PPE 1 [20], (b) 3D-printed PPE 2 [21], (c) 3D-printed PPE 3 [22], (d) Smart PPE 1 [23], (e) Smart PPE 2 [24], (f) Smart PPE 3 [25], (g) Smart PPE 4 [26], (h) Green PPE [30], (i) 3D-printed isolation wards from Winsun Construction Technology Co., Ltd [32]. PPE: personal protective equipment.



The Randi International think tank platform company Winsun Construction Technology Co., Ltd. has tried to overcome this problem by making 3D-printed isolation wards [32], as shown in Figure 2(i). These strong 3D wards are made from industrial and construction solid waste from urban demolition, making the wards two or three times stronger than the traditional reinforced concrete house. The wards also have an "ecological toilet" that disposes of patients' waste without risking further spread of the virus. This solution has great scope for the future as the wards can be easily broken down, transported, and reassembled, making them ecologically protective, which will be key when outbreaks occur in new areas.

Testing Methods

Overall, 8 articles were selected for review. The articles were divided into two main categories: molecular and antigen tests [14,33,34]. The ongoing COVID-19 pandemic outbreak has posed new challenges for public health diagnostic laboratories as the infection has become widespread internationally. Rapid and scaled-up diagnostic testing is a crucial step in slowing down the pandemic as it allows more time for treating patients before symptoms manifest and reduces the risk of patients unwittingly spreading the disease [35-37]. As such, some inventions have been developed to improve the testing speed and to optimize the testing workflow.

The traditional method of testing is for trained health care workers to collect an oral or nasal swab sample and test the sample by reverse transcription-polymerase chain reaction (RT-PCR) [8]. However, this approach currently has a major limitation as the results of the swab test are received days later, with reports suggesting that the tests are taking at least four days to return. New testing methods are required to increase the volume of tests and decrease the time taken to obtain results [38]. In Table 2, several inventions for COVID-19 testing are summarized.

Table 2. Selected inventions for rapid testing.

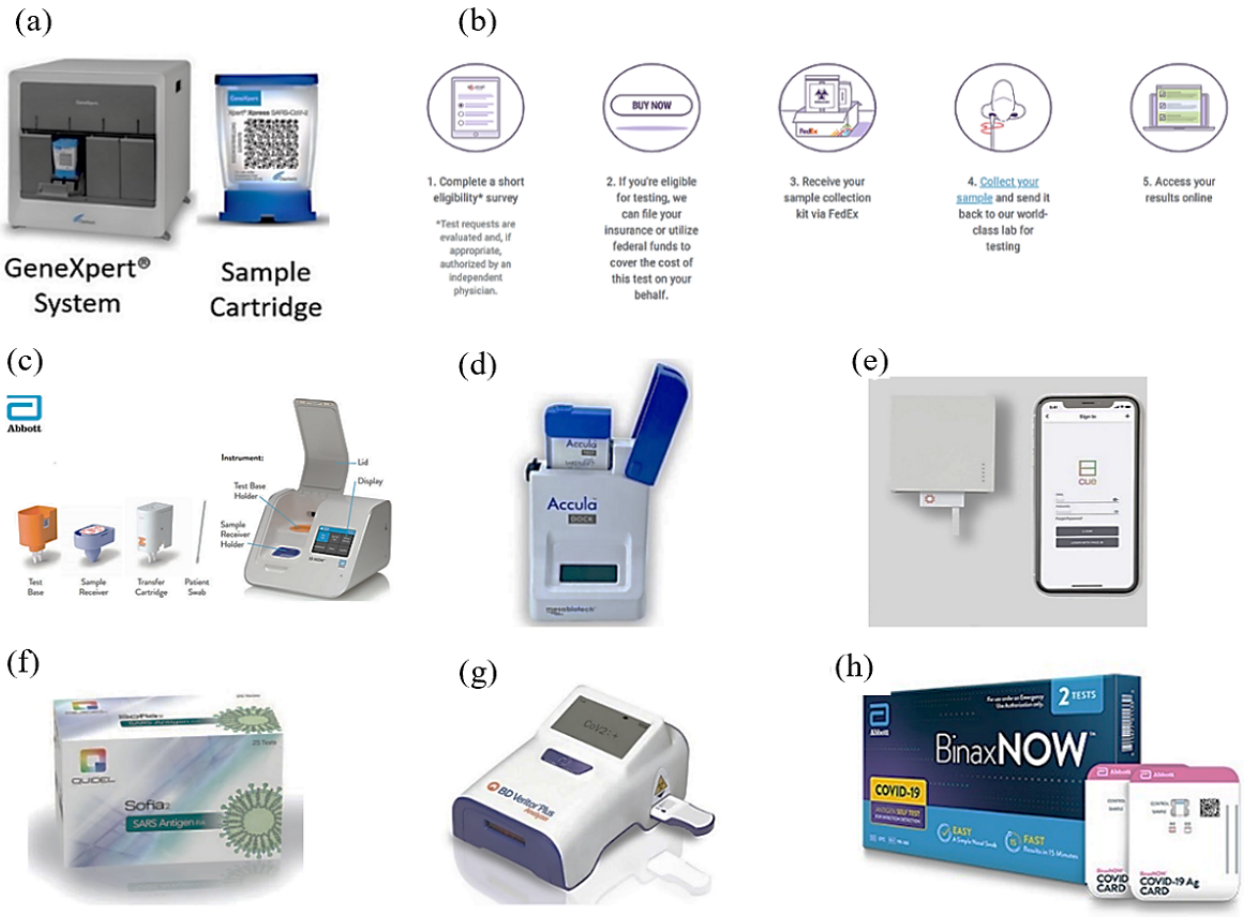
Test types and study groups	Countries	Descriptions	Pros and cons
Molecular tests			
Cepheid's Xpert Xpress SARS-CoV-2 test, 2020 [39]	United States	Automated in vitro diagnostic test for the qualitative detection of SARS-CoV-2 RNA	• Pros: rapid as it is a fully automated process • Cons: this test might miss several positive patient specimens.
Abbott's ID NOW COVID-19 rapid test procedure, 2020 [40]	United States	RT-PCR[a] to detect nucleic acid from SARS-CoV-2 RNA	• Pros: it is designed to have a small size and allow for room temperature storage. • Cons: false-negative results for low positive samples
LabCorp COVID-19 test home collection kit, 2020 [41]	United States	At-home sample collection	• Pros: reduces the risk of exposure of health providers and other patients to the infection. • Cons: a high false-negative result
Accula SARS-CoV-2, 2020 [42]	United States	RT-PCR and lateral flow assay	• Pros: fast turnaround, self-contained, and simple workflow • Cons: the positive agreement was low for samples with low viral load.
Cue COVID-19, 2021 [43]	United States	Isothermal nucleic acid amplification assay	• Pros: very good positive and negative percent agreement with central laboratory tests • Cons: about 8.6% of the initial tests need to be retested.
Antigen tests			
Sofia SARS Antigen FIA[b], 2021 [44]	United States	Immunofluorescence-based lateral flow assay	• Pros: rapid results to identify patients with infection • Cons: lower sensitivity
BD Veritor System for Rapid Detection of SARS-CoV-2, 2020 [45]	United States	Chromatographic digital immunoassay	• Pros: high degree of agreement for SARS-CoV-2 detection • Cons: no data for the efficacy of asymptomatic population
Abbott BinaxNOW Antigen Self-Test, 2021 [46]	United States	Immunochromatographic membrane assay	• Pros: good usability • Cons: test sensitivity decreased with decreasing viral loads.

[a]RT-PCR: transcription-polymerase chain reaction.

[b]FIA: fluorescent immunoassay.

Cepheid's Xpert Xpress SARS-CoV-2 test, as shown in Figure 3(a), is an automated in vitro diagnostic test for the qualitative detection of SARS-CoV-2 RNA [39]. The sample (such as a nasopharyngeal swab) is loaded into a cartridge; the cartridge is then loaded into a module; and the specimen is processed via fully automated nucleic acid extraction, amplification, amplified probe detection, and result reporting. The testing speed is rapid, enabling health care providers to obtain results within an hour of obtaining a patient sample. Once a cartridge is loaded into a module, the total time to result is about 50 minutes, with each module capable of running 28 Xpert Xpress SARS-CoV-2 tests per day. If the Xpert Xpress SAR-CoV-2 is left running, the instruments can run more than 200 patient specimens in a day [47].

Figure 3. (a) Cepheid's Xpert Xpress SARS-CoV-2 test [39], (b) the work procedure of LabCorp COVID-19 test home collection kit [41], (c) Abbott's ID NOW COVID-19 rapid test procedure [40], (d) Accula SARS-CoV-2 test [42], (e) Cue COVID-19 [43], (f) Sofia SARS Antigen FIA [44], (g) BD Veritor System for Rapid Detection of SARS-CoV-2 [45], and (h) Abbott BinaxNOW Antigen Self-Test [46]. FIA: fluorescent immunoassay.



Abbott's ID NOW COVID-19 rapid test, as shown in Figure 3(c), uses RT-PCR to detect nucleic acid from SARS-CoV-2 RNA, which targets the RdRp gene [40]. It can provide positive results in 5 minutes and negative results in 13 minutes. Its small size and ability for room temperature storage enable use for testing local patients in a variety of health care environments. Patients can be tested and diagnosed on the same day as the point of care. Simple operation via visual touchscreen means it can be easily used by health care providers. Abbott is currently manufacturing 50,000 ID NOW test units per day and plans to increase its manufacturing capacity to 2 million tests per month by June 2020 [49]. However, the test is intended for testing swabs directly without elution in virus transport medium because virus transport medium samples were shown to reduce performance in low positive samples, leading to false-negative results when samples were diluted below the assay's limit of detection [50].

In both above rapid diagnostic tests, if the virus mutates in the target region, COVID-19 may not be detected. Moreover, false-negative results may occur if a specimen is improperly collected, transported, or handled. False-negative results may also occur if there are inadequate levels of virus present in the specimen because the RT-PCR tests have a limit of detection, which is the minimum amount of viral RNA that the test will detect [51,52]. Besides improving the testing speed, optimizing the testing workflow is also helpful for increasing the testing volume and decreasing the procedure time.

Pixel by LabCorp produced a COVID-19 test, as shown in Figure 3(b), that allows for at-home sample collection. Patients can self-swab to collect their nasal samples and mail their samples in an insulated package to a LabCorp lab for testing. It allows for sample collection within the safety of the home and is beneficial because it reduces the risk of exposure to health providers and other patients to the infection [41]. It would also cut down on demand for PPE that is needed to collect specimens using the traditional testing method [53]. Test kits can be deployed on a large scale so masses of the population can be tested to help slow the spread of COVID-19. However, this self-collection kit could cause a high false-negative result if some customers perform the collection procedure incorrectly [54,55].

In the category of antigen test, the Sofia SARS Antigen FIA (fluorescent immunoassay) uses sandwich immuofluoresence-base lateral flow for the qualitative detection of SARS-CoV-2 nucleocapsid protein antigen. Based on the clinical evaluation, there was a significant reduction in turnaround time from sample collection to test results. Compared to RT-PCR, the turnaround time was reduced from 20.1 hours to 1.2 hours for Sofia SARS Antigen FIA. However, a previous study also suggested that antigen test is less suitable for both

very early and late stages of SARS infection as it has lower sensitivity at high cycle threshold values [44]. The other 2 antigen tests are BD Veritor System and Abbott BinaxNOW antigen self-test [48,56].

Medical Treatments

Overall, 6 articles were selected for review. The major challenge was how to apply novel ideas to speed up the production of ventilators. Ventilators are a form of life support that takes over the work of breathing when a person is not able to breathe enough air on their own [57]. Individuals who develop COVID-19 are at risk of developing serious lung complications such as pneumonia and, in severe cases, acute respiratory distress syndrome [58,59]. In severe cases, which account for 1 in 6 people, patients require ventilatory assistance. Governments have become increasingly aware of the demand for ventilators and have started upping production [60]. For example, the United Kingdom has added another 8000 ventilators to their existing 8000, while the United States estimates it will need 60,000-160,000 additional ventilators [61,62]. Table 3 shows some major research groups or companies that are currently working on ventilators.

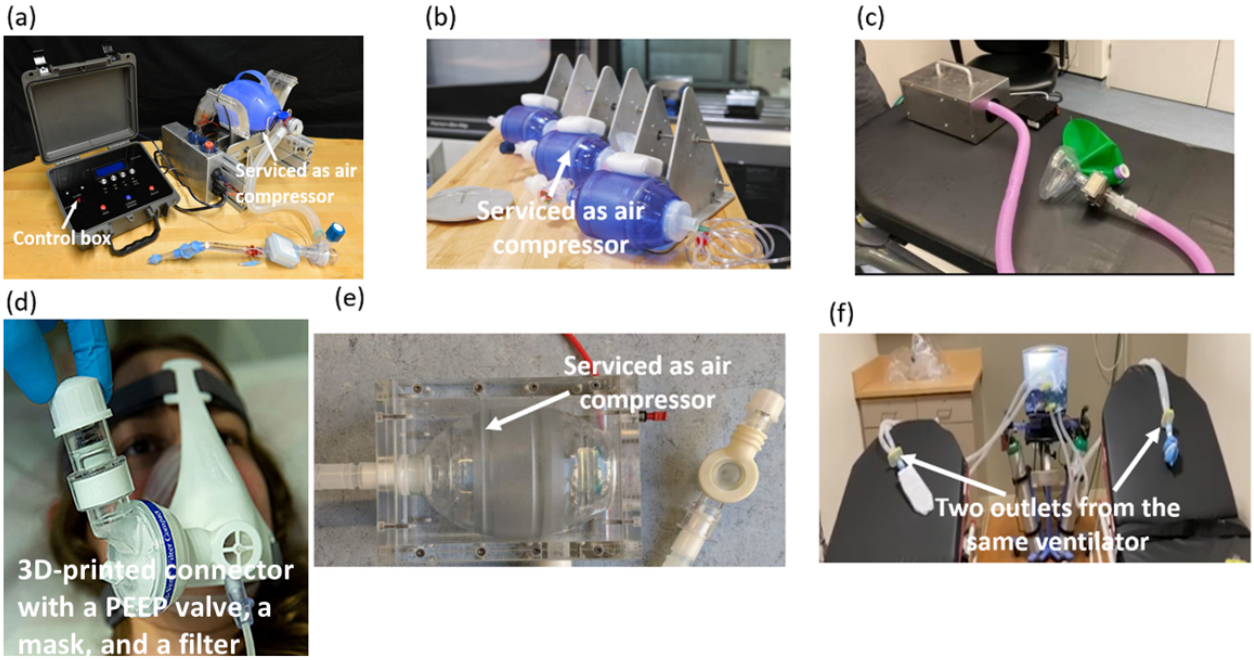
Table 3. Selected papers and major contributions.

Study groups	Countries	Descriptions	Pros and cons
MIT, 2020 [63]	United States	"Bridge" ventilators that automate manual resuscitators	• Pros: aid breathing for less acute patients • Cons: N/A[a]
Virgin Orbits, 2020 [64]	United States	"Bridge" ventilators that automate manual resuscitators	• Pros: aid breathing for less acute patients • Cons: N/A
Glangwili Hospital, 2020 [65]	United Kingdom	Snood-type mask	• Pros: rapid production • Cons: N/A
Materialize, 2020 [66]	Belgium	Positive end-expiratory pressure for patients without a true ventilator.	• Pros: rapid assembly as it is 3D printed • Cons: N/A
OxVent ventilator, 2020 [67]	United Kingdom	Built from off-the-shelf components	• Pros: portable and scalable • Cons: not under rigorous quality test
Patients-shared ventilator, 2020 [68]	United States	Accommodate 2 patients at the same time	• Pros: maximize the usage of valuable hospital equipment • Cons: potential health and safety risk

[a]N/A: not applicable.

With the heavy demand for ventilators, researchers and companies have started to design highly scalable, innovative ideas to match these demands. MIT and Virgin Orbits have designed similar "bridge" ventilators that automate manual resuscitators, as shown in Figure 4(a) and 4(b); they aim to aid breathing for less acute patients, therefore alleviating the use of current ventilators in intensive care units [63,64]. Furthermore, a group from Glangwili Hospital is using mechanical technology to build a snood-type mask, as shown in Figure 4(c), which is connected to a filter to purify the air of coronavirus particles and to supply it to the user [65].

Figure 4. Ventilators designed by (a) MIT [63], (b) Virgin Orbits [64], (c) Glangwili Hospital [65], and (d) Materialize [66]. (e) OxVent ventilator [67]. (f) Patient-shared ventilator [68]. PEEP: positive end-expiratory pressure.



Materialize developed a technology to provide positive end-expiratory pressure for patients without a true ventilator. A source of oxygen was the only requirement to achieve ventilator function [66]. As shown in Figure 4(d), the design consists of a 3D-printed connector that connects a positive end-expiratory pressure valve, a mask, and a filter. A multidisciplinary team of engineers and medics at the University of Oxford and King's College London have developed a new ventilator called OxVent, as shown in Figure 4(c), which is made from off-the-shelf components and equipment with certain elements that can be produced through 3D-printing techniques [67]. The OxVent is portable and inflates the patients' chest by injecting compressed air. Another solution to respond to the shortage of ventilators was developed in several hospitals, where they shared the same ventilator between 2 patients with some normal tubes instead of building a new ventilator, as seen in Figure 4(f) [68]. An operation protocol for ventilator sharing has been developed by engineers and medics as a response to this innovation to ensure safety [69].

Discussion

Principal Findings

The shortage of medical equipment, such as masks and ventilators, has been the biggest challenge. Although insufficient stockpiling of medical equipment is one of the reasons attributed to the shortage, the most important reason is the high labor dependency of the medical equipment industry. The shortage of labor and the high infection risk in a crowded working environment have limited the capacity of the medical equipment industry. Approaches should be considered for the medical equipment industry for future responses. It is time to optimize the current processing flow and improve the degree of automation so that the dependence on labor can be reduced. Many cases have been reported on the use of 3D printers for producing medical equipment on a small scale, such as masks, ventilator parts, and quarantine rooms. Although 3D-printing technology could significantly reduce the amount of labor required for production, cost and efficiency are still challenges at this stage. Other critical labor-intensive industries, such as the food processing industry and delivery industry, have also been reported as imposing high risks of large-scale infection [70-72]. Labor shortages in these industries have led to shortages of basic human necessities. For such industries, improving the degree of automation and reducing the degree of labor dependence are also necessary measures to ensure better responses to future pandemics.

On the other hand, the shortage of lifesaving machines such as ventilators during the pandemic could illustrate a point: medical technology research, supported by taxpayer money, may not be sufficient for handling global outbreaks such as COVID-19. Traditional funding mechanisms have singularly focused on supporting "high-risk, high-reward" research activities to support creative scientists pursuing highly innovative research rather than low-cost and scalable technologies that could address the public health demands during the pandemic. Technologies developed to address the COVID-19 pandemic should meet epidemiological needs and help manage outbreaks. They need to be low-cost scalable solutions that are practical for patients and health care workers as well as being widely accessible to the global community. However, publicly funded medical research has long been skewed toward ideas proposed by research-intensive, highly developed, and resource-abundant researchers.

Comparison With Prior Studies

Personal Protective Equipment

PPE is an intervention that has become a necessity as a first-line preventative method against the pandemic, and the culture of

wearing PPE, particularly the wearing of face masks, may continue in the long run [28]. In the health care setting, the wearing of PPE may become an indefinite feature, and therefore, the development of PPE, particularly in terms of safety and convenience, may be of paramount importance. Current developments have focused on streamlining the production of PPE in preparation for future pandemics, increasing the convenience and experience of the wearer, and making the production of the PPE more sustainable by using reusable resources [18,29]. While these are exciting prospects, researchers and developers must not forget that developing the protection provided by PPE is the most important feature. The developments mentioned in this article still require approval from governing bodies with regards to safety and, therefore, must continue to focus on producing PPE that is in line with the guidelines set by governing bodies with regards to acceptable requirements of protection [18,73]. The other challenge is producing the aforementioned PPE developments on a large scale and at a low cost. While currently this may be difficult, technological considerations toward reducing production costs to increase the accessibility of products may be beneficial.

Testing Methods

One challenge among the inventions developed to slow the spread of COVID-19 is the ability to pass rigorous scientific testing. The inventions reported in this review paper have not been sufficiently tested for their safety and efficiency. Most of them are temporary solutions intended to be used only during shortages of medical resources. However, these medical devices still need Food and Drug Administration approval before they can be offered as commercial products on the market. Many prospective COVID-19 inventions will likely be rejected for safety reasons. Lessons can be learned from this pandemic to serve as guidance to improve the response to future pandemics and outbreaks.

Medical Treatment

The implementation of highly technological solutions, which require long-term development and expensive setup in pandemic response, may face many obstacles. While robotic technologies have great potential as tools to meet specific clinical needs, robots are unlikely to be widely adopted for COVID-19–related applications due to cost and manufacturing time. Robots capable of unique tasks need to meet epidemiological requirements, which could be costly, impractical, and most likely accessible only to the wealthiest hospitals and businesses, which means only a small proportion of people can receive the benefit. Investigating solutions to the pandemic shall consider underprivileged communities that are most vulnerable to both infection and continued transmission. Furthermore, tools for outbreak control need to be mass-produced and distributed quickly; however, with the exponential spread of SARS-CoV-2 around the globe, the time required to fabricate complex robotics would be prohibitive to this acute demand.

One possible area to improve is the ability to provide appropriate palliative care. Radbruch et al [74] discuss the importance of palliative care in the COVID-19 response. They highlight the need for two key measures to be taken throughout the world: first, to increase national reserves of opioid medications while controlling costs by implementing pooled purchasing platforms, and second, to provide basic palliative care training to all primary caregivers and health care professionals in emergency departments and intensive care units [74]. This type of response is practical because it addresses the need for public health responses to COVID-19 to be inexpensive and widely accessible.

Other Considerations

One challenge in this pandemic is the high infection rate of health care workers [73,75], which has led to a shortage of health care workers [76,77]. The high infection rate is caused by the close contact between health care workers and patients during diagnosis and treatment, so it is important to reduce contact in order to reduce the infection rate of health care workers in future pandemics. Two methods could be used to achieve this purpose. The first is to optimize the current diagnosis workflow and environment. Remote prediagnosis through the internet or phone could increase the work efficiency of health care workers and reduce contact time. Separate pathways and rooms for patients and doctors could be set up in areas of high transmission risk to reduce the amount of shared area and thus eliminate unnecessary contact. The second is to apply more medical robotics in the treatment process. Medical robotics could enable social distancing between patients and doctors during treatment. In addition, robotics could help improve the efficiency of health care workers; for example, tracheal intubation currently requires 3 people, but it could be done by 1 person with assistance from medical robotics [4]. Besides medical robotics, other types of robotics can be applied in hospitals for sterilization, drug or food delivery, sample transfer, and diagnostic testing [78-81].

Study Limitations

The paper only investigated the small to medium size supporting medical equipment for COVID-19. Large equipment such as computed tomography or magnetic resonance imaging scanners have not been included in this study. Moreover, the paper only provides a qualitative comparison between the technologies. The search strategy was not comprehensive as it was limited to two databases: Google and ScienceDirect. Even though some of the complexities were unveiled regarding supporting technologies, a quantitative analysis would have also added value to the review results. Moreover, the protocol that was not registered with PROSPERO (international prospective register of systematic reviews) might have affected the results in one way or the other. There was no formal appraisal of the included studies as well as the overall evidence from included studies.

Conclusion

The study objectives were to evaluate existing support technologies for COVID-19 prevention, diagnosis, and treatment. A total of 18 technologies in the areas of PPE, testing methods, and medical treatment were selected for review. The engineering characteristics of each invention were summarized, and the potential to make a significant impact on the pandemic response was evaluated and discussed. One major hurdle to adopting the technologies discussed in this paper or any other prospective technologies was that COVID-19–related research is still in the early stages, so even if innovations look promising,

their safety and efficiency have not yet been tested and evaluated in a rigorous scientific manner.

The unexpectedly large and widespread impact of the COVID-19 pandemic has led to many challenges in the management of the disease for both public health agencies and hospitals. Shortages of essential medical resources, including SARS-CoV-2 testing kits, ventilators, and personal protective equipment, have been the biggest challenge throughout the world. In this review paper, technologies developed during the COVID-19 pandemic in response to clinical and public health needs were considered for review. In order to better respond to pandemics in the future, several directions have been discussed. For example, national reserves of critical medical supplies should be increased to improve preparation. Regarding the manufacturing of medical equipment, this pandemic has highlighted the need for the automation degree of medical manufacturing to be increased and for production workflows to be optimized. Finally, a shift in the approach to funding scientific research should be implemented during pandemics to promote low-cost, scalable solutions.

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Authors' Contributions

ZZ and RL carried out the data search and paper preparation. YM, II, AMAR, WS, HR, and ZTHT participated in the paper edits.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020.
[DOCX File , 20 KB - xmed_v3i2e30344_app1.docx]

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Abbreviations

FFF: fused filament fabrication
FIA: fluorescent immunoassay
PPE: personal protective equipment
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RT-PCR: reverse transcription-polymerase chain reaction

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Case Report

Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review

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Abstract

Subarachnoid hemorrhage is associated with high morbidity and mortality, and cerebral arterial vasospasm is one of its main complications that determines neurological prognosis. The use of intravenous milrinone is becoming more common in the treatment of vasospasm. This molecule has positive inotropic and vasodilating properties by inhibiting phosphodiesterase-3. Its most described side effects are cardiac arrhythmias and arterial hypotension. In this paper, we raise a new issue concerning milrinone and discuss an undescribed side effect of this treatment, left ventricular outflow tract obstruction (LVOTO). Dynamic LVOTO is a clinical situation favored by hypovolemia, decreased left ventricular afterload, and excessive inotropism that can lead to severe hemodynamic failure and pulmonary edema. To our knowledge, this is the first study describing milrinone-induced LVOTO. This could compromise cerebral perfusion and therefore the neurological prognosis of patients. While it is known that catecholamines may induce LVOTO, milrinone-induced LVOTO appears to be a new pathophysiological entity of which neurosurgical intensivists should be aware.

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KEYWORDS

ventricular outflow obstruction; subarachnoid hemorrhage; vasospasm; intracranial; milrinone; hemorrhage; neurosurgery; neurology; surgery; pharmaceutical

Introduction

Subarachnoid hemorrhage (SAH) by aneurysmal rupture accounts for 1% to 5% of all strokes [1,2]. One of the main complications conditioning SAH prognosis is cerebral arterial vasospasm, which occurs in 50% to 70% of cases [3]. Cerebral vasospasm is mostly asymptomatic, but may be complicated by secondary ischemic neurological deficit. Early management of asymptomatic forms of vasospasm can prevent ischemic complications and improve functional prognosis [4]. The first-line prophylactic treatment for cerebral vasospasm is nimodipine [5]. However, cerebral vasospasm can occur despite this prophylactic treatment, and several curative treatments have been proposed. Some of them, such as papaverine or milrinone, are administered directly in the vessel during cerebral arteriography [6,7]. Intravenously administered molecules are also proposed in this indication such as sildenafil, magnesium sulfate, or milrinone [8-12]. Milrinone appears to be a promising treatment to alleviate cerebral vasospasm [11]. It is a phosphodiesterase-3 inhibitor, with positive inotropic effect and systemic arterial vasodilator effect, whose main therapeutic indication is cardiogenic shock [13]. However, milrinone can induce cardiac arrhythmias by inhibiting the degradation of cyclic adenosine monophosphate, which leads to an increase in intracellular calcium.

In this paper, we raise new issues concerning milrinone and report an undescribed side effect of this treatment that we observed in two patients hospitalized in a neurosurgical intensive care unit (ICU) for SAH (with two different clinical presentations): dynamic left ventricular outflow tract obstruction (LVOTO). This is characterized by a pressure gradient between the left ventricle and the aorta. The narrowed left ventricular outflow tract is the site of substantial flow, which can lead to anterior translation of the mitral valve (systolic anterior motion [SAM]) and regurgitation of the valve. Fixed LVOTO is due to particular anatomical conditions that can be corrected by surgery. Dynamic LVOTO is favored by the addition of predisposing factors (decreased preload and afterload, increased inotropism). Clinically, LVOTO may induce hemodynamic failure up to shock, and neurosurgical intensivists should be aware of this complication of milrinone infusion.

Clinical Presentations of Left Ventricular Outflow Tract Obstruction Induced by Milrinone

To our knowledge, we describe here the two first cases of LVOTO induced by milrinone.

Ethical Considerations

Informed consent was obtained from all individual patients described in this paper.

This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The Comité d'Ethique pour la Recherche sur Données Existantes et/ou hors loi Jardé (CERDE-HLJ) of the Rouen University Hospital provided the ethical approval (E2021-91).

Acute and Severe Left Ventricular Outflow Tract Obstruction Induced by Milrinone

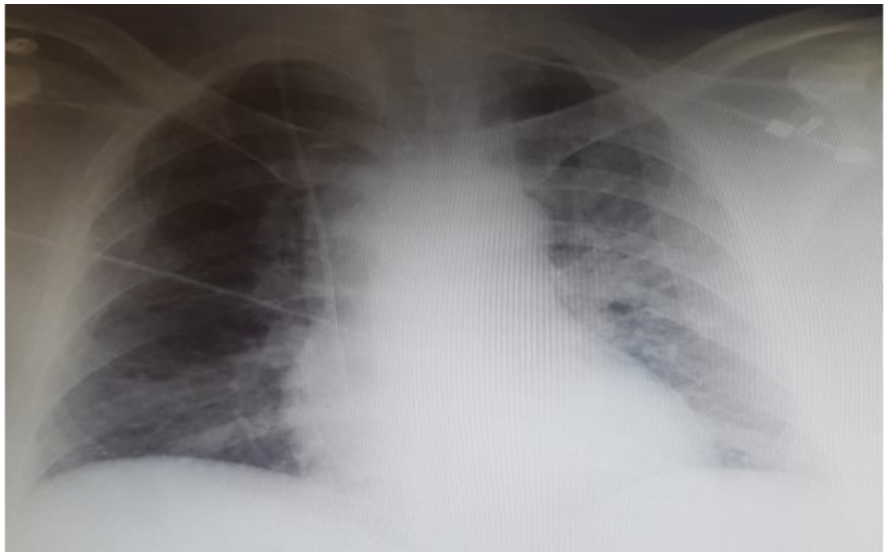
A 48-year-old male was admitted in a neurosurgical ICU for a Fisher 4 and World Federation of Neurosurgical Societies (WFNS) 1 SAH, by rupture of a right terminal and internal carotid aneurysm. His medical history included arterial hypertension, essential tremors, and active smoking. He had no cardiological follow-up and was not taking long-term medication. Cardiac auscultation was normal on admission. An emergency external ventricular drainage was performed to treat acute hydrocephalus followed by a radioembolization of the two aneurysms 24 hours after admission. Prophylactic treatment with nimodipine was administered orally. Faced with an unfavorable neurological evolution on the third day, with the appearance of aphasia and right hemineglect, another angio–computerized tomography (CT) was performed, showing a diffuse vasospasm. A treatment with intravenous milrinone was started, initially at an infusion rate of 0.5 µg per kg per minute and increased 2 hours later to 1 µg per kg per minute because of good hemodynamic tolerance. The introduction of milrinone was followed by a partial regression of aphasia, and nimodipine was maintained.

Due to the reappearance of complete aphasia 7 days after ICU admission, the patient benefited from in situ dilatations of the anterior and posterior cerebral arteries for refractory vasospasm. This procedure was followed by a complete regression of neurological symptoms.

Two weeks after ICU admission, while the patient was awake, extubated, apyretic, and hemodynamically stable without catecholamines, he presented a brutal hemodynamic failure with a systolic blood pressure inferior to 40 mmHg, with 120 bpm tachycardia and arterial oxygen desaturation up to 75%. A previously unknown systolic heart murmur was found. The patient remained fully conscious during this episode. He benefited from fluid therapy by 2 liters of crystalloids, orotracheal intubation due to respiratory failure, and norepinephrine infusion, which was rapidly increased at 2 µg per kg per minute. A transthoracic echocardiography was performed and showed an intraventricular gradient of obstruction, a hypercontractile left ventricle with telesystolic exclusion, and a grade 4 mitral regurgitation with SAM of the mitral valve. The interventricular septum thickness was normal, excluding ventricular hypertrophy, and cardiac ventricles were not dilated. Chest X-ray showed unilateral alveolar opacity of the left lung, consistent with an acute pulmonary edema (Figure 1). A chest CT scan did not find pulmonary embolism or aortic dissection. The situation improved within 3 hours of milrinone stopping, allowing a decrease in the doses of norepinephrine and a normalization of cardiac auscultation. Although milrinone was administered at a constant dosage of 1 µg per kg per minute, the clinical presentation led to finding the origin of the shock: an accidental bolus of milrinone. The main hypothesis is that the catheter plicated when the patient was placed in a sitting position, the electric syringe did not stop, and the bolus of milrinone occurred when the obstruction was removed. The patient was extubated the following day, and norepinephrine was definitively stopped 2 days after the accident. The control echocardiography performed 2 days after the shock showed a

complete regression of LVOTO, SAM, and mitral insufficiency. The neurological outcome was finally favorable with hospital discharge 1 month after ICU admission.

Figure 1. Thoracic radiography of the first patient. Mitral regurgitation associated with left ventricular outflow tract obstruction is most often eccentric and travels to the left pulmonary veins, resulting in unilateral acute pulmonary edema in this patient.

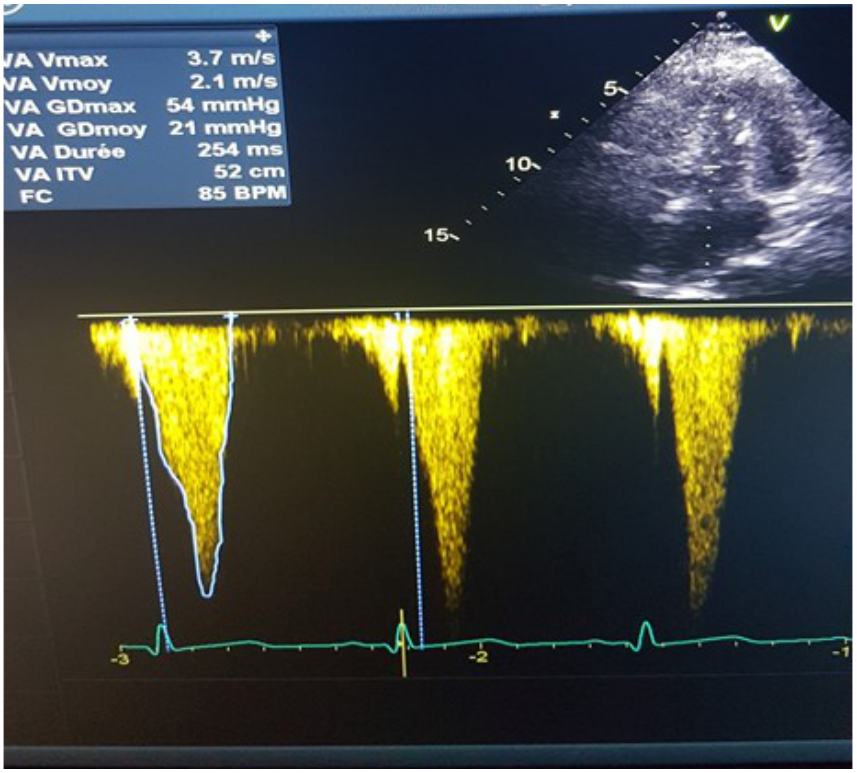


Subacute and Moderate Left Ventricular Outflow Tract Obstruction Induced by Milrinone

A 69-year-old patient was admitted in a neurosurgical ICU for a Fischer 4 and WFNS 4 SAH secondary to a right giant carotid and ophthalmic aneurysm rupture. Her medical history included hypothyroidism and osteoporosis. She had no history of heart disease and had no regular cardiac follow-up. Cardiac auscultation was normal at admission. Neurological management was marked by an emergency external ventricular drainage to treat acute hydrocephalus, followed by radioembolization of the aneurysm and the initiation of nimodipine treatment. A follow-up cerebral angio-CT performed 7 days after ICU admission revealed diffuse cerebral vasospasm, which prompted the introduction of milrinone (0.5 µg/kg/min, then increased to 1 µg/kg/min because of good hemodynamic tolerance). One day later, the patient was febrile with an inflammatory syndrome leading to the diagnosis of a *Staphylococcus epidermidis* meningitis on ventricular drain. Antibiotic therapy by linezolide was therefore started, and a change of ventricular drain was performed 48 hours after the initiation of antibiotic therapy.

A systolic murmur was reported 3 days after milrinone initiation. It was midsystolic, heard in the second right intercostal space, intense, and radiating to the carotid arteries, strongly suggestive of aortic stenosis. The patient presented a stable hemodynamic state but a Glasgow Coma Score fluctuating between 12 and 15. Transthoracic echocardiography was performed at the onset of this heart murmur to look for a valvulopathy. The echocardiography revealed a gradient of left intraventricular obstruction with a maximum telesystolic peak measured at 54 mmHg (Figure 2) and a hypercontractile left ventricle with telesystolic exclusion. Left ventricle filling pressures were estimated to be low (E/A ratio equal to 0.7). The interventricular septum thickness was normal. Within 24 hours after the exam, an arterial hypotension appeared, which resolved after fluid therapy by 1 L of crystalloids. In view of the hemodynamic improvement and the good neurological course, treatment with milrinone was continued at the same dose, and there was no follow-up echocardiography before stopping the treatment. Milrinone and nimodipine were stopped 21 days after the onset of SAH, allowing ICU discharge the next day. At ICU discharge, the patient no longer had systolic murmur, and the echocardiography showed no intraventricular obstruction gradient nor telesystolic exclusion of the left ventricle. Finally, the patient was discharged without neurological deficit.

Figure 2. Apical 5 cavities view of transthoracic echocardiography. Diagnostic of left ventricular outflow tract obstruction is assessed here by a maximal pressure gradient measured at 54 mmHg. Velocity peak is maximum in telesystolic.



Pathophysiology of Left Ventricular Outflow Tract Obstruction

The dynamic LVOTO phenomenon is secondary to a decreased preload and a decreased postload with increased inotropism thus reducing the telediastolic and telesystolic volumes of the left ventricle [14-16]. These conditions often occur in common situations in the ICU, such as the use of positive inotropes in hypovolemic patients, or during septic shock [17]. They are also described in postoperative mitral or aortic valve replacement, in intraoperative noncardiac surgery, or in patients with hemorrhagic shock [16]. They result in a reduction of the size of the left ventricle in systole and in the development of an obstruction that may be medio-ventricular or caused by a SAM. Both types of obstruction, combined or not, are possible [17]. In case of SAM, the attraction of the large mitral valve toward the interventricular septum creates an opening of the valve that leads to functional mitral regurgitation, which can be important as in our first case. This mitral insufficiency disappears after SAM correction.

The difference must be made between fixed LVOTO, due to underlying anatomical factors (excessive mitral tissue, mitro-aortic angle less than 120°, septal hypertrophy) that are sometimes correctable by surgery. In patients with hypertrophic obstructive cardiomyopathy (HOCM), the onset or aggravation of the stenosis may be seen during hypovolemia, vasodilatation, physical exertion, or dobutamine stress ultrasound [16-18]. In patients who are HOCM free in the ICU, obstruction is found in the presence of a classic triad: hyperkinetic left ventricle, tachycardia, and hypovolemia [19]. Thus, logically, catecholamines are described as a potential inducer of LVOTO. This has mostly been described with inotropes such as dobutamine but also with dopamine and norepinephrine [20-25].

Diagnosis of Left Ventricular Outflow Tract Obstruction

Diagnosis of LVOTO is difficult and can only be done with echocardiography. The diagnosis relies on the presence of an intraventricular pressure gradient (measured in continuous Doppler) with a velocity peak ≥1 m/s (or LVOTO pressure gradient at least 30 mmHg) or an anterior systolic movement of the large mitral valve, which is attracted into the left ventricle flushing chamber (SAM) [16,17]. A meso- or telesystolic exclusion of the middle part of the left ventricle may also be seen. This entity differs from fixed LVOTO because it occurs on a healthy heart, with a normal thickness of the interventricular septum.

The main differential diagnosis in this context of SAH is neurogenic myocardial stunning. This occurs in the acute phase of SAH. Unlike LVOTO, beta receptor overstimulation results in myocardial sideration. The common feature of the two conditions is the worsening with the use of catecholamines.

Imputability of Milrinone in the Occurrence of Left Ventricular Outflow Tract Obstruction

We did not find any study describing milrinone-induced dynamic LVOTO. When looking for studies dealing with hemodynamic effects of milrinone, several of them have described a decrease in systemic and pulmonary vascular

resistance, an increase in cardiac index, an improvement in diastolic function, and a decrease in pulmonary capillary wedge pressure [26-29]. Other side effects frequently reported are headache, tachycardia, arterial hypotension, arrhythmias (especially atrial fibrillation), and ventricular extrasystoles [7,26-29]. These complications occur more frequently in patients with impaired left ventricular ejection fraction.

However, our cases showed the occurrence of LVOTO after milrinone infusion start in two patients without any cardiac disease before ICU admission. Indeed, in our first case, the only predisposing factor appeared to be a punctual bolus of milrinone, resulting in acute LVOTO with SAM, functional mitral insufficiency, and shock. Mitral regurgitation associated with LVOTO is most often eccentric and travels to the left pulmonary veins [30], resulting in unilateral acute pulmonary edema in this patient. In our second case, the hemodynamic effects of milrinone (afterload decrease and increased inotropism) were added to a relative decrease in preload induced by sepsis. The consequence was then a symptomatic subacute and less severe form of LVOTO clinically translated by the appearance of a new heart murmur and arterial hypotension requiring fluid therapy. The systolic murmur persisted after punctual use of crystalloids, and only disappeared when the milrinone infusion was stopped. These elements support, in our opinion, the hypothesis that the use of milrinone is the main and triggering mechanism in this case, sepsis being only an aggravating factor.

Given our observations and on the basis of LVOTO pathophysiology, we think that milrinone, by combining a positive inotropic effect with a systemic arterial vasodilator effect, could be a molecule that strongly promotes the occurrence of LVOTO.

Implication of Milrinone-Induced Left Ventricular Outflow Tract Obstruction for Neurosurgical Intensivists

Milrinone plays an important role in the treatment of cerebral vasospasm, and several neurosurgical ICU teams are using it for their patients with SAH. However, our reports and the analysis of the LVOTO pathophysiology suggest that in patients that are hypovolemic or septic, milrinone should probably be used with caution. The onset of LVOTO due to milrinone may be difficult to diagnose because of the lack of a specific clinical sign. However, its consequences are potentially serious since the occurrence of shock could worsen cerebral ischemia and neurological prognosis in patients already treated for arterial vasospasm. Echocardiography should probably be proposed early in patients with hemodynamic instability associated with milrinone. The use of echocardiography should probably be proposed in the presence of the aforementioned triggers or in case of hemodynamic instability in patients treated with milrinone. Prospective studies on a larger patient population are needed to determine the incidence of these disorders and their impact on the prognosis of patients treated for arterial vasospasm with milrinone.

Treatment of Left Ventricular Outflow Tract Obstruction Induced by Milrinone

In patients with septic shock, LVOTO appears to be an independent risk factor for mortality [17]. It therefore makes sense to try to reduce or even eliminate this complication among patients in the ICU. The treatment is mostly based on the management of the triggering factors such as the correction of a hypovolemia, the stop of inotropic treatments, and the treatment of a sepsis. The occurrence of tachycardia, which is frequent in neurosurgical ICU, should be carefully monitored, as it aggravates the dynamic LVOTO. In some cases, the use of α-agonists vasoconstrictors or the introduction of a beta-blocker to decrease the ventricular pressure gradient may be proposed [19].

Conclusion

LVOTO is probably an underestimated clinical situation in neurosurgical ICU. It may occur in patients without any previous cardiac diseases, and its diagnosis relies on echocardiography. There are numerous triggering factors that are frequent in patients in the ICU and that cumulatively promote its occurrence. Milrinone, because of its positive inotropic effect and systemic arterial vasodilator effect, appears to be a molecule that may provide LVOTO. Further studies are needed to evaluate the incidence of dynamic LVOTO and its impact on the prognosis of patients with cerebral vasospasm treated with milrinone.

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Data Availability

The raw data supporting the observations reported in this manuscript can be made available on request by the authors to any qualified researcher.

Authors' Contributions

CB and ML were involved in the acquisition of patients’ data, in the review conception and design, and in the manuscript draft. JLC, PG, AB, JB, and TC were involved in the acquisition of patients’ data, in the analysis and interpretation of data, and in the manuscript revision.

Conflicts of Interest

None declared.

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Abbreviations

CT: computerized tomography
HOCM: hypertrophic obstructive cardiomyopathy
ICU: intensive care unit
LVOTO: left ventricular outflow tract obstruction
SAH: subarachnoid hemorrhage
SAM: systolic anterior motion
WFNS: World Federation of Neurosurgical Societies

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Peer-Review Report

Peer Review of "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study"

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Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.07.21255061v1

Companion article: https://preprints.jmir.org/preprint/30777

Companion article: https://med.jmirx.org/2022/2/e37005/

Companion article: https://med.jmirx.org/2022/2/e30777/

(JMIRx Med 2022;3(2):e37003) doi:10.2196/37003

KEYWORDS

patient readmission; quality assurance; health care; catchment area; health; community networks; regional medical programs

This is a peer-review report submitted for the paper "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study."

Round 1 Review

Major Comments

- Title: For this study [1], please include the type of study in the title. If you are considering 30-day readmission, please specify it in the title.

Abstract

- Please move the objective section to the end of the background section, and it is recommended that it is written the same as in the study title.
- Methods: Please start this section with the study design. Study setting, study variables, and outcomes and their measurements should be mentioned, briefly. Eligibility criteria have not been provided.
- Methods: Excessive readmission ratio: I think it is excessive readmission risk ratio because no person-year has been reported. Thus, to improve the reporting, please revise it in the whole document.
- Results: To facilitate the interpretation of the study results, please convert beta coefficients by exponentiating them.
- Please use expanded forms of the abbreviations the first time they are mentioned. The expanded form of some abbreviations has not been provided.
- Keywords: Please write these according to the Medical Subject Headings (MeSH) system.
- Introduction: The necessity of this study is not clear. Please provide a paragraph about the importance and necessity of this study and why you designed and conducted this study.
- Methods: It is recommended to write this section according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) standard writing and refer to it in the first paragraph of the Methods section.
- Please start this section with the study design. A retrospective study is not a study design and refers to the type of data collection.
- Please provide information about institutional review board (IRB) approval of this study.
- Study variables and their measurement should be provided.
- Statistical analysis: please use converted forms of beta coefficients.
- Results: The Results section is very long. Please avoid providing data both in the text and the table.
- Please use converted forms of beta coefficients in the Results section.
- Please identify adjusted and unadjusted beta coefficients in the Results section both in the Abstract and full text.
- I do not think there is a "perspective section" in the JMIR structure. You can add it to the Discussion and Conclusion section if it is necessary.
- Tables: They are not in the scientific form. Please revise them according to JMIR guidelines.

Round 2 Review

I would like to thank the authors for considering all the reviewers' comments.

However, there is no IRB or research ethics committee approval.

According to the authors' statement “all data used in this work is made publicly available by the Hospital Reduction Readmission Program (HRRP) and Office of Statewide Health Planning and Development (OSHPD).” It is recommended to mention it in the Acknowledgments section and the first paragraph of the study design.

Conflicts of Interest

None declared.

Reference

1. Pinheiro D, Hartman R, Mai J, Romero E, Soroya S, Bastos-Filho C, et al. The association of shared care networks with 30-day heart failure excessive hospital readmissions: longitudinal observational study. JMIRx Med 2022;3(2):e30777 [FREE Full text]

Abbreviations

HRRP: Hospital Reduction Readmission Program
IRB: institutional review board
MeSH: Medical Subject Headings
OSHPD: Office of Statewide Health Planning and Development
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Peer-Review Report

Peer Review of "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study"

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Institute for Data Science and Informatics, University of Missouri, Columbia, MO, United States

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.07.21255061v1

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Companion article: https://med.jmirx.org/2022/2/e30777/

Abstract

(JMIRx Med 2022;3(2):e37057) doi:10.2196/37057

KEYWORDS

patient readmission; quality assurance; health care; catchment area; health; community networks; regional medical programs

This is a peer-review report submitted for the paper "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study."

General Comments

Thank you for the opportunity to review this study [1] of the association of shared care networks with heart failure (HF) excessive hospital readmissions. Hospital readmission is a very current topic. Nonetheless, several issues should be noted.

Specific Comments

Major Comments

1. In "study population and design" in "methods," the authors mentioned, "hospitals with less than 2 repeated measures of higher-than-expected HF readmission in the HRRP (Hospital Reduction Readmission Program) or without discharge data in the OSHPD (Office of Statewide Health Planning and Development) were excluded." Does this mean this study only considered hospitals with repeated higher-than-expected HF readmission? Ignoring hospitals without repeated higher-than-expected HF readmission may introduce bias to the analysis. Please clarify why you have chosen this data inclusion criterion.
2. In "data sources" in "methods," the authors collected excessive readmission ratio (ERR) data from 2012 to 2017. In almost every year, the HRRP updated the inclusion criteria of HF readmission (eg, lists of eligible diagnosis codes and procedure codes in the planned readmission algorithm). In this case, how did you fairly compare the ERR across different years?
3. Is the "Uncovering Shared Care Areas and Localization Index from Hospital-Patient Discharge Data" in "methods" a literature review of other studies or the method the authors used in this study? Please clarify. If it is a literature review, it should go in the "introduction."

Conflicts of Interest

None declared.

Reference

1. Pinheiro D, Hartman R, Mai J, Romero E, Soroya S, Bastos-Filho C, et al. The association of shared care networks with 30-day heart failure excessive hospital readmissions: longitudinal observational study. JMIRx Med 2022;3(2):e30777 [FREE Full text]

Abbreviations

ERR: excessive readmission ratio
HF: heart failure
HRRP: Hospital Reduction Readmission Program
OSHPD: Office of Statewide Health Planning and Development

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Peer-Review Report

Peer Review of "Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: Scoping Review"

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.03.15.21253509v1

Companion article: https://preprints.jmir.org/preprint/31272

Companion article: https://med.jmirx.org/2022/2/e36345/

Companion article: https://med.jmirx.org/2022/2/e31272/

(JMIRx Med 2022;3(2):e36347) doi:10.2196/36347

KEYWORDS

COVID-19; pandemic; SARS-CoV-2; health care; hospitals; health care strategy; hospital resilience; interventions; crisis response; crisis preparedness; public health

This is a peer-review report submitted for the paper "Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: Scoping Review."

Round 1 Review

General Comment

This paper's [1] title mentions that the authors conducted a scoping review but used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method. The authors should clarify the difference between scoping review and systematic review.

Specific Comments

Major Comments

1. Provide a table of the studies that were selected for final analysis (study title, publishing year, research methods, main findings of each study)

2. State the study exclusion reasons clearly with a subheading in the Methods section

3. Revise your study limitations according to the study inclusion and exclusion criteria

4. Provide the list of all studies that were included at the initial stage without inclusion and exclusion limitations in a supplementary file

Minor Comments

5. English editing is required

Conflicts of Interest

None declared.

Reference

1. Stennett J, Hou R, Traverson L, Ridde V, Zinszer K, Chabrol F. Lessons learned from the resilience of Chinese hospitals to the COVID-19 pandemic: a scoping review. JMIRx Med 2022;3(2):e31272 [FREE Full text]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Peer-Review Report

Peer Review of "Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: Scoping Review"

Ángela González-Santos[1], MSc

Department of Physiotherapy, Faculty of Health Sciences, University of Granada, Granada, Spain

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.03.15.21253509v1

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Companion article: https://med.jmirx.org/2022/2/e31272/

(JMIRx Med 2022;3(2):e36685) doi:10.2196/36685

KEYWORDS

COVID-19; pandemic; SARS-CoV-2; health care; hospitals; health care strategy; hospital resilience; interventions; crisis response; crisis preparedness; public health

This is a peer-review report submitted for the paper "Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: A Scoping Review."

Round 1 Review

General Comments

1. This paper [1] is a scoping review with the aim to study the resilience during the COVID-19 pandemic of China's hospitals during the first half of 2020.

Specific Comments

Major Comments

- The background clearly presents the nature of the context, what is already known as well as the gap in knowledge and the need to conduct this study. The objectives of the scoping review are clear. The design is presented, and the authors follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) Checklist.
- The characteristics of the sources of evidence and eligibility criteria are provided. The authors describe all information sources in the search and present the full search strategy for at least one database.
- Authors define the selection of sources of evidence, the data charting process, and all variables for which data were sought. They describe the methods used for conducting a critical appraisal of included sources of evidence, and the methods used for the synthesis of results.
- Results are correctly presented and cited in their manuscript section. The authors summarize the main results of the study, discuss the limitations of the scoping review, and provide a general conclusion of the outcomes.

Minor Comments

1. The authors refer to Table 4 three times in the manuscript; however, this table is not attached to the document. The same occurs with Table 3 that is referred to on page 7, second paragraph.
2. In relation to the PRISMA-ScR checklist, the eligibility criteria are not pointed out in the abstract section of the manuscript.
3. The registration number of the scoping review's protocol is missing. The authors do not indicate if the protocol is available.
4. There are some typos in the manuscript, for example:
   - Authors use the acronym PPE (personal protective equipment) several times in the manuscript. Please indicate its meaning the first time it appears in the manuscript (page 10).
   - In the abstract section, the word "found" appears in a smaller size than the rest of the words.

Conflicts of Interest

None declared.

Reference

1. Stennett J, Hou R, Traverson L, Ridde V, Zinszer K, Chabrol F. Lessons learned from the resilience of Chinese hospitals to the COVID-19 pandemic: a scoping review. JMIRx Med 2022;3(2):e31272 [FREE Full text]

Abbreviations

PPE: personal protective equipment
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Peer-Review Report

Peer Review of “Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review”

Sunil Munakomi[1]

Department of Neurosurgery, College of Medical Sciences, Bharatpur, Nepal

Related Articles:

Companion article: https://preprints.jmir.org/preprint/31019

Companion article: https://med.jmirx.org/2022/2/e37114/

Companion article: https://med.jmirx.org/2022/2/e31019/

Abstract

(JMIRx Med 2022;3(2):e37032) doi:10.2196/37032

KEYWORDS

ventricular outflow obstruction; subarachnoid hemorrhage; vasospasm; intracranial; milrinone; hemorrhage; neurosurgery; neurology; surgery; pharmaceutical

This is a peer-review report submitted for the paper “Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review.”

Review Round 1

This paper [1] deals with a rare event on the occurrence of left ventricular outflow obstruction in a patient treated with milrinone for vasospasm following an aneurysmal bleed.

Major Comments

1. The rationale for radioembolization of aneurysms needs to be elaborated.
2. The probable differential diagnosis of stunned myocardium syndrome in the acute phase needs to be mentioned.

Conflicts of Interest

None declared.

Reference

1. Baulier C, Lessert M, Chauvet JL, Garel P, Bergis A, Burdeau J, et al. Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report. JMIRxMed 2022;3(2):e31019 [FREE Full text] [doi: 10.2196/31019]

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Peer-Review Report

Peer Review of “Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review”

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Clinical Trials Innovation Unit, Translational Research Institute, University of Arkansas for Medical Sciences, Little Rock, AR, United States

Related Articles:

Companion article: https://preprints.jmir.org/preprint/31019

Companion article: https://med.jmirx.org/2022/2/e37114/

Companion article: https://med.jmirx.org/2022/2/e31019/

Abstract

(JMIRx Med 2022;3(2):e37056) doi:10.2196/37056

KEYWORDS

ventricular outflow obstruction; subarachnoid hemorrhage; vasospasm; intracranial; milrinone; hemorrhage; neurosurgery; neurology; surgery; pharmaceutical

This is a peer-review report submitted for the paper “Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review.”

Review Round 1

Reviewer AA

General Comments

This is an interesting paper [1]. Overall, the information is well presented. That said, there are some areas that need improvements.

Specific Comments

Major Comments

1. This type of left ventricular outflow tract obstruction (LVOTO) should be addressed as dynamic LVOTO.
2. LVOTO per se should be briefly explained in the “Introduction” for the benefit of noncardiology readers: what LVOTO means, types of LVOTO such as fixed and dynamic, and a brief and simple explanation of dynamic LVOTO.
3. For the second patient, pages 7 and 8 state “In view of the hemodynamic improvement and the good neurological course, treatment with milrinone was continued at the same dose.” It looks like a repeat echo was done only after stopping milrinone. Was any echo repeated after hemodynamic improvement while the patient was continued on milrinone? How did you come to the conclusion that LVOTO is because of milrinone? He also had meningitis/sepsislike state (mentioned as an inflammatory syndrome in the manuscript), which in itself could predispose to LVOTO. Additionally, LVOTO can occur postoperatively after noncardiac surgery in patients with no known heart disease, and this patient also had a surgical procedure in the form of ventricular drain. These aspects are well discussed in reference 16 of the manuscript.
4. What is the explanation for unilateral left sided pulmonary edema for the first patient (as pulmonary edema is mostly bilateral in heart failure).

Minor Comments

1. The authors mention vasospasm was diagnosed using a computerized tomography (CT) scan. Plain CT scans are not used for the diagnosis of vasospasm, and they need to be more specific as to how vasospasm was diagnosed (eg, CT angio, Doppler study, or perfusion scan).

Review Round 2

Specific Comments

Major Comments

1. Page 6, lines 10-12 states “Although milrinone was administered at a constant dosage of 1 µg/kg/min, the clinical presentation led to find the origin of the shock: an accidental bolus of a milrinone due to a plication of the central venous catheter line during nursing care”. Would recommend clarifying this statement and explaining what exactly you mean by plication and how it resulted in an accidental bolus of milrinone.
2. Bedside limited echocardiography is a routine practice to check the effect of various interventions in the intensive care unit. Therefore, it should be explained why echocardiography was not repeated in the second patient after hemodynamic improvement while the patient was continued on milrinone. Just relying on “systolic murmur” is not enough. Moreover, a murmur is also not described in detail. The murmur description should include intensity, quality, radiation, timing (pan systolic/short systolic), etc.
3. “Mitral regurgitation associated with LVOTO is most often eccentric, and travels to the left pulmonary veins, resulting in unilateral acute pulmonary edema in this patient.” Please provide a reference for this.

Conflicts of Interest

None declared.

Reference

1. Baulier C, Lessert M, Chauvet JL, Garel P, Bergis A, Burdeau J, et al. Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report. JMIRxMed 2022;3(2):e31019 [FREE Full text] [doi: 10.2196/31019]

Abbreviations

CT: computerized tomography
LVOTO: Left Ventricular Outflow Tract Obstruction

Edited by E Meinert; submitted 04.02.22; this is a non–peer-reviewed article;accepted 04.02.22; published 11.04.22.

Please cite as:
Chalwadi UK
Peer Review of “Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review”
JMIRx Med 2022;3(2):e37056
URL: https://med.jmirx.org/2022/2/e37056
doi:10.2196/37056
PMID:

Peer-Review Report

Peer Review of “Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model”

Bozhidar Chakalov[1]

University of California, Davis, Davis, CA, United States

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.23.21256005v1

Companion article: https://preprints.jmir.org/preprint/30144

Companion article: https://med.jmirx.org/2022/2/e38008/

Companion article: https://med.jmirx.org/2022/2/e30144/

(JMIRx Med 2022;3(2):e37985) doi:10.2196/37985

KEYWORDS

COVID-19; pandemic; socioeconomic status; mortality; nonpharmaceutical interventions; prediction model; low-income status; life expectancy; public health; income groups

This is a peer-review report submitted for the paper “Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model.”

Review Round 1

General Comments

The paper [1] is very well written and is very timely. I believe that this model will be informative in that it shows how long-term solutions rather than short term are needed to avoid greater losses in the long term. However, as the authors say, the model is based on somewhat weaker empirical research, so I look forward to seeing this model validated with data.

Specific Comments

Major Comments

1. I think it should be made clearer that this model is applied to US and European scenarios.

2. I believe that the paper and research are well motivated and show a necessity for more research on the proportional impact of socioeconomic status on years of life lost.

Minor Comments

3. There are several cases where the authors should correct some typos (eg, the European [the European what?] and sill vs still).

Conflicts of Interest

None declared.

Reference

1. John J. Modeling years of life lost due to COVID-19, socioeconomic status, and nonpharmaceutical interventions: development of a prediction model. JMIRx Med 2022;3(2):e30144 [FREE Full text]

Edited by E Meinert; submitted 14.03.22; this is a non–peer-reviewed article;accepted 14.03.22; published 12.04.22.

Please cite as:
Chakalov B
Peer Review of "Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model"
JMIRx Med 2022;3(2):e37985
URL: https://med.jmirx.org/2022/2/e37985
doi:10.2196/37985
PMID:27892505

Peer-Review Report

Peer Review of “Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model”

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.23.21256005v1

Companion article: https://preprints.jmir.org/preprint/30144

Companion article: https://med.jmirx.org/2022/2/e38008/

Companion article: https://med.jmirx.org/2022/2/e30144/

(JMIRx Med 2022;3(2):e38420) doi:10.2196/38420

KEYWORDS

COVID-19; pandemic; socioeconomic status; mortality; nonpharmaceutical interventions; prediction model; low-income status; life expectancy; public health; income groups

This is a peer-review report submitted for the paper “Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model.”

Review Round 1

This paper [1] develops a model that compares the years of life lost (YLL) due to COVID-19 and the potential YLL due to the socioeconomic consequences of its containment. The results highlight the importance of socioeconomic status (SES) in evaluating the effect of nonpharmaceutical interventions (NPIs) during COVID-19. However, the methods, especially the empirical sample characteristics from which the life table is derived, are not clear.

Specific Comments

Major Comments

1. Needs to describe more about the data, study design, and study sample in more detail

2. Needs to discuss how the missing data was handled

3. It is important to consider a theoretical framework that can guide the selection of NPIs, indicators of SES, and the equivalent socioeconomic damages (on page 11). Right now, it is more arbitrary than scientific based.

4. The Discussion also needs to consider other factors (eg, pre-existing conditions, neighborhood resources, or occupation types). These are important social determinants of health factors

Minor Comments

1. The tables need to be adjusted in terms of the decimal points and more informative legends to guide readers.

Conflicts of Interest

None declared.

Reference

1. John J. Modeling years of life lost due to COVID-19, socioeconomic status, and nonpharmaceutical interventions: development of a prediction model. JMIRx Med 2022;3(2):e30144 [FREE Full text]

Abbreviations

NPI: nonpharmaceutical intervention
SES: socioeconomic status

YLL: years of life lost

Edited by E Meinert; submitted 31.03.22; this is a non–peer-reviewed article;accepted 31.03.22; published 12.04.22.

Please cite as:
Anonymous
Peer Review of "Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model"
JMIRx Med 2022;3(2):e38420
URL: https://med.jmirx.org/2022/2/e38420
doi:10.2196/38420
PMID:

Peer-Review Report

Peer Review of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"

Artur Strzelecki[1], PhD, DSc

Department of Informatics, University of Economics in Katowice, Katowice, Poland

Related Articles:

Companion article: https://preprints.jmir.org/preprint/35356

Companion article: https://med.jmirx.org/2022/2/e38695/

Companion article: https://med.jmirx.org/2022/2/e35356/

(JMIRx Med 2022;3(2):e38665) doi:10.2196/38665

KEYWORDS

COVID-19; epidemiology; Google Trends; infodemiology; infoveillance; Italy; public health; SARS-CoV-2; vaccinations; vaccines; social media analysis; social media

This is a peer-review report submitted for the paper "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis."

Round 1 Review

General Comments

The subject of the brief paper [1] "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: a Retrospective Infodemiological Analysis" is timely and valuable to the audience of JMIRx Med. Overall, the paper is well structured, reads exceptionally well, and covers the existing literature quite well. The analysis of the data is interesting and well documented.

The author of the paper has selected keywords used in the Google Search engine, which could reveal an intention to take a vaccine against COVID-19 in Italy and compared this interest with headlines in the second most read newspaper in Italy. The paper has a transparent and replicable procedure to collect data and do statistical tests.

The results show a marked and significant cross-correlation between web queries on vaccine reservations and actual vaccinations against COVID-19 in Italy. On the other hand, the cross-correlation between vaccine-related news and vaccine web searches is low.

Specific Comments

Minor Comments

1. I think that the limitations of this study are much broader than those listed in the work. There is a strong vaccine hesitation movement across different European countries, which could at least be mentioned in the work. The authors only noticed news in a newspaper on rare side effects of vaccination. This is what strongly influences, on the one hand, queries entered into a search engine and, on the other hand, a decrease in the number of vaccinations.

Conflicts of Interest

None declared.

Reference

1. Rovetta A. Google Trends as a predictive tool for COVID-19 vaccinations in Italy: a retrospective infodemiological analysis. JMIRx Med 2022;3(2):e35356 [FREE Full text]

Edited by E Meinert; submitted 11.04.22; this is a non–peer-reviewed article;accepted 11.04.22; published 19.04.22.

Please cite as:
Strzelecki A
Peer Review of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"
JMIRx Med 2022;3(2):e38665
URL: https://med.jmirx.org/2022/2/e38665
doi:10.2196/38665
PMID:

Peer-Review Report

Peer Review of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"

Zubair Shah[1]

College of Science and Engineering, Hamad Bin Khalifa University, Ar-Rayyan, Qatar

Related Articles:

Companion article: https://preprints.jmir.org/preprint/35356

Companion article: https://med.jmirx.org/2022/2/e38695/

Companion article: https://med.jmirx.org/2022/2/e35356/

(JMIRx Med 2022;3(2):e38724) doi:10.2196/38724

KEYWORDS

COVID-19; epidemiology; Google Trends; infodemiology; infoveillance; Italy; public health; SARS-CoV-2; vaccinations; vaccines; social media analysis; social media

This is a peer-review report submitted for the paper "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis."

Round 1 Review

General Comments

The paper [1] uses Google Trends (GT) to identify correlations between search queries and vaccinations. GT has been used previously by others for similar and other problems. The paper is well written. The Methods section can be improved. The Results section has a good explanation.

Specific Comments

Major Comments

1. The novelty of the paper is limited.
2. The Introduction is short and can be extended to include more relevant studies.
3. The Methods section needs more details. For instance, how GT works, especially when keywords are two words "vaccine reservation." Does it search for all queries that include both words vaccine and reservation or vaccine OR reservation, or does it search for an exact match ("vaccine reservation")? More search terms can be included, such as synonyms of reservation like an appointment or booking. Additionally, how was data normalized? What is lag week?

Conflicts of Interest

None declared.

Reference

1. Rovetta A. Google Trends as a predictive tool for COVID-19 vaccinations in Italy: a retrospective infodemiological analysis. JMIRx Med 2022;3(2):e35356 [FREE Full text]

Abbreviations

GT: Google Trends

Edited by E Meinert; submitted 13.04.22; this is a non–peer-reviewed article;accepted 13.04.22; published 19.04.22.

Please cite as:
Shah Z
Peer Review of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"
JMIRx Med 2022;3(2):e38724
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Peer-Review Report

Peer Review of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"

Angela Chang[1]

Department of Communication, University of Macau, Macao, Macao

Related Articles:

Companion article: https://preprints.jmir.org/preprint/35356

Companion article: https://med.jmirx.org/2022/2/e38695/

Companion article: https://med.jmirx.org/2022/2/e35356/

(JMIRx Med 2022;3(2):e38726) doi:10.2196/38726

KEYWORDS

COVID-19; epidemiology; Google Trends; infodemiology; infoveillance; Italy; public health; SARS-CoV-2; vaccinations; vaccines; social media analysis; social media

This is a peer-review report submitted for the paper "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis."

Round 1 Review

This brief paper [1] examines the effective approach to investigating vaccine adherence against COVID-19 via Google Trends. The topic is interesting and important to provide actionable data to the World Health Organization or other related health organizations to prioritize their risk communication efforts. The manuscript is nicely written and easy to understand. These data are of potential interest, but there are some concerns.

Major Comment

1. The methodological strength is poor. It should discuss the overarching sampling method, measures, and procedures to justify the Google and news media content in this study.
2. In line with the methodology concern, the chosen keywords are questionable too.
3. Additionally, there is no rationale for sampling the historical archive of the newspaper "La Repubblica." Is this the second most read Italian newspaper online?
4. Confounding is a statistical concept that is important to all researchers. The concept of confounding is explained with the help of an amusing but true example. The methods to deal with confounding should be more detailed, with more applications and disadvantages to be examined.
5. The role of the mass media was considered as a confounding factor. Actually, confounding is said to exist when a third factor, known as the confounding variable, explains the association between two variables. One of the results indicated that vaccine reservation queries (VRQs) and news about COVID-19 vaccines have been low and characterized by lags. I am afraid this could be a failure to identify and control for confounding, which could result in the faulty interpretation of study outcomes. So, you really can't say for sure whether the lack of news influence (ie, from one specific website only) leads to the unwillingness of vaccination.
6. Another study outcome linked the VRQs and vaccinated for their positive linear relation. Instead of a valuable research question, it sounds like common sense that most laymen would agree with.
7. Following the abovementioned concern, it is not sustainable that the conclusion shows that Google Trends is a surveillance and prediction tool for vaccine adherence against COVID-19 in Italy.

Minor Comments

1. Please list the ethics issue for this study if approved.
2. The first letters of a term should correspond to the initials, for example, "vaccine reservation" (VRQ).

Conflicts of Interest

None declared.

Reference

1. Rovetta A. Google Trends as a predictive tool for COVID-19 vaccinations in Italy: a retrospective infodemiological analysis. JMIRx Med 2022;3(2):e35356 [FREE Full text]

Abbreviations

VRQ: vaccination reservation query

Edited by E Meinert; submitted 13.04.22; this is a non–peer-reviewed article;accepted 13.04.22; published 19.04.22.

Please cite as:
Chang A
Peer Review of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"
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doi:10.2196/38726
PMID:

Peer-Review Report

Peer Review of "Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach"

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Central University of Technology, Bloemfontein, South Africa

Related Articles:

Companion article: https://psyarxiv.com/2rbku/

Companion article: https://preprints.jmir.org/preprint/33502

Companion article: https://med.jmirx.org/2022/2/e38587/

Companion article: https://med.jmirx.org/2022/2/e33502/

(JMIRx Med 2022;3(2):e38581) doi:10.2196/38581

KEYWORDS

human behavior modeling; cognitive twins; human digital twins; cybersecurity; cognitive systems; digital twins; Metaverse; artificial intelligence

This is a peer-review report submitted for the paper "Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach."

Round 1 Review

General Comments

This paper [1] proposes a Cybonto conceptual framework for cybersecurity. It highlights the possibility of using human cognitive digital twin and digital twin systems for proactive cybersecurity strategies.

The paper was well written, the problem was clearly stated, the conceptual framework was well explained, and the author demonstrates an in-depth knowledge of cybersecurity ontologies, human cognitive digital twins, and behavioral or cognitive theories.

Looking forward to seeing the future works on this study.

Conflicts of Interest

None declared.

Reference

1. Nguyen TN. Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach. JMIRx Med 2022;3(2):e33502 [FREE Full text]

Edited by E Meinert; submitted 07.04.22; this is a non–peer-reviewed article;accepted 07.04.22; published 20.04.22.

Please cite as:
Oladele DA
Peer Review of "Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach"
JMIRx Med 2022;3(2):e38581
URL: https://med.jmirx.org/2022/2/e38581
doi:10.2196/38581
PMID:

Peer-Review Report

Peer Review of “Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach”

Jorge Ropero[1], PhD

Universidad de Sevilla, Sevilla, Spain

Related Articles:

Companion article: https://psyarxiv.com/2rbku/

Companion article: https://preprints.jmir.org/preprint/33502

Companion article: https://med.jmirx.org/2022/2/e38587/

Companion article: https://med.jmirx.org/2022/2/e33502/

(JMIRx Med 2022;3(2):e38583) doi:10.2196/38583

KEYWORDS

human behavior modeling; cognitive twins; human digital twins; cybersecurity; cognitive systems; digital twins; Metaverse; artificial intelligence

This is a peer-review report submitted for the paper “Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach.”

Round 1 Review

General comments

This paper [1] deals with the use of Digital Twins in Cybersecurity, proposing a conceptual framework. The starting point is interesting, but I have found the following issues.

Specific Comments

Major Comments

1. The author states that this paper proposes an application of Digital Twins (DT) and Human Digital Twins (HDT) for the first time. This is not exact, as, in the last 2 years, there have been some approaches to the use of DT in cybersecurity.

The author should include some of these ideas in the literature review. Some examples are listed below.

Lou X, Guo Y, Gao Y, Waedt K, Parekh M. An idea of using Digital Twin to perform the functional safety and cybersecurity analysis. *INFORMATIK 2019: 50 Jahre Gesellschaft für Informatik–Informatik für Gesellschaft (Workshop-Beiträge)*. Gesellschaft für Informatik eV. 2019;295:283-294.

Scheibmeir J, Malaiya YK. Multi-model security and social media analytics of the digital twin. ASTEJ. 2020;5(6):323-330.

Atalay M, Angin P. A digital twins approach to smart grid security testing and standardization. IEEE International Workshop on Metrology for Industry 4.0 & IoT 2020 Jun 3; Rome, Italy. pp 435-440.

Pokhrel A, Katta V, Colomo-Palacios R. Digital twin for cybersecurity incident prediction: A multivocal literature review. Proceedings of the IEEE/ACM 42nd International Conference on Software Engineering Workshops 2020 Jun 27; Seoul, Republic of Korea. pp 671-678.

Saad A, Faddel S, Youssef T, Mohammed OA. On the implementation of IoT-based digital twin for networked microgrids resiliency against cyber attacks. IEEE transactions on smart grid. 2020 Jun 9;11(6):5138-5150.

Olivares-Rojas JC, Reyes-Archundia E, Gutiérrez-Gnecchi JA, Molina-Moreno I, Cerda-Jacobo J, Méndez-Patiño A. Towards Cybersecurity of the Smart Grid using Digital Twins. IEEE Internet Computing. 2021 Mar 3.

2. In the literature review, the author should add a definition of DT and HDT, how HDT surges from the concept of DT, a comparison between both techniques, and finally a list of the main uses of DT and HDT.

3. In the literature review, the author claims that there is no grounded vision of the power of DT and HDT. In addition to the fact that, as I mentioned before, there are already applications of DT to cybersecurity, nothing is mentioned about proactive cyber defense existing techniques. What can DT and HDT add to the existing techniques?

Husák M, Bartoš V, Sokol P, Gajdoš A. Predictive methods in cyber defense: Current experience and research challenges. Future Generation Computer Systems. 2021 Feb 1;115:517-530.

4. The author states that the framework targets the cognitive process of a malicious actor as an HDT within a DT system. What is the purpose of this? The author must explain why these decisions were made.

5. Regarding Table 1, how was the total score calculated? There should be a description of every item. How was the score of every item calculated? An explanation is necessary.

6. Related to the above, it is good to have all the information in GitHub, but, at least a brief and clear description of the obtention of cybersecurity-related behavioral theories, and another description of the ontology should be provided in the manuscript or in a Multimedia Appendix.

7. An explanation of Figure 1 is needed.

8. Without a clear description, the rest of the paper, although interesting, is difficult to follow.

9. In broad terms, I understand the goal of the ontology, but it is so abstract that it is difficult for me how to apply it to proactive cyber defense. Some examples would be welcome.

10. Last, a general comment: this is the Journal of Medical Internet Research. Though other topics are welcome, and it is clear that security is capital in the medical field, some particular comments about cybersecurity in the medical field would be desirable.

Minor Comments

11. In the introduction, the author states that “incredibly,” HDT offers the capability of running large-scale simulations. Why “incredibly”?

12. In the introduction, the author claims that “Analyzing the Cybonto ontology informed the Cybonto conceptual framework.” I do not understand this sentence.

13. The author defines the in-group environment acronym as IGE, but it appears as IEG in the rest of the paper.

Round 2 Review

General Comments

Though all the comments have not been directly addressed by the author, the author has considered some aspects (many of them related to the state of the art) to be beyond the scope of the paper and has structured the article in a more ordered way. Thus, the paper is much easier to understand.

The inclusion of the Discussion section is key to see the applicability of the framework.

Specific Comments

Major Comments

1. In Table 2, what are PR, EC, BC, and DC?

Conflicts of Interest

None declared.

Reference

1. Nguyen TN. Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach. JMIRx Med 2022;3(2):e33502 [FREE Full text]

Edited by E Meinert; submitted 07.04.22; this is a non–peer-reviewed article;accepted 08.04.22; published 20.04.22.

Please cite as:
Ropero J
Peer Review of “Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach”
JMIRx Med 2022;3(2):e38583
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doi:10.2196/38583
PMID:

Peer-Review Report

Peer Review of "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.12.16.21267811v1

Companion article: https://preprints.jmir.org/preprint/35862

Companion article: https://med.jmirx.org/2022/2/e38755/

Companion article: https://med.jmirx.org/2022/2/e35862/

(JMIRx Med 2022;3(2):e38730) doi:10.2196/38730

KEYWORDS

COVID-19; sport; injury; prevalence; cause; data; statistics; pain; training; practice; physiology; adaptation

This is a peer-review report submitted for the paper "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"

Round 1

General Comments

This paper [1] compares the number of injuries in the National Football League between 3 consecutive years to analyze the impact of the COVID-19 pandemic. Although the paper is investigating an interesting subject, I believe it lacks enough analysis and final conclusion. One important addition to this paper could be an analysis of the differences between the hours of exercise in those 3 years. With the current paper, we do not know if there was actually a decrease in the number of hours each player exercised. This extra analysis will help to understand if the increase in injuries were really resulted from less exercise or if it was because of health issues such as mental and physical problems caused by the pandemic.

Specific Comments

1. Please define resistance exercise and postresistance exercise.
2. Please refrain from citing a figure in the abstract.
3. Why didn't you include sick days in your analysis?

Conflicts of Interest

None declared.

Reference

1. Puga TB, Schafer J, Agbedanu PN, Treffer K. COVID-19 Return to Sport: NFL Injury Prevalence Analysis. JMIRx Med 2022;3(2):e35862 [FREE Full text]

Edited by E Meinert; submitted 13.04.22; this is a non–peer-reviewed article;accepted 13.04.22; published 22.04.22.

Please cite as:
Anonymous
Peer Review of "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"
JMIRx Med 2022;3(2):e38730
URL: https://med.jmirx.org/2022/2/e38730
doi:10.2196/38730
PMID:

Peer-Review Report

Peer Review of "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"

Felicianus Pereira[1]

Shaheed Benazir Bhutto Dewan University, Karachi City, Pakistan

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.12.16.21267811v1

Companion article: https://preprints.jmir.org/preprint/35862

Companion article: https://med.jmirx.org/2022/2/e38755/

Companion article: https://med.jmirx.org/2022/2/e35862/

(JMIRx Med 2022;3(2):e38731) doi:10.2196/38731

KEYWORDS

COVID-19; sport; injury; prevalence; cause; data; statistics; pain; training; practice; physiology; adaptation

This is a peer-review report submitted for the paper "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"

Round 1

General Comments

This paper [1] has focused on a relevant topic in sports. Athletes are at high risk of injury when they have not performed required training, or do not have a solid training base (as highlighted in the periodization plan).

Specific Comments

1. Was ethical approval taken to conduct this study?
2. Regarding injuries suffered by athletes, were contact injuries accounted for? (As this is a possible confounding variable in this study.)

Conflicts of Interest

None declared.

Reference

1. Puga TB, Schafer J, Agbedanu PN, Treffer K. COVID-19 Return to Sport: NFL Injury Prevalence Analysis. JMIRx Med 2022;3(2):e35862 [FREE Full text]

Edited by E Meinert; submitted 13.04.22; this is a non–peer-reviewed article;accepted 13.04.22; published 22.04.22.

Please cite as:
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JMIRx Med 2022;3(2):e38731
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doi:10.2196/38731
PMID:

Peer-Review Report

Peer Review of “Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study”

Chelsea Jones[1], PhD

Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada

Related Articles:

Companion article: https://preprints.jmir.org/preprint/22912

Companion article: https://med.jmirx.org/2022/2/e38010/

Companion article: https://med.jmirx.org/2022/2/e22912/

(JMIRx Med 2022;3(2):e38007) doi:10.2196/38007

KEYWORDS

depression; diabetes; electronic health records; acute care; PLS-SEM; path analysis; equation modelling; accident; emergency care; emergency; structural equation modelling; clinical data

This is a peer-review report submitted for the paper “Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study.”

Round 1 Review

General Comments

This paper [1] takes structural equation modelling (SEM) and uses it in a novel way that could be beneficial for researchers and clinicians alike. The results and discussion are transparent, and do not overstate the findings. The researchers created a complex model that could demonstrate the benefits of use of this data analysis method in other health care contexts. The future directions and recommendations are realistic.

Specific Comments

Major Comments

1. Lacks a statement of the study design. SEM is the method of analysis, not the study design.

Minor Comments

1. Write out “A&E” in title and first mention in text of abstract.
2. In the Introduction and second section, you have 2 statements that are in close proximity and convey similar information. I would consider revising. Introduction statement: “Therefore, we sought to determine whether SEM could be used to make this data set more ‘research friendly’ by attempting to create clinical constructs and model some well-known clinical associations between depression and accident & emergency (A&E) use in patients with type 2 diabetes.” Next section statement: “Therefore, we sought to test whether SEM could be applied to a large routine clinical data set from East London to model these associations between depression, diabetic care, diabetic control, and A&E utilization, while assessing the impact of current mental health care provision.” Perhaps go with the second one.
3. Measures of Mental Health Diagnosis and Care - The information on the AUDIT seems misplaced or excessive since other outcome measures are not explained in that amount of detail. Consider removing: “Scores on the AUDIT range from 0-40, with higher scores indicating higher risk of dependence. The AUDIT C consists of the three consumption questions from the AUDIT and scores can range from 0-12, with higher scores indicating higher risk.”
4. I don't think you need to state this: “A full description of the adult mental health care cluster codes used by the NHS can be found here: (link).” Just state those are the clusters you chose, and why.
5. Data Source: Consider explaining what the intended purpose of each data source/database is. These are largely unknown to anyone outside the UK health care context and will require more detail.
6. More explanation of what partial least squares SEM (PLS-SEM) is might be beneficial for the reader.
7. May benefit from explanation of why PLS versus covariance-based (CB) and other SEM types since the sample size was large (PLS-SEM is a great choice in my mind, but others may want more justification).
8. State whether the structural model is reflexive or formative and justification for this.

9. Discussion: there are 2 similar comments in close proximity: "This might be related to a problem with the data set, which will be described later in the Discussion" and "This is not in agreement with previous research, which has shown that improvement of depressive symptoms through the use of psychotherapy and pharmacotherapy is associated with improved glycemic control. The opposite association reported in this study is likely related to issues with data quality, which will be outlined later."
10. In the Limitations section, link those statements to the above issue (10) for clarity.
11. A statement in Future Directions and Recommendations could address issues with the data set and what should/could be done to improve this.

Conflicts of Interest

None declared.

Reference

1. Ronaldson A, Freestone M, Zhang H, Marsh W, Bhui K. Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study. JMIRx Med 2022;3(2):e22912 [FREE Full text]

Abbreviations

CB-SEM: covariance-based structural equation modelling
PLS-SEM: partial least squares structural equation modelling
SEM: structural equation modelling

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Please cite as:
Jones C
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JMIRx Med 2022;3(2):e38007
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doi:10.2196/38007
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Peer-Review Report

Peer Review of “Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study”

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/22912

Companion article: https://med.jmirx.org/2022/2/e38010/

Companion article: https://med.jmirx.org/2022/2/e22912/

(JMIRx Med 2022;3(2):e38488) doi:10.2196/38488

KEYWORDS

depression; diabetes; electronic health records; acute care; PLS-SEM; path analysis; equation modelling; accident; emergency care; emergency; structural equation modelling; clinical data

This is a peer-review report submitted for the paper “Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study.”

Round 1 Review

Major Comments

1. In this paper [1], the general research hypothesis should be interpreted and clarified more in the Introduction.
2. Please redesign Figure 1 with better quality and interpretations.
3. Recommendations and limitations are absent.

Minor Comments

1. Order keywords alphabetically.

Conflicts of Interest

None declared.

Reference

1. Ronaldson A, Freestone M, Zhang H, Marsh W, Bhui K. Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study. JMIRx Med 2022;3(2):e22912 [FREE Full text]

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Peer-Review Report

Peer Review of "Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study"

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Faculty of Informatics, Eötvös Loránd University, Budapest, Hungary

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.06.10.21258728v1

Companion article: https://preprints.jmir.org/preprint/31521

Companion article: https://med.jmirx.org/2022/2/e37206/

Companion article: https://med.jmirx.org/2022/2/e31521/

(JMIRx Med 2022;3(2):e37119) doi:10.2196/37119

KEYWORDS

physical activity; university students; university; exercise; students; inactive; curricula; healthy lifestyle; higher education

This is a peer-review report submitted for the paper "Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study."

Round 1 Review

General Comments

This paper [1] was about the physical activity pattern of university students aiming at measuring this for the first time systematically as well as creating a new tool in order to have more accurate results. The authors collected a large body of data over several years, which gives an accurate and realistic perspective of the physical activity patterns of university students in India. It was an honour to read this remarkable job the authors did over the years.

Specific Comments

1. I find the Introduction part quite short compared to the literature mentioned in the Discussion. I learned more about the literature from the Discussion than from the Introduction. I'd suggest writing a slightly longer introduction with details on activity patterns of different age groups. This could also point to the missing age group data this paper focuses on.

2. The authors mention in the first paragraph of the introduction "an increased engagement with video games, cell phones, television, computers, and social media are possibly some of the important contributing factors to this trend among youth." I'd write in more detail about this or have a bigger emphasis on this perspective in the paper, both in the introduction and in the discussion, as the manuscript was submitted to the Journal of Medical Internet Research.

3. The authors mention in Methods, in the study design and sampling, "time and other limitations." I'd rather mention these in the limitations part of the Discussion, and I'd explicitly say what the other limitations not listed here are. The authors write "approximately 4600 students" in this section. On the other hand, I read the exact number later on. I'd suggest writing the exact number because it is accessible.

4. In the "translation and revalidation" subheading, the authors mention "professional" who did the translation and retranslation. I find it important to expand what kind of professionals they were? Translators, interpreters, psychologists, English teachers, or what profession did they have? You also mention "suitable corrections were made." What does this mean? Were certain items deleted based on a set of criteria? I am not sure I understand the last sentence "both the versions of the tool were used in the study to collect data based on student preference." I wonder if it would be possible to make it clear what two versions were used?

5. In the "development of a new tool," I was wondering in what language did you state these questions? My understanding is that in Hindi. I'd suggest writing it explicitly if so. I also wonder why these 5 items were used? what was the process of creating these items? Were there possibly more and then you deleted the ones that did not work? What did you base your decision on to use these exact 5 items?

6. In the "validation of the new tool" you write "acceptable range." I suggest giving a literature reference on what you based

your decision on, what is acceptable, and what is not. I read the manuscript and you reported the Cronbach alpha. In my understanding, this means the tool is reliable; however, it was not validated. For example, correlation with other tools.

7. The authors reported the data collection was between 2016 and 2019. This is a long stretch of time, and physical activity patterns can change in different groups year by year. I'd suggest for the authors to consider a statistical analysis on the data year by year. For example, people who filled out the questionnaire in 2016, the ones in 2017, and so on.

8. I read in the results you reported significant and not significant results. I'd consider writing a sentence about the direction of significant results. For example, "the difference between physical activity of students of different age groups was statistically significant." I'd find it useful to read a sentence about which age group was more active and which one less active.

9. I'd find it useful if I could read the results in hour as well, besides reading them in minutes. As far as I understand, the tool used reports in minutes. However, it would be easier to read if I could read it also in hours.

10.I'd suggest using the last sentence of the results in the Discussion. "Hence, it can be presumed that the students in these faculties receive some or other kind of motivation to lead a physically active lifestyle as a part of their curriculum.

11. The authors write in the Discussion, "this is possibly one of the first studies from India that looks at psychical activity…". I'd suggest not to use the phrase "possibly." After having read the literature in India about psychical activity of students, it can be said if this is the first or one of the first papers reporting on the matter.

12. I'd find it useful to have a section for abbreviations.

Conflicts of Interest

None declared.

Reference

1. Verma AK, Singh G, Patwardhan K. Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study. JMIRx Med 2022;3(2):e31521 [FREE Full text]

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Peer-Review Report

Peer Review of "Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study"

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Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.06.10.21258728v1

Companion article: https://preprints.jmir.org/preprint/31521

Companion article: https://med.jmirx.org/2022/2/e37206/

Companion article: https://med.jmirx.org/2022/2/e31521/

(JMIRx Med 2022;3(2):e37322) doi:10.2196/37322

KEYWORDS

physical activity; university students; university; exercise; students; inactive; curricula; healthy lifestyle; higher education

This is a peer-review report submitted for the paper "Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study."

Round 1 Review

General Comments

It is very positive to see analysis of physical activity in different populations and different age groups, and this paper [1] is a very welcome study in terms of physical activity in India and in relation to students. This is an important area as, when trying to engender habits and physical activity across the lifespan, it is in the younger age groups where sustained impact can be made. However, I feel that this paper addresses the issue quite superficially and would benefit from more in-depth analysis.

Specific Comments

Major Comments

1. Throughout the paper, there is no point at which the categories of inactive, active, and highly active are defined—this is a major omission as it is impossible to gauge how this compares to, for example, World Health Organization or other national guidelines in terms of minutes physical activity per week or metabolic equivalent minutes (apologies if this is indeed in the paper and I have missed it).

2. Demographics: although the authors should be commended for looking at differences between gender and age, there is no comment on socioeconomic status. For example, earlier in the paper, when describing the university, it would be useful to know what the demographics of the student population are (ie, do they represent general society or higher socioeconomic status?) This is important, as socioeconomic status (in the United Kingdom at least) is a major driver of physical activity. It would be useful for the reader as to how the subject population compares with the general population.

3. It is unclear to me how the metabolic equivalent minutes values of the subject population relate to that of the general population, and internationally. Over 4000 metabolic equivalent minutes per week is several times over World Health Organization guidance, and I would expect some analysis of how and why this might be the case.

4. In the discussion, there is a lot of description of the results from previous studies, and comparison with the current study, but without any analysis as to why there are similarities or differences. I also felt there was no real incorporation of the perceptions into the discussion, and no real analytical depth.

5. In the discussion, there is no real discussion of the limitations of the approach used, and no contextual framing of the findings.

Minor Comments

Abstract; objectives: Line beginning "the study also aims..." not quite clear: perhaps "This study also aims to capture student perceptions about the balance between curricular activities and leading a physically active lifestyle..."?

Introduction: (a) "being overweight" rather than overweight; (b) it would be useful to describe briefly what the few studies regarding students show.

Methods: validation of the new tool—more information on this would be useful: does the Cronbach alpha number represent test-retest reliability? In which case, how was validity measured?

Data collection and data entry: "written consent was obtained from each of the participants"

How were outliers excluded? How did the authors define "erratic entries"? Is this according to International Physical Activity Questionnaire cleaning criteria?

Views and opinions of the students: I would want more description of the items where there was discrepancy.

Table 8: there is a comment at the end of this section regarding why the authors feel students in different faculties are performing different levels of physical activity. This belongs in the discussion.

Discussion: the study on pooled data: was this from university students?

Tables: Table 4: why was a Mann Whitney Test used if the data presented are in mean SD (ie, if the data are nonparametric, shouldn't the median IQR be used?)

Tables 6-8: it would be helpful to have the questions in the table to enable the reader to better see how they relate.

Conflicts of Interest

None declared.

Reference

1. Verma AK, Singh G, Patwardhan K. Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study. JMIRx Med 2022;3(2):e31521 [FREE Full text]

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Salman D
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Peer-Review Report

Peer Review of “Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study”

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Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.06.21.21258931v1

Companion article: https://preprints.jmir.org/preprint/32902

Companion article: https://med.jmirx.org/2022/2/e37242/

Companion article: https://med.jmirx.org/2022/2/e32902/

(JMIRx Med 2022;3(2):e37145) doi:10.2196/37145

KEYWORDS

pharmacogenomics; pain management; drug-drug interaction; DDI; pharmacy; prescriptions; genetics; genomics; drug-gene interaction; pain

This is a peer-review report submitted for the paper “Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study.”

Review Round 1

General Comments

This paper [1] touches a very important and clinically relevant issue of adverse drug interactions with genetic variations and how these variants affect the patient’s response to the specific drug. It focuses on utilizing pharmacogenetic (PGx) testing in clinical practice, which takes into account these relevant drug-genome interactions when prescribing drug therapy. They appropriately chose an acceptable sample size >150 and follow them for a significant period of time (>18 months). Importantly, they have performed retrospective studies, which makes a good case for the utility of PGx testing. They also lay a good background on what other technologies for PGx testing are being routinely used in current clinical settings.

Specific Comments

Major Comments

I have no negative comments for this paper, here are some positive comments:

1. I especially find it very impressive that various figures and tables were added to the paper, which shows their thorough work. Figure 1 clearly describes PGx testing compared to urine drug toxicology reports. Figure 2 indicates the potential drug-gene and drug-drug interactions as provided by the PGx testing and suggests alternatives in case of serious and moderate interactions based on information from various regulatory bodies. Tables 1 and 2 are of significant interest because they focus on genotype, phenotype, and population frequencies for the genes in the panel. Figure 3 focuses on the importance of PGx testing in identifying moderate to serious drug-drug or drug-gene interactions.

Overall, I find this study very impactful especially with the advent of individualized drug therapy and targeted drug recommendations.

2. The results and discussion focus on how recommendations and dosage were changed based on PGx reports and resulted in favorable outcomes for the patients. This shows the utility of PGx in areas where health care professionals are not aware of these interferences or interactions between drug-gene and drug-drug.

3. I am not sure how many clinically relevant genes have changed or updated since April 2016, but this paper lays the groundwork for a more up-to-date gene panel to be used. I would be interested in seeing the outcome with a more up-to-date gene list but that does not necessarily have to be addressed in this paper.

Minor Comments

4. This was a very legibly worded paper, and I found no issues with the English or the scientific language that was used.

Conflicts of Interest

None declared.

Reference

1. Tagwerker C, Carias-Marines MJ, Smith DJ. Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study. JMIRx Med 2022;3(2):e32902 [FREE Full text]

Abbreviations

PGx: pharmacogenetic

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Peer-Review Report

Peer Review of “Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study”

Madara Hetti Arachchilage[1], PhD

Zoetis Inc, Urbana, IL, United States

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.06.21.21258931v1

Companion article: https://preprints.jmir.org/preprint/32902

Companion article: https://med.jmirx.org/2022/2/e37242/

Companion article: https://med.jmirx.org/2022/2/e32902/

(JMIRx Med 2022;3(2):e37513) doi:10.2196/37513

KEYWORDS

pharmacogenomics; pain management; drug-drug interaction; DDI; pharmacy; prescriptions; genetics; genomics; drug-gene interaction; pain

This is a peer-review report submitted for the paper “Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study.”

Review Round 1

General Comments

Authors of this manuscript [1] have determined the impact of pharmacogenetic (PGx) testing on pain medication prescribing. A retrospective analysis was conducted with 171 patients in a pain management clinic during 2016 to 2018 within the western United States. A novel deep sequencing (>1000X) PGx panel is described encompassing 23 genes combined with PGx dosing guidance, drug-gene interaction, and drug-drug interaction reporting to prevent adverse drug reaction events. This manuscript is interesting and well-written. However, the Methods and Discussion section of the manuscript could be improved for clarity. Please refer to my comments below.

Specific Comments

Major Comments

Abstract

1. What was the primary outcome of this study? Is it to report the number of cases where PGx information could be used to optimize drug dosing?

2. “This study demonstrates a successful implementation of PGx testing utilizing an extended PGx panel combined with a customized, informational report to help improve clinical outcomes.” Did authors develop a software platform to generate a customized, informational report to help improve clinical outcomes? I do not see any discussion on this matter. What were the parameters of the effectiveness and safety of treatment in evaluated patients? Did you do any statistical testing to find an association between the presence of a polymorphic gene variant and the impact of pharmacotherapy? Did you have a control group?

Introduction

3. I would be interested in having a brief introduction to currently available PGx panels, and what the strengths of the panel in this study are.

Methods

4. “23 genes were selected based on having the most clinical utility in PGx at the time of design in April 2016 (ADRA2A, CES1, COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DRD1, DRD2, F2, F5, GNB3, HTR1A, HTR2A, HTR2C, MTHFR, OPRM1, SLC6A2, SCL6A4, SLCO1B1, VKORC1).” What were the criteria used to narrow down genes that authors considered of most clinical utility in PGx?

5. “75 target regions were covered by 82 amplicons with an average amplicon size of 250 base pairs (bp)” Can you elaborate on 75 target regions? Did the authors have multiple target regions per gene? If so, details should be provided.

6. What were the medical conditions of patients with pain management in this study? Was it varied across patients in this cohort? I would like to see the authors’ discussion on this.

7. “PGx reporting were obtained retrospectively from patients (n = 171) in a pain management clinic representing an ethnically diverse patient population from 2016 to 2018 within the western

United States." Although authors report that they have an ethnically diverse patient population, no descriptive statistics on demographics, age, and clinical information was provided.

8. What factors were tested on urine toxicology and progress report?

Results and Discussion

9. While the manuscript describes 3 patients (patient A, B, and C) who did not stick to the treatment regimen and drug response adversaries, did patients who stuck to treatment regimens based on PGx testing show any side effects or did they do any survey for reporting pain symptoms? For example, were they tested for adverse drug reactions or partial or complete response to treatments?

10. I would like to see a discussion on key limitations of this study and further improvement on this study.

11. Have you looked into genotype frequencies of different ethnic populations in your study? What benefits do you anticipate by studying PGx-guided treatment interventions on diverse ethnic populations?

Conclusion

12. "This study demonstrates the predictive value of PGx testing combined with a customized informational report to help improve clinical outcomes, which resulted in increased utilization on patients in a pain management setting." On what basis do the authors claim increased utilization on patients in a pain management setting? Did you do any statistical analysis to back up this statement?

Conflicts of Interest

None declared.

Reference

1. Tagwerker C, Carias-Marines MJ, Smith DJ. Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study. JMIRx Med 2022;3(2):e32902 [FREE Full text]

Abbreviations

PGx: pharmacogenetic

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Peer-Review Report

Peer Review of "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study"

Mathew Mbwogge, MEPA, MSc

Related Articles:

Companion article: https://psyarxiv.com/ytz8p/

Companion article: https://med.jmirx.org/2022/2/e37241/

Companion article: https://med.jmirx.org/2022/2/e32859/

(JMIRx Med 2022;3(2):e37121) doi:10.2196/37121

KEYWORDS

Extended Parallel Process Model; COVID-19; lockdown; public acceptance; nonpharmaceutical measures; Likert scale; France

This is a peer-review report submitted for the paper "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study."

Round 1 Review

General Comments

The COVID-19 pandemic has led to huge psychological and social repercussions [1-3], affecting both the way people interact and their perception of the pandemic [4]. Nonpharmaceutical interventions including social distancing, stay-at-home orders, and curfews were found to be effective measures for reducing the number of cases [5] but may have increased psychological [6] and emotional [7] distress. The evaluation of nonpharmaceutical COVID-19 measures through the involvement of the public is key to determining their effectiveness and impact, as this may help develop more effective and user-friendly interventions.

The authors of the paper "Acceptance of COVID-19 preventive measures as a trade-off between health and social outcomes" [8] investigated the acceptance of COVID-19 preventive measures and its association with COVID-19 perception among 2004 subjects and found the acceptance rates for personal protective measures and collective measures to be 86.1% and 70%, respectively. They also found that acceptance of measures was positively associated with perceived efficacy, perceived severity, and fear. Other studies that investigated the public's acceptance of preventive measures found that moral considerations predicted higher acceptance for collective measures compared to personal considerations [9] and that men and younger individuals showed lower acceptance of preventive measures [10]. In addition, trust in science was found to be a greater predictor of adoption than trust in politics [10].

The paucity of published literature regarding this subject makes the present paper of high interest to the journal's readership. The paper's overall structure is in accordance with the journal's IMRD structure. The Abstract is well structured, summarizing the main points of the paper. The introduction is well-articulated in relation to implemented measures (with dates) and their evolution and is supported with references. The reported methods seem convincing, making use of the renowned Likert scale [11] in measuring the public's agreement to measures, as well as the Extended Parallel Process Model [12] that has also been deployed in other studies that examined the impact of preventive interventions [13]. There is a good flow in the data analysis justified with references, with an explanation of how they moved from statistically significant variables in model 1 to loading the multivariate model and, last but not least, the authors made the data readily available, which altogether gives meaning to the presented results. The discussion is well structured, even though informal, starting with the key findings followed by the interpretation, limitations, and conclusion. The English used is simple enough for the readership's understanding of the paper.

That said, this paper needs to be improved to better align with the journal's guidelines and be more appealing to its readership. Kindly refer to the specific comments below.

Specific Comments

1. Your title needs to follow the guidelines of the journal to which you are submitting.

2. The "Background" and "Methods" subsections of your Abstract need to be improved.

3. The specific objectives of the paper need to stand out as a subsection.

4. Major subsections are missing in your introduction, methods, and the results.

5. Some subsections in the Methods section warrant improvement.

6. The structure of the Discussion section needs to align with the guidelines.

7. The in-text citations and references must comply with the journal's guidelines.

8. Tables and figures in the appendix need to be moved to the body of the text.

Major Comments

1. Format your title to include the country and study design. Kindly refer to the guidelines for titles [14]. For instance, "Acceptance of COVID-19 preventive measures as a trade-off between health and social outcomes in France: Cross-sectional Study". By the way, I have not seen anywhere in the body of your paper where health and social outcomes mentioned in your title have been articulated.

2. The beginning of your background in the Abstract ("A better understanding of the factors underlying their acceptance may contribute greatly to the design of more effective public health programs during the current and future pandemics") does not make it clear to the reader to whom you are alluding. Kindly rephrase.

3. Your objectives need to be improved. I guess along the lines of (1) measure the public's acceptance of COVID-19 preventive measures and (2) assess the association of the public's acceptance of these measures and their perception of COVID-19.

4. In the "Methods" subsection of your Abstract, kindly add a summary of how data for each objective was analyzed and the statistical package that was used to perform the analysis. Please note that your Abstract (currently

5. It would be good to include the following items under Introduction after the background: (1) study rationale, to justify your study and to present the Extended Parallel Process Model, and (2) specific objectives, to clearly outline your study objectives.

6. Kindly start your Methods section with a subsection "Study Design" and specify your study design.

7. The statement under Participants and Procedures—that is, "The objective of the research was to assess the emotional, cognitive, and behavioral responses of the French people to the COVID-19 epidemic during the full lockdown (wave 1) and thereafter (wave 2)"—should not be there. You might want to move this to the study aim or specific objectives.

8. The second to last statement under Participants and Procedures ("For this study, we analyzed data from a 2-week survey administered 6-8 weeks after the first lockdown between June 25 and July 5, 2020") does not fit quite well under this subsection. I suggest you rephrase as "This was a 2-week survey administered 6-8 weeks after the first lockdown of June 25 through July 5, 2020" and incorporate it into your Study Design subsection.

9. The last sentence under Participants and Procedures needs to be moved to a section entitled "Ethical Considerations" to be created at the end of the Methods section (just before the Results section).

10. Kindly start your Results section with the subsection "Participant Characteristics" to give a summary of participant characteristics. Kindly move your Table 1 in the appendix to accompany your participant characteristics.

11. You need to move Tables 2-4 in the appendix to where they are first mentioned in the Results section for easy comprehension. It becomes easy to refer to the tables while reading. In addition, bear in mind that you are allowed to include up to a total of 5 tables in the body of your text.

12. Move Figure 1 to where it is first mentioned in your Results section.

13. Kindly organize your Discussion into (1) Principal Results, (2) Comparison With Prior Studies, (3) Study Limitations, and (4) Conclusion.

14. The in-text citations and references must be in line with the AMA citation style, in accordance with the journal guidelines [15]. Kindly refer to the references accompanying this report.

Minor Comments

15. Based on your title, I guess your study aimed to evaluate the acceptance of COVID-19 nonpharmaceutical measures. I suggest you add to your background (both in the Abstract and the Introduction) a study aim similar to the above and use the last sentence of your background in the Abstract to create a separate "Objectives" subsection before the Abstract's "Methods" subsection.

16. I suggest you rephrase sentence #2 in the methods subsection of your Abstract as "For objective 1, participants were asked the extent to which they supported 8 COVID-19 preventive measures using a 4-point Likert scale", and start the following sentence with "For objective 2, COVID-19 perceptions…"

17. In the results subsection of the Abstract, could you please include figures for positive and negative associations and highlight if these were statistically significant or not?

18. Kindly include "Likert scale", "France" and "Nonpharmaceutical measures" in your keywords.

19. Under Measurements, kindly substantiate your use of the Likert scale with suitable references. You might want to use this link [16].

20. For your beginning statement under Data Analysis, I suggest you use "frequencies (N)" instead of "numbers (N)".

21. I like the flow and harmony between Participants and Procedure, Measurements, and Data Analysis. You did well to have organized these by objective. In your Data Analysis, could you please highlight how you assessed the model fit (goodness of fit) of your multivariate model?

22. I suggest you organize your Results section, which already is in good shape, by study objective after "Participant

Characteristics" so that it flows well in the measurements and data analysis subsections.

23. Relating your study results to the title, readers might expect to see where you articulated the trade-off between health and social outcomes. This is not the case. It might be worthwhile to rephrase your title.

24. Kindly format your tables [17] and figures [18] following the journal guidelines.

25. I suggest you start your Conclusion by highlighting the study objectives.

26. It is important to include citations from the journal to which you are submitting or its sister journals.

Round 2 Review

General Comments

The authors of the paper titled "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study" [8] have implemented the recommendations to the letter. However, a new and close look warrants a few more modifications. Kindly refer to minor comments below.

Specific Comments

Major Comments

1. The phrase "The aim of this study was to evaluate the acceptance of COVID-19 nonpharmaceutical prevention measures in France", in the Objectives subsection should be moved to be the last sentence of the Background subsection in your Abstract.

2. Under Rationale, I think you should start the second sentence as "This study was based on the Extended Parallel Process Model."

3. The last sentence of your Rationale is not suitable for this section, so I suggest removing it.

4. The starting sentence of your Specific Objectives should be part of your Rationale instead, so you may want to move that from there.

5. All weblinks in the body of your text should be cited as references. The journal to which this manuscript is submitted does not allow the use of weblinks in the body of the text.

6. The phrases "EPPM factors were estimated using an unweighted least-square factorial analysis, followed by a Promax rotation, and 5 factors were extracted accordingly" and "The raw scale scores were transformed to a 0-100 scale. Higher scores in the respective scales are indicative of greater perceived efficacy, lack of fear control, severity, susceptibility, or avoidance" should be moved to Data Analysis.

7. Tables 1, 3, and 4 still need to be updated to comply with the journal guidelines. You will notice in this link [17] that item categories like "Age in years" and "Professional status" should be in their own row while the items under each category start on the next row.

8. As part of the participant characteristics, kindly include the mean age of participants and if the mean age difference between men and women was statistically significant.

9. Regarding your statement "The raw scale scores were transformed to a 0-100 scale", there is a serious debate about calculating Likert scale scores from responses. Kindly be clear on how you converted the responses to scores.

10. Kindly include your Figure 1 in the body of the text. All figures uploaded online must also be included in the body of the text, as per the guidelines.

11. Kindly move the first sentence of your Principal Results ("The aim of this study was to evaluate the acceptance of COVID-19 nonpharmaceutical measures and, more specifically, to measure the public's acceptance of these measures and their association with COVID-19 perceptions") to be the starting sentence of your Conclusion.

12. Kindly ensure that all percentages reported in the body of your text (apart from those from other studies) are expressed in absolute values in parentheses; for instance, 20% (5/25).

13. Evidence suggests that there are also issues around sex and gender reporting [19-21]. Since sex is biological, it will be good to make clear in your methods that the sex definition was based on self-reported sex [20].

Conflicts of Interest

None declared.

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PMID:

Peer-Review Report

Peer Review of "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study"

Sina Azadnajafabad[1]

Non-Communicable Diseases Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Related Articles:

Companion article: https://psyarxiv.com/ytz8p/

Companion article: https://med.jmirx.org/2022/2/e37241/

Companion article: https://med.jmirx.org/2022/2/e32859/

(JMIRx Med 2022;3(2):e37378) doi:10.2196/37378

KEYWORDS

Extended Parallel Process Model; COVID-19; lockdown; public acceptance; nonpharmaceutical measures; Likert scale; France

This is a peer-review report submitted for the paper "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study."

Round 1 Review

General Comments

This paper [1] tried to explore the acceptance of the COVID-19 preventive measures and their relationship with perception of the disease via an online survey among the French population. The overall drafted manuscript is acceptable; however, the notion of the paper is a little outdated and numerous publications regarding the COVID-19 are available now that used this method. Evaluation of policies like mask use mandates is not a hot topic now and may not add much to the evidence.

Conflicts of Interest

None declared.

Reference

1. Constant A, Conserve D, Gallopel-Morvan K, Raude J. Cognitive factors associated with public acceptance of COVID-19 nonpharmaceutical prevention measures: cross-sectional study. JMIRx 2022;3(2):e32859 [FREE Full text] [doi: 10.2196/32859]

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PMID:

Peer-Review Report

Peer Review of “Supporting Technologies for COVID-19 Prevention: Systemized Review”

Mathew Mbwogge

Related Articles:

Companion article: https://preprints.jmir.org/preprint/30344

Companion article: https://med.jmirx.org/2022/2/e38693/

Companion article: https://med.jmirx.org/2022/2/e30344/

(JMIRx Med 2022;3(2):e38606) doi:10.2196/38606

KEYWORDS

COVID-19; medical treatments; personal protective equipment; testing methods

This is a peer-review report submitted for the paper "Supporting Technologies for COVID-19 Prevention: Systemized Review"

Round 1 Review

General Comments

The need for effective and rapid response mechanisms to the COVID-19 pandemic has seen the emergence of new technologies. The European Parliament has organized such technologies into 10 broad categories. Many studies have reported the emergence of new digital tools as a direct response to COVID-19. While some of the studies report that these technologies make a major impact on the management of COVID-19 despite some challenges in their real-life usage, others acknowledge that COVID-19 control is critical, which calls for regular stocktaking, given the rapid advances in the field. Following the above, the authors of the paper “Supporting Technologies for COVID-19 Prevention: Systemized Review,” [1] in an attempt to stay on top of these advances, investigated the emerging technologies relating to the COVID-19 pandemic. The topic addressed in this paper is of interest to the journal’s readership and the international community. Being an important topic, it would have been important to report the review based on specific reporting guidelines to make it more appealing. The paper does not comply with the journal guidelines. Apart from the lack of a research objective, the paper is lacking in its methodology due to the lack of use of reporting guidelines. As such, the results remain doubtful. The general structure and English warrant improvement. If this paper must be brought to standard, the following specific comments are worth considering.

Specific Comments

1. The title of the paper does not conform to the journal guidelines.

2. The abstract of your paper needs to be structured following the recommended guidelines.

3. This paper neither has a research objective nor question to permit its evaluation.

4. You need to follow the guidelines of the journal to which you are submitting.

5. Kindly refer to the new PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist to see how you can report your search results.

6. You need to have a look at the reviews published in the journal you are submitting to.

7. The English of your paper needs to be improved.

8. The Methods section lacks clarity and warrants improvement.

9. Your references need to be in line with the journal guidelines.

The above specific comments are further divided into the below major and minor comments.

Major Comments

1. Firstly, you need to identify and report the type of review you conducted, to help in the evaluation of your paper. If this is a narrative review, kindly indicate clearly in your paper.

2. The title of your paper needs to be structured in line with the journal guidelines. I suggest the following: (1) Emerging Medical Technologies for Fighting COVID-19: Systematic Review; or (2) Emerging Medical Technologies for Fighting COVID-19: Narrative Review

3. Your abstract needs to be structured in line with the journal guidelines, to include the Background, Objective, Methods, Results, and Conclusion subsections. Additionally, be aware that the PRISMA checklist also provides additional information that must appear in the Abstract section of systematic reviews.

4. Kindly restructure the manuscript using the IMRD format using the following word template;

5. It is absolutely important to read through the journal guidelines to which you are submitting.

6. Kindly put your study in context as part of your introduction. Use the provided reference if you need help with how to put your study in context.

7. This study is without a research objective. State your research question and objectives.

8. Kindly report the Methods section using the subsections below:

- Study objectives
- Eligibility criteria for selected studies
- How literature was searched
- The method used to synthesize results
- Data management and analysis
- Quality assessment (including the risk of bias assessments)
- How missing data were handled
- Heterogeneity assessment
- The method used to present data and results

The above may vary depending on the type of review you undertook. A simple literature review of emerging technologies will normally not require some of the above subsections.

9. It is very important to indicate the guidelines used to report your review results.

10. Your results section should be reported based on your research objectives (yet to be defined) and should include the following:

a. Search results: [a] flow diagram based on the new PRISMA flow chart and [b] characteristics of included studies (table and discussion).

b. Risk of bias assessment

c. Synthesis results (report results based on objectives and the different technology categories)

d. Overall assessment of the body of evidence

e. Heterogeneity

Again, as highlighted above, a literature review will not require some of the above points (eg, assessment of overall evidence and heterogeneity). That said, if you carried out a narrative review, I suggest using the following reported guidelines. I also find the structure of this referenced narrative review and systematic review more robust (use these as references in reporting your review). In reporting a narrative review, it is important to bear in mind how narrative reviews are evaluated. Moreover, be aware that review papers are expected to be submitted with a filled template of the guidelines used.

11. You need to have a look at studies that have reported on similar topics for inspiration.

12. See guidelines for the structure of the Discussion section. Present your Discussion into (1) principal findings and (2) comparison with prior studies.

13. Kindly include a subsection “study limitations” as part of the Discussion section.

14. Your references have to be in line with the recommended journal guidelines. Set your reference manager to the American Medical Association (AMA) citation style and make sure to include a PubMed ID at the end of each reference. You can search the PubMed IDs of various articles at https://pubmed.ncbi.nlm.nih.gov. In the absence of a PubMed ID, kindly include a DOI (verify your DOIs using https://www.doi.org/).

15. Include a subsection “Author Contribution” after the Acknowledgments section to state the contribution of each author included in this paper.

16. Include a subsection “Conflicts of Interest” after Author contributions to declare any conflict of interest.

17. Kindly list all Multimedia Appendices before the References.

18. For referenced websites, ensure to make as much effort as possible to get and reference the PDF version of the article (ie, in the absence of a PMID and DOI).

19. Create a section “Abbreviations” after your references to list and expand all abbreviations in the text.

20. I suggest starting your Conclusion with a statement on the study objectives followed by a summary of findings, then lessons learned from your findings, and finally, suggested direction of future research.

Minor Comments

1. Kindly include only the corresponding author in the manuscript and create/include all coauthors in the metadata section of the online manuscript management system (MMS) of your journal profile.

2. End your introduction with the aim of the study.

3. Kindly format your table following the journal guidelines.

4. You may want to start your Table 1 with study ID, by merging columns 1, 2, and the last as 1 column. For instance, the first cell will be “Rendeki et al,” followed by “setting or country” in the second column, and then the description, etc.

5. Following from (24) above, I recommend having (1) a table of characteristics of included studies for each category of technology or (2) present a single table of “Characteristics of included studies” under the Search Results subsection of the Results section, after the PRISMA flow diagram.

6. I suggest attempting to format your Figure 1 following the new PRISMA diagram.

7. Review all your figures and their captions in line with the guidelines. Apart from being uploaded as Multimedia Appendices, all figures must appear in the body of the text where they are first mentioned. Use a single sentence as the caption for each figure, which should appear at the bottom of the figure.

8. Following from (7) above, you may want to combine figures (a) to (i) to form a single figure as is the case with Figure 4.

9. I advise downloading Grammarly to assist you with the editing of your paper.

10. There is a need to justify your outcome prioritization. I suggest organizing your technology categories in line with the European Parliament categorization.

11. Ensure that titles and subtitles of your "Comparison with Prior studies" subsection of the Discussion are the same as the titles and subtitles of your Results section (Prevention, Diagnosis, Treatment, etc), and as suggested in (10) above.

Round 2 Review

General Comments

I acknowledge that the authors of the paper titled "Supporting Technologies for COVID-19 Prevention: Systemized Review" [1] have done well to improve on the overall structure and presentation of the paper, with a much better flow. Comments that were made in the previous round were based on the understanding that this was a standard "systematic review" type paper, but this is not the case. However, this paper still warrants some improvements. Kindly refer to the below major comments.

Specific Comments

Major Comments

1. Systematic reviews require a predefined robust search strategy that is exhaustive, has an appraisal scheme for each type of study (both risk of bias and quality) with well-cited tools, has a clearly outlined method for synthesizing results, has a method of assessing all the evidence emanating from the literature, and most especially, has a clearly stated guideline used in reporting the review. Given that this review does not formally appraise the included studies for risk of bias and quality, neither does it have a clearly outlined method of synthesis, it will be appropriate to identify your study either as a (1) literature review, (2) systemized review, (3) narrative review, or simply (4) overview, none of which forcefully require a comprehensive search and formal appraisal of studies, and are not typically aimed at a narrative synthesis. It is enough to note here that even "systematic reviews with narrative synthesis" and "rapid reviews" that may omit some aspects of a standard systematic review follow specific citable guidelines in their methods and synthesis approach, to say the least.

2. It is absolutely important to bear in mind that reviews have their terminologies, as is the case with randomized controlled trials or other studies. You wrote "In this paper, 150 news articles and scientific reports on COVID-19–related innovations during 2020-2021 were firstly checked, screened, and shortlisted to form a pool of candidates yielding a total of 18 publications for review" and yet elsewhere you said, "After the initial candidates were selected, they were subjected to eliminating evaluations." I do not think the term "candidate" can be used to refer to records retrieved in reviews. You may want to rephrase those and elsewhere (Introduction and Methods sections) in the body of your text and use "records" or "articles" instead.

3. Your "results" and "conclusions" subsections of the Abstract are not robust in a way that helps the reader understand what you found and what you learned or deduced from the findings and your recommendations. Kindly include a sentence or two each for personal protective equipment, testing methods, medical treatment, and other considerations in the "results" subsection.

4. Kindly include the following phrase in the "methods" subsection of your Abstract: "The keywords 'COVID-19 technology,' 'COVID-19 invention,' and 'COVID-19 equipment' were used in a Google search to generate related news articles and scientific reports." Additionally, indicate when (exact date) the search was performed.

5. Regarding your PRISMA diagram, your numbers for records identified from other databases (websites) do not add up. You excluded 15 articles from the 30 you sought to retrieve, and it follows that you apparently excluded all 15 articles you assessed for eligibility, but you contradictorily still included the 15 articles in this review. Kindly verify and correct your PRISMA chart.

6. Your PRISMA diagram shows that you searched other websites other than Google; it will be absolutely helpful and more robust to indicate these websites under your "Search strategy."

7. You did well to have included the PRISMA flow. Kindly substantiate your phrase "The selection of the article followed the guideline of PRISMA 2020" with a suitable reference.

8. Under "Testing methods" in your Results section, kindly also allude to "pooled" and "rapid testing (serology and antigen)" technologies as these are indispensable innovations to increasing the turnaround time and for timely detection. This updated Cochrane review as well as this list of 42 rapid testing technologies considered to be of acceptable performance by the UK government can help you identify suitable new technologies to add to this review. Regarding their pros and cons, it might be worthwhile to also look at the extent to which information provided by manufacturers is helpful for each technology considered if possible.

9. Coming to your Study Limitations, your phrase "Also, the paper only provides a quantitative comparison between the technologies" does not seem to be coherent with your synthesis approach. I think this should be a qualitative comparison since you made use of textual descriptions to draw similarities and dissimilarities between the data. Tabular presentations facilitate the narrative but do not make it quantitative. Kindly phrase and include the following in your Study Limitations as well:

a. The search strategy was not comprehensive as it was limited to 1 database (Google).

b. The fact that the protocol was not registered with PROSPERO (international prospective register of systematic reviews) might have affected the results in one way or the other.

c. Even though you unveiled some of the complexities regarding supporting technologies, a quantitative analysis would have also added value to the review results.

d. You did not do a formal appraisal of the included studies and the overall evidence from included studies. This must have affected your results.

10. Tables 1 through 3 make up 17 articles instead of 18 according to the number of retained articles. Kindly verify.

Minor Comments

1. Your "Conflicts of Interest" should follow the journal guidelines. Kindly use "None declared."

Round 3 Review

General Comments

Unfortunately, I still have the 3 following concerns.

Specific Comments

Major Comments

1. Recommendation #3: I am happy that the authors of this paper [1] improved on the results following the recommendation in point 3, but this recommendation was primarily referring to the Results and Conclusion subsections in the Abstract. The current wording in the Results of the Abstract should be moved to the Methods subsection of the Abstract. This means that you are yet to produce a summary of your findings (results) in the Abstract. Additionally, kindly increase the word count of the Conclusion subsection in the Abstract to reflect the main Conclusion of the paper.

2. The authors have also done well to have deployed the current PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flowchart. However, your flow diagram shows that you included 5 articles from a previous version of this review indicating this paper is about updating a previous review, and I do not think it is the case. Except otherwise, kindly leave this box empty and move this number (n=5) to either "Records identified from Databases" or "Records identified from Websites." My humble suggestion is that since you seem to have identified 200 records from Google search and ScienceDirect, under "Records identified from Databases (n=200)," kindly specify "Google=150" and "ScienceDirect=50" for readers to be clear about how many articles were retrieved from which database. Under "Records identified from Websites," kindly put "n=5," assuming that the 5 previously published reviews were identified from websites. If these were identified through Google search, ScienceDirect, or Cochrane, then kindly include under Records identified from Databases and leave "Records identified from Websites" empty.

3. You need to correct your statement "Three previous review papers were also included" as this seems to be 5 in the flow diagram.

Conflicts of Interest

None declared.

Reference

1. Zhao Z, Li R, Ma Y, Islam I, Rajper AMA, Song W, et al. Supporting Technologies for COVID-19 Prevention: Systemized Review. JMIRx Med 2022;3(2):30344 [FREE Full text]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO: international prospective register of systematic reviews

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PMID:

Peer-Review Report

Peer Review of “Supporting Technologies for COVID-19 Prevention: Systemized Review”

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/30344

Companion article: https://med.jmirx.org/2022/2/e38693/

Companion article: https://med.jmirx.org/2022/2/e30344

(JMIRx Med 2022;3(2):e38728) doi:10.2196/38728

KEYWORDS

COVID-19; medical treatments; personal protective equipment; testing methods

This is a peer-review report submitted for the paper "Supporting Technologies for COVID-19 Prevention: Systemized Review".

Review Round 1

General Comments

The manuscript [1] talks about medical technologies during COVID-19. The review is nice to read. I could not find Table 2.

Specific Comments

Major Comments

1. My main concern is that several technologies are missing, so I am not sure if the review on Google search was carried out properly. There must be definitely over 90 technologies. If you check the Federal Drug Administration (FDA) In Vitro Diagnostics, there are over 240 test kits alone. Additionally, I am not sure how you reach to 38 items from 90, or are there so many unrelated items?
2. The images in the figures, especially on company products, need actual permission from the original company or inventor. For example, the image citing reference 2 is a Britsh Broadcasting Corporation (BBC) article, but the actual image is from a hospital whose permission is needed, rather than citing BBC.
3. Several topics are outdated as of now, such as personal protective equipment. The interest in smart or green personal protective equipment has declined dramatically as vaccination has picked up. Therefore, the text needs to be aligned with current needs, such as low-temperature storage technologies to store vaccines, etc. The ventilators section is interesting, but such images have been shown before in many places. As such, it will be difficult to garner readership based on the sections.
4. Several points are being repeated throughout the manuscript, such as lack of manpower and resources. The flow of the text could be more fast paced by removing general statements and sticking to facts only.
5. New and interesting topics could be added based on the current status of the pandemic, such as technologies centering around vaccination or at-home testing.

Conflicts of Interest

None declared.

Reference

1. Zhao Z, Li R, Ma Y, Islam I, Rajper AMA, Song W, et al. Supporting Technologies for COVID-19 Prevention: Systemized Review. JMIRx Med 2022;3(2):30344 [FREE Full text]

Abbreviations

BBC: British Broadcasting Corporation
FDA: Federal Drug Administration

Edited by E Meinert; submitted 13.04.22; this is a non–peer-reviewed article;accepted 14.04.22; published 24.05.22.

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Peer-Review Report

Peer Review of “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study”

Anonymous

Related Articles:

Companion article: https://arxiv.org/abs/2108.06820

Companion article: https://preprints.jmir.org/preprint/32935

Companion article: https://med.jmirx.org/2022/2/e38549/

Companion article: https://med.jmirx.org/2022/2/e32935/

(JMIRx Med 2022;3(2):e38519) doi:10.2196/38519

KEYWORDS

SARS-CoV-2; COVID-19; variants of concern; case fatality rates; virulence; vaccine effectiveness; correlation study

This is a peer-review report submitted for the paper “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study.”

Round 1 Review

General Comments

This paper [1] used ecological data to study the correlation between SARS-CoV-2 variants and the fatality rates. It introduced a new indicator to correct for the lagging of the reported death since the initial infection. When applying this indicator to different countries, it demonstrated that the spreading of variants coincided with the surge in death while also acknowledging the potential confounding factors such as vaccination rates. Although the conclusions drawn in this paper showed some inconsistency with other observational/community-based epidemiological studies, the paper also explored the correlation between disease risk factors and the reported death.

Specific Comments

Major Comments

1. The author should provide more characterizations of the proxy case-fatality rate (pCFR). For example, the author should compare the pCFR and the case-fatality rate (CFR) while doing the analysis, such as correlation analysis.

2. The author mentioned “One could equally well average the infection rate over the period from 28 to 14 days,” but no figure was also presented. Comparing different parameters used to construct the pCFR is essential for the reader to evaluate the robustness of the proposed indicator.

3. Related to the first point, the author should probably also compare the raw CFR 7-day rolling average and the pCFR 7-day rolling average.

4. The death rate is also related to the capacity of the health care system, such as available intensive care unit (ICU) facilities or bed occupancy. Thus, the CFR on a particular day might also depend on the CFR (as an approximation to the ICU occupancy) the day before. While the author reported the absolute pCFR percentage in most of the figures, these results should also be confirmed by replotting the percentages as relative percentages. For example, one could report the daily pCFR as the percentage change to the previous day (or the previous 7-day rolling average).

5. By doing point 4 above, the relative pCFR can be used to compare different included countries that have daily CFRs that are highly variable.

6. The risk factor correlation analysis can be misleading. The author should state very clearly that ecological data were used for the analysis, both in the Introduction and Discussion sections. It has been shown that a population-based correlation provided little insight into understanding the disease pathology. (Portnov B, Dubnov J and Barchana M. On ecological fallacy, assessment errors stemming from misguided variable selection, and the effect of aggregation on the outcome of epidemiological study. J Expo Sci Environ Epidemiol 2007; 17:106-121).

7. It is unclear that the definitions of each of the variables (risk factors) are included in the correlation analysis. While I assume it is the same as those cited in the second reference, some of the analysis methodologies seem imprecise. For example, epidemiologists usually model the age as ordinary variables and test for the trend (eg, using ANOVA) but not by using the

median age. The author might want to revisit some of the analyses performed.

8. As the author also pointed out, many of these risk factors are correlated with each other. A better way to adjust for these potential confounding effects is by modeling all these risk factors in a regression model.

9. The author should explain the choice of "shift by 60 days" in Figure 12.

Minor Comments

10. The author should consider unifying the color scheme used in the manuscript. For example, some figures are plotted in grayscale, but similar figures can also appear in a colored version.

11. In equation 2, "Total cases on day (N-14) - Total cases on day (N-21)," the "-" between the two phrases can be misleading. The author should consider rewriting the "-" as "to."

12. The author should also consider replotting the correlation analysis into heat maps. The author did not justify the use of a line plot for plotting each risk factor.

13. Furthermore, the author should consider clustering the risk factor and plotting a dendrogram with the heat map. Therefore, it will give readers a better idea of the correlation among each risk factor and the correlation among each of the cutoff dates (in Figure 6) or regions (in Figure 7).

Round 2 Review

This draft has been greatly improved but the author should still consider the following:

1. Rewrite the denominator of equation 11 using the summation sign

2. In the current manuscript, equation 2 appeared before equation 1.

3. There were multiple equation 2s. Equation 1 also appeared twice: in the main text and in the supplementary text.

4. It is better to always mention the year for the date/period that was referenced in the manuscript (eg, "B.1.1.7 (Alpha) and B.1.351 (Beta) strains dated from mid-October and mid-May respectively" and "that could be due to masking by the fraction of Delta cases peaking in Argentina in mid-May" in the Result section).

5. The meaning of the statement "The positive aspect of that limitation is that trends in pCFR can spot burn through cases in unvaccinated of less than vigilant groups" is unclear.

6. The author mentioned "The red points are due to anomalous entries in the tables of (13)" in the Result section. It would be better to clean the data for the suspected anomalous entries mentioned in the Methods section while plotting the smoothened graph.

7. Regression results should be listed in tables that show (at least) effect size and *P* value.

Conflicts of Interest

None declared.

Reference

1. Barletta WA. The influence of SARS-CoV-2 variants on national case-fatality rates: correlation and validation study. JMIRx Med 2022;3(2):e32935 [FREE Full text]

Abbreviations

CFR: case-fatality rate
ICU: intensive care unit
pCFR: proxy case-fatality rate

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Peer-Review Report

Peer Review of “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study”

Ramesh Poluru[1], PhD

The INCLEN Trust International, New Delhi, India

Related Articles:

Companion article: https://arxiv.org/abs/2108.06820

Companion article: https://preprints.jmir.org/preprint/32935

Companion article: https://med.jmirx.org/2022/2/e38549/

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(JMIRx Med 2022;3(2):e38522) doi:10.2196/38522

KEYWORDS

SARS-CoV-2; COVID-19; variants of concern; case-fatality rates; virulence; vaccine effectiveness; correlation study

This is a peer-review report submitted for the paper “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study.”

Round 1 Review

I would like to appreciate the author for this study [1] addressing the influence of SARS-CoV-2 variants on national case-fatality rates. The manuscript is concise and well written, and is recommended for possible consideration in its current form.

Before publishing the manuscript, I suggest the author presents an Appendix with (a) data with absolute numbers, (b) illustration for smoothed values of the proxy case-fatality rate for at least one country (Figures 8-11), and (c) alternatively discussion on the analytical framework in detail in the Method of Analysis section.

In conclusion, the subject addressed in this manuscript is worth investigation, and the manuscript is recommended for possible consideration after addressing the above minor concerns.

Conflicts of Interest

None declared.

Reference

1. Barletta WA. The influence of SARS-CoV-2 variants on national case-fatality rates: correlation and validation study. JMIRx Med 2022;3(2):e32935 [FREE Full text]

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Peer-Review Report

Peer Review of “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study”

Mathew Mbwogge, MSc

Related Articles:

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KEYWORDS

SARS-CoV-2; COVID-19; variants of concern; case-fatality rates; virulence; vaccine effectiveness; correlation study

This is a peer-review report submitted for the paper “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study”

Round 1 Review

General Comments

Emerging variants of concern (VOCs) have increased the uncertainty about bringing the pandemic to an end [1]. Countries will not only have to focus on stepping up vaccination efforts but effective surveillance as well to monitor and characterize the more transmissible and deadly variants [2-5]. The most prominent confirmed cases include Alpha, Delta, Beta, Eta, and Kappa [6]. This, in addition to flagging the need for more sustainable measures, raises concerns over their impact on case-fatality rates (CFRs) in different countries.

The authors of the paper [7] “The influence of SARS-CoV-2 variants on national case fatality rates” attempted to investigate the impact of VOCs on (1) proxy CFRs and (2) the vulnerability of persons living with comorbidities, using open source data of reported daily cases. They found little variations in the association between World Health Organization data-driven factors and the average proxy CFR and concluded that the increase in the impact of VOCs may be attributed to the fact that those living with comorbidities are more susceptible to infection severity. Other studies that evaluated the impact of new variants found them to be associated with higher rates of hospitalization and death. In the United Kingdom for instance, studies among cohorts infected with the B.1.1.7 variant (VOC-202012/1) compared to those with normal infections found an increased risk of hospitalization [4] and deaths [5,8,9] in the intervention group, using the TaqPath assay. According to expert opinion on some of these results, patients with the Kent or Delta variant (B.1.1.7) were 64% more likely to die [10]. The CFR was higher among men than women and increased with age.

This paper has been structured in compliance with the IMRD approach. The authors capitalized on prior published data and the concept on which the analysis was based [11] to generate new data, which seems logical. The English used is simple enough for the readership but demands improvement.

Even though the paper’s methods and analysis are based on a published concept, the fact that this was done by the same authors and no other authors have been cited making use of the same concept makes the paper’s methods weak. The study rationale has not been well established, thereby making the study objectives and research questions less robust. Besides, not only is data about variants of concern lacking and the interpretation of the results not well articulated, but the conclusion also arrived at is not clear enough in relation to the defined objectives. Kindly refer to the following major and minor comments.

Specific Comments

Major Comments

1. Kindly refer to the journal guidelines to see how titles are formatted. Well-formatted titles should include the main outcome of interest, the subject matter, and the study design.

2. Your interest is to measure the influence of VOCs, not SARS-CoV-2 variants as reflected in your title. You may want to correct that.

3. Your abstract must include (1) Background, (2) Objective, (3) Methods, (4) Results, and (5) Conclusions. Kindly use this source to see how to structure your paper [12].

4. The phrase I quote “may increase the vulnerability of persons with certain comorbidities” in the Abstract is not an objective.

Kindly rephrase together with the first objective that appears too long.

5. You need to include (1) Study Rationale and (2) Specific Objectives in your Introduction as subsections. The "Specific Objectives" subsection should normally be the last part of your Introduction.

6. In your Study Rationale, make efforts to trace other studies that have made use of similar methods in predicting the impact of VOCs. This section needs to at least include some basic data about VOCs (prevalence or impact on hospitalizations and mortality). You may want to make use of this reference [6].

7. Given that this paper is based on VOCs, it would be sensible to include in your Introduction and as part of your background literature evidence of a literature review of the different VOCs (their characteristics and virulence). Readers will be keen to discover the new variants in circulation. The availability of data on VOCs and variants under investigation is key because it flags the need for vaccination, increases uptake, and signals policy makers about the importance of modifying surveillance policies.

8. If you decide to include research questions or hypotheses to be tested in your paper, kindly associate these with your research objectives. This makes it easy for readers to see how you transformed each objective into a question, as well as the hypothesis to be tested.

9. Kindly start your Methods section with the subsection "Study Design" and clearly state your study design. This is particularly important not just for reviewers but for those undertaking systematic reviews.

Studies are often excluded or not simply traced as a result of a lack of a clearly stated research design. Besides, it is the place of the author to inform readers of the study design and not for readers to determine the design that was used. Authors making use of study designs that are new to the journal's readership always make an effort to cite articles making use of similar designs regarding the subject matter.

10. I suggest structuring your Methods section as follows:

- Study design
- Data sources and setting (including providing a brief description of each country being profiled and the triggers and specific reasons for choosing particular countries to include in your analysis)
- Study variables/outcomes (kindly specify here, the comorbidities you were interested in together with definitions for outcomes like case fatality)
- Data analysis (include equations here and specify any underlying assumptions). Clearly explain how you run the correlations and time series, and report any statistical program that was used.

11. Explain how adjustments for age, sex, ethnicity, type of VOC, seasonality, etc, in the correlations were made. For instance, the impact on the national CFR may be contingent on the type of variant [13]. Comorbidities may exacerbate during winter and make it difficult to attribute increased mortality among those with comorbidities to VOCs [10].

12. In your data analysis, kindly explain how you arrived at using the Pearson product moment correlation. Kindly justify if your data was linear and report the values of normality tests that were performed prior to choosing the approach of analysis.

13. Kindly report how the different linearity assumptions were verified (for linear data).

14. In your data analysis, kindly report how you determined the strength of association between the proxy national CFRs and the different covariates.

15. The Results section seems to be a mix of data analysis, results, and discussion. Kindly move texts relating to the above to their respective subsections. For instance, readers will not expect to see any explanations in the Results section as this should normally appear under discussion, where you normally should explain why results appear the way they are. Additionally, equations relating to data analysis should not appear under results.

16. A look at your study results shows that this paper has 3 objectives I state (1) to assess the fluctuations in the daily proxy national CFRs, (2) to investigate the correlation between average national proxy CFRs and potential cofactors/comorbidities, and (3) to describe the correlation between proxy national CFRs of country pairs by region. You might want to amend your study objectives accordingly.

17. I suggest you organize and report your results by objective (1, 2, and 3) for a better flow.

18. You reported to have made use of the Pearson correlation coefficient but have not reported the coefficients obtained from the correlation anywhere. Kindly clarify.

19. Kindly structure the Discussion section following the journal guidelines. I suggest:

- Summary Findings
- Strength and Limitations
- Interpretation of Results
  - Fluctuations in the daily proxy national CFRs
  - Linear correlation of the averaged CFR and potential cofactors
  - Linear correlation between proxy CFRs for country pairs by region
- Implications for Policy and Research
- Conclusion

20. Your need to compare your results with those of other studies in your "Interpretation of Results" in your discussion, by citing other studies on the same subject matter and preferably undertaken in the same countries being profiled. This helps to situate the study within the existing literature. I understand this might be challenging for some objectives. Kindly provide explanations for the results in the event of a lack of suitable studies.

21. Your conclusion needs to state your results within the context of your study objectives and give the significance and implications to future research, surveillance, and policy.

22. Kindly refer to the guidelines for referencing or have a look at published articles in the journal to which this work is submitted. Your references need to follow the AMA citation style. Please refer to the references of this report.

Minor Comments

23. The Methods subsection of your Abstract needs to summarize your study design, data sources, and how data was analyzed including any statistical packages.

24. Kindly ensure that the conclusion of your paper is under the subtitle "Conclusion."

25. Move all abbreviations to the end or as the last section of your paper.

26. Please be aware that you are not allowed to include more than 8 figures in your paper. You may want to merge some and move others to multimedia appendices. I did not find Figure 2 very necessary and you might want to move that.

27. All figures to be published in the body of your paper must also be uploaded online. Kindly refer to the journal guidelines.

28. I suggest moving Table A to the "Data Sources and Setting" subsection and labeling it as Table 1.

29. You need to cite more papers including those from the journal to which you submitted.

30. Kindly include a PubMed ID at the end, for each reference (searchable at crossref.org). Kindly refer to the references in this peer-review report.

31. Endeavor to cite the PDF version of articles for all web links if possible.

Round 2 Review

General Comments

I am happy that the authors of the paper titled "SARS-CoV-2 variants of concern: Influences on national case fatality rates" have addressed all concerns raised in the previous round, thereby giving the paper a new and improved outlook. However, these have not been addressed in a manner satisfactory enough. The study title even though modified from "The influence of SARS-CoV-2 variants on national case fatality rates" still needs to comply with the journal guidelines [12]. The study objectives are not consistent across the different sections. Some sections need to be reorganized for a better flow. The English used for reporting warrants improvement. Kindly refer to the below minor comments to improve the paper further.

Specific comments

Minor comments

1. Could you please identify this study as a "Correlation Study" [13]? For instance "The influence of SARS-CoV-2 variants on national case-fatality rates: Correlation and Validation Study"

2. The current text in the Results subsection of the Abstract should be part of the Methods subsection of the Abstract. Kindly move it to the start of your Methods subsection. Could you please summarize your findings into say 5 to 10 lines in the Results section of your Abstract? One will expect to see some figures reported from the main results in this subsection. You may want to ensure that your word count for the Abstract is not above 450 by decreasing the word count in your Methods and Conclusions subsections.

3. The discoverability of your paper can be improved by including SARS-CoV-2, COVID-19, and 2019-nCoV in your keywords. Kindly modify "Country correlation" to "Correlation study."

4. The Objectives section of your Introduction seems to include the study background information; otherwise, I do not understand why it should be that lengthy. Kindly move the subtitle "Objectives" (better phrased as "Specific Objectives") to the end of your Introduction and state your specific objectives. The Objectives subsection should not be more than a paragraph. All other text should either be part of your study background literature or rationale. The Specific Objectives subsection should be formatted as follows:

"Specific Objectives

The principal objectives of this study are to (1) establish a valid proxy national CFR and assess its daily fluctuations, (2) investigate the correlation between average national proxy CFRs and potential cofactors/comorbidities on a global and regional basis, and (3) describe the correlation between proxy national CFRs of country pairs by region."

Please do not include any other text before the Methods section. Additionally, kindly ensure that the above specific objectives and those in your Abstract are the same for consistency.

5. The use of the word "reference" in most of your statements (eg, "To evaluate any changes in the susceptibility to co-factors, one can follow the method introduced in reference") may not be appropriate. I suggest you state author names instead of using "reference" when referring to a particular research work. Kindly rephrase these all through the body of the manuscript.

6. For standard reporting and to be in line with the journal guidelines, I suggest replacing the title "Method of Analysis" with "Methods." It will be good to identify this study as a "Correlation and Validation" study under your "Study Design" subsection. This should be a single statement or at most 5 lines if you need to explain why you used the design and make reference to other papers.

7. Regarding your analysis approach in the study methods, it will be good to provide a few lines on how each of the assumptions for running a Pearson product moment correlation was satisfied [14].

8. Kindly change the title "Discussion and Conclusion" to "Discussion." I still suggest you structure your Discussion in line with the journal guidelines [15]. You may want to refer to papers published in JMIR to help you with how to structure the Discussion section. Based on journal guidelines, well organized and standard Discussion sections will bring out the subtitles (not as paragraphs) "Summary of Findings," Study Limitations," "Comparison With Prior Studies," and the "Conclusion." Even in a situation where you do not have enough papers to cite under "Comparison With Prior Studies," the subsection will still

include your reasons and explanations of why results appear the way they do.

9. I guess your current Conclusion that appears quite lengthy includes materials for the Discussion section. Kindly size down and move a majority of the material to the Discussion section (specifically to the "Comparison With Prior Studies" subsection).

10. I note that the "Summary of Findings" in the Discussion should be a carbon print in terms of length and text of the "Results" subsection in the Abstract. For coherence and consistency, the more you can make these the same, the better. The same should be the case with the "Objectives" subsection in the Abstract and the "Specific Objectives" subsection at the end of your Introduction.

11. Kindly define a study aim in one sentence based on your 3 specific objectives and start your Conclusion with this study aim. This reminds readers of what you set out to do and helps them marry it with what you found. This should be followed by the main findings in just a few lines, lessons learned, what the findings mean for public health, and future research.

12. Just like the "Summary of findings," it is common practice not to expect the Conclusion of a paper to be lengthy since all explanations relating to the results should be part of your "Comparison With Prior Studies" subsection in the Discussion.

13. As per the journal guidelines, kindly move your Abbreviations subsection to after the references.

14. Ensure you follow the journal guidelines to report your P values.

Conflicts of Interest

None declared.

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Abbreviations

CFR: case-fatality rate
VOC: case-fatality rate

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Peer-Review Report

Peer Review of "The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study"

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Related Articles:

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KEYWORDS

SARS-CoV-2; COVID-19; variants of concern; case-fatality rates; virulence; vaccine effectiveness; correlation study

This is a peer-review report submitted for the paper "The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study."

Round 1 Review

General Comments

This paper [1] presents the changes in the case-fatality rate (CFR) due to COVID-19 variants in different countries.

Specific Comments

Major Comments

1. Abstract

1.1. Should include a conclusion section

1.2. Results: A summary of the results in terms of variation in CFR according to the variants needs to be mentioned.

Main Manuscript

2. Objective

2.1. Specify the year for November 1

2.2. Figure 2: What do the different shades indicate? It should be clarified in the footnote. November spelling.

3. Methods of Analysis

3.1. Data sources should be specified for the different countries. The analysis should also mention the methods used for data analysis and presentation in the tables. The data on the infected case load should be used along with the CFR/proxy CFR (pCFR).

3.2. pCFR: Full form when used first. The proxy CFR or pCFR should be used consistently in the text.

4. Results

4.1. Figure 7: What was the source of the data for the cofactors in these countries? It should be specified.

4.2. Correlation between regional CFRs: The pairing of the countries should be mentioned in the Methods. Which statistical test was used for this correlation analysis? This should be mentioned in the Methods.

5. Discussions and Conclusions

Discussion and Conclusion should be separated.

Conflicts of Interest

None declared.

Reference

1. Barletta WA. The influence of SARS-CoV-2 variants on national case-fatality rates: correlation and validation study. JMIRx Med 2022;3(2):e32935 [FREE Full text]

Abbreviations

CFR: case-fatality rate
pCFR: proxy case-fatality rate

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Peer Review Report

Peer Review of “Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers’ Perspectives”

Anonymous

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Companion article: https://med.jmirx.org/2022/2/e33025/

(JMIRx Med 2022;3(2):e37050) doi:10.2196/37050

KEYWORDS

pediatrics; caregivers; health care services; public hospital; Malaysia; public-private-partnership; children

This is a peer-review report submitted for the paper “Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers’ Perspectives."

Round 1 Review

General Comments

Thanks for the opportunity to review this manuscript [1] entitled “Caregivers’ Perspective—Satisfaction With Healthcare Services at the Paediatric Specialist Clinic of the National Referral Centre in Malaysia.” The authors report on an important topic, and their research work will contribute to the existing literature. Overall, the manuscript is well written with enough details in different sections. The tables are informative. The following are comments/concerns for the authors to consider.

Specific Comments

- Abstract: include data/numbers in the Results section rather than general summary statements
- Introduction: include any a priori hypotheses
- Introduction: to support the rationale for the review, the authors should include additional recent promising evidence that supports the feasibility, acceptability, and efficacy of digital health interventions in different chronic medical conditions to provide context for the applicability of lessons learned in the study across other fields [2-7].
- Discussion: two recent reviews focused on pediatric/adolescent care and COVID-19 with mobile health (mHealth)/eHealth and adolescent/children psychosocial well-being, both worth discussing [8,9]
- Discussion: the authors could consider including a paragraph on study strengths.
- Discussion: it is critical to discuss the value of including direct patient input in the development of mHealth interventions, and other key considerations for end users should be sought early on in the process of app or digital health intervention design to ensure long- and short-term engagement [10-13].
- Discussion: the authors should expand and elaborate more on how their findings support or contrast available literature and provide suggestions for future research directions that would address existing knowledge gaps.
- Discussion: the authors should also acknowledge the lack of economic data to support the use of digital health interventions to date [14,15].

Round 2 Review

General Comments

No additional comments.

Conflicts of Interest

None declared.

Editorial Notice

JMIR Publications has a single-blind peer-review policy, wherein reviewer identity is concealed until publication. In exceptional cases, a reviewer may request to remain anonymous in the final publication. When an anonymous reviewer requests citation(s) of their own work, we cannot guarantee that the reviewer's identity will remain concealed.

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Abbreviations

mHealth: mobile health

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Peer-Review Report

Peer Review of “Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers’ Perspectives”

Bruno José Nievas-Soriano[1], MD, PhD

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Companion article: https://med.jmirx.org/2022/2/e33025/

(JMIRx Med 2022;3(2):e37051) doi:10.2196/37051

KEYWORDS

pediatrics; caregivers; health care services; public hospital; Malaysia; public-private-partnership; children

This is a peer-review report submitted for the paper "Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers’ Perspectives."

Round 1 Review

General Comments

This paper [1] describes interesting research about factors affecting the satisfaction of caregivers at a national referral center. I really liked the research performed and the article. Nevertheless, I think that there are some minor aspects that perhaps could be better described so the readers can better understand the results and their external validity. The authors do explain the limitations adequately, but perhaps some aspects could be clarified within the main text of the article.

Specific Comments

Major Comments

1. In Methods, the authors write that “This cross-sectional study was conducted at the Tunku Azizah Hospital, Kuala Lumpur, Malaysia. Subjects were caregivers to children seen with an appointment at the clinic.” They also write that “This study was conducted at the hospital’s Paediatric Specialist Clinic by convenience sampling. Self-administered, structured questionnaires were distributed to consenting participants. Subjects who agreed to participate were given questionnaires after seeing the doctor and while waiting for the date of their next consultation.”

Selection bias is probably the most important limitation of this research. Selection bias is almost unavoidable, so the authors must make a considerable effort to clearly describe where they obtain the sample from, so the readers can have a clear idea of the main features of that sample, which also should be described. To better understand the results (and therefore the conclusions), it would be very interesting to know, in more detail, how the patients were chosen, the attrition rate, or other factors related to the sample selection. Therefore, I would propose that the authors better describe where the sample is obtained from and how they were chosen.

2. In that same section, the authors write that “A total of 600 questionnaires distributed to the clinic, and we received 502 responses, giving a rate of 83.7%. Of these 502 responses, 43 were unusable and were excluded from this study, and the remaining 459 (91.4%) questionnaires were analysed. Some 2,238 patients were registered for an appointment at the clinic during this data collection period.”

It would be interesting if they describe in the article if they performed any sample size estimation and which method did they employ, in that case.

3. The authors write that “This was part of a hospital-level survey assessing satisfaction among caregivers attending the clinic using the SERVQUAL instrument.”

They properly describe the dimensions of the questionnaire, but perhaps it would be useful to know if this tool has been validated (or has required transcultural adaptation) to be used with this specific sample.

Despite these aspects, which are easily solvable, I think that this is a very interesting article that can be useful for other researchers.

Minor Comments

Some sentences and some paragraphs are perhaps a bit too long, and therefore, they are a bit confusing to read, but overall, the article is very well written.

Conflicts of Interest

None declared.

Reference

1. Selvarajah T, Yamamoto E, Saw YM, Kariya T, Hamajima N. Satisfaction with health care services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional study of caregivers' perspectives. JMIRx Med 2022;3(2):e33025 [FREE Full text]

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Peer-Review Report

Peer Review of “Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study”

Anonymous

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(JMIRx Med 2022;3(2):e37172) doi:10.2196/37172

KEYWORDS

mask; protection; COVID-19; influenza; transmission; intervention; infectious disease; respiratory; simulation; model; prevalence; efficacy

This is a peer-review report submitted for the paper “Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study.”

Round 1 Review

General Comments

The manuscript [1] entitled “Masks in Post COVID-19 World: Better Alternative to Curtailing Influenza?” undertakes the question as to whether the use of masks should continue after the COVID-19 pandemic for influenza. The authors use a susceptible-exposed-infected-recovered model to evaluate mask parameters.

Specific Comments

The variety of combinations of mask prevalence and mask efficacy are very helpful and give strength to the paper.

Major Comments

1. An additional introductory paragraph on the susceptible-exposed-infected-recovered model would strengthen the manuscript and open it up to a wider audience, as this topic is of interest to many.

2. An additional 1 to 3 paragraphs in the Discussion are needed, comparing this study to similar studies.

3. I suggest the authors use color-blind–friendly colors for the figures.

Minor Comments

4. This statement needs rewording: “vaccines of course only have to be administered once while face masks need to be worn continuously.” I suggest separating this away from the rest of the sentence and making it a cleaner statement.

5. The last sentence of the Discussion is a run-on sentence. Please fix.

Conflicts of Interest

None declared.

Reference

1. Froese H, A Prempeh AG. Mask use to curtail influenza in a post–COVID-19 world: a modeling study. JMIRx Med 2022;3(2):e31955 [FREE Full text]

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Peer-Review Report

Peer Review of “Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study”

Julia Frederick[1]

Department of Environmental Health Science, University of Georgia, Athens, GA, United States

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(JMIRx Med 2022;3(2):e37240) doi:10.2196/37240

KEYWORDS

mask; protection; COVID-19; influenza; transmission; intervention; infectious disease; respiratory; simulation; model; prevalence; efficacy

This is a peer-review report submitted for the paper “Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study.”

Round 1 Review

General Comments

This paper [1] investigates how influenza cases can be decreased by the implementation of masks by a varying proportion of the population. It uses previous research and historical case rates by the Centers for Disease Control and Prevention (CDC) to form its model. Overall, this paper’s model is an informative look at a potential scenario for future flu seasons. As it calculates a lot of its variables from a data set, knowing what these values will be and how they compare with the current literature can make the reader’s confidence in the model stronger.

Specific Comments

Major Comments

1. The final sentence of the Abstract needs to be completed or reworked to explain “other practical aspects.”

2. I’m assuming that this is all focused on solely the United States since it is using CDC data. However, noting that this is US-centric and giving a brief description of how the CDC acquires this data will help the reader understand the data set, especially with many of the CDC data sets being underrepresentative of actual case rates because they are highly dependent on medical reports. In the case of the flu, how many people get the flu but never report to the CDC or see a doctor to get treatment because symptoms are mild?

3. A creation of a table of or explicitly stating the variables and values used in the model is important for understanding. Especially when it comes to the calculated variables like B(t). Is that the same for each of those curves or is it changing with the different curves? If so, how much does it vary?

Minor Comments

4. How much does the virulence of the flu strains for that year versus the efficacy of the vaccine that year affect the data you are working with? Are there years that you think the masks would have helped substantially more than other years because the vaccine efficacy was lower than expected?

5. What is the typical mask efficacy for respiratory viruses? How does this “real-world” efficacy rate compare to the efficacy rates that you are using in your model?

Conflicts of Interest

None declared.

Reference

1. Froese H, A Prempeh AG. Mask use to curtail influenza in a post–COVID-19 world: a modeling study. JMIRx Med 2022;3(2):e31955 [FREE Full text]

Abbreviations

CDC: Centers for Disease Control and Prevention

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Peer-Review Report

Peer Review of “Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet”

Anonymous

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(JMIRx Med 2022;3(2):e37323) doi:10.2196/37323

KEYWORDS

user-centered design; genomic medicine; patient portals; electronic health records; return of results; bioethics; EHR; genetics; genetic testing; patient preferences; design; human factors

This is a peer-review report submitted for the paper “Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet."

Round 1 Review

General Comments

This paper [1] describes the results of an interview study of patients regarding preferences for receiving genetic test results through an electronic patient portal. All participants had already had a genetic test and were active users of their patient portal. Some suggestions/comments to consider to improve manuscript:

Specific Comments

Major Comments

Introduction

1. The actual purpose and study rationale/goal of the study was not described until the middle of the *Methods* section (minus the abstract). At the end of the *Introduction*, no information about the study was provided, and so, I was a little lost when transitioning from the *Introduction* to the *Methods* section for a study that hadn’t been mentioned at all. The second sentence in the *Data Collection* section could be moved up as the last sentence of the Introduction.
2. Toward the end of the *Introduction*, the inclusion about barriers to the utilization of patient portals is very broad and not specific to genetics. I would suggest limiting it to genetic test results.

Methods

1. Perhaps include a *Study Overview* section before *Participant Recruitment* if you do not wish to introduce the study in the *Introduction*.
2. Either provide the semistructured interview guide or provide more detail about the content and structure (eg, funnel approach?).
3. There is no mention of the analysis of content-related themes in the *Data Analysis* section.

Results

1. Confirm whether the patient demographics were the same for both study groups. Perhaps redo the table to include a breakdown of demographics between the two groups.
2. Clarify if the content recommendations came from the group that was asked to compare their experiences receiving genetic vs nongenetic test results through a patient portal.
3. Did you conduct any analysis to factor in patients’ background (eg, education, gender, age) or the specific type of experience with genetic testing to provide some context of their responses?
4. Without a better understanding of what the questions were, it is not totally clear if the questions were totally open-ended or if you asked them to provide feedback on specific suggestions (like the summary sheet). I assume the questions were more open-ended, given the data analysis description, but the results appear to be narrowly confined.
5. It seems to me that design recommendation #3 about smartphone functionality is not specific to genetics and should not be reported as a recommendation.
6. Some confusion about recommendations—is a simple coversheet (design recommendation #1) the same as an

electronic summary (design recommendation #2) and a patient-friendly results summary (domain 2 subheading, content recommendations #2-#4).

Discussion

1. Include some discussion of the implementation of the recommendations. Many would take considerable time to complete for multiple testing vendors/lab reports. Are they really feasible? Do you anticipate that the laboratories will do some of this work or will it fall to test orderer?
2. In the section *Comparison to Prior Work*, I would suggest including more discussion about the format and design of current lab reports. Many are made available through labs on their websites. It is difficult to generalize lab reports for different indications/purposes and come up with a best fit with respect to design/formatting. Certainly, patient feedback will be valuable for learning how to improve the comprehension of genetic testing lab reports. Many results cannot be analyzed without the consideration of more clinical information. Test reports are intended for health providers, and thus the style, jargon, and information will understandably differ for patients. The authors should consider reviewing reports intended for patients (eg, 23andMe), which are delivered electronically.

Minor Comments

1. Remove the extra numbers outside at the bottom of table.

Reference

1. Korngiebel DM, West KM. Patient recommendations for the content and design of electronic returns of genetic test results: Interview study among patients who accessed their genetic test results via the internet. JMIRx Med 2022;3(2):e29706 [FREE Full text]

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Peer-Review Report

Peer Review of “Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet”

Anonymous

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(JMIRx Med 2022;3(2):e38486) doi:10.2196/38486

KEYWORDS

user-centered design; genomic medicine; patient portals; electronic health records; return of results; bioethics; EHR; genetics; genetic testing; patient preferences; design; human factors

This is a peer-review report submitted for the paper “Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet.”

Round 1 Review

General Comments

This paper [1] covers the design and content of test results, specifically genetic test results, that are reported to patients via patient portals or direct communications. It is a qualitative study regarding these two components, and it focuses on an area that is rarely covered when discussing how to communicate test results to patients. Based on that, it adds a nice component to the literature that is becoming more recognized as an important factor in patient engagement and patient communication.

Specific Comments

As it is a small study with a limited population, the generalizability is somewhat limited. However, it opens the door for additional studies as well as the possibility of piloting some of the design recommendations from this study in a more applied milieu and incorporating both usability and functionality statistics, as well as the qualitative component, for a full picture of how best to interact with patients and provide them pertinent information.

Major Comments

1. In the final paper, I would recommend not including the quoted comments from the qualitative interviews. I would put those in the supplemental materials, as they are interesting, but they do not add that much to the paper itself.

Minor Comments

1. One area that is mentioned but not emphasized is the extension of the results of this qualitative study to the communication of nongenetic tests to patients. The same sort of principles should apply in terms of the cover sheet and the detailed explanation. Some of us already do this with our patients, but an extension of this study would allow some evidence to support that practice.
2. It would be nice to expand the study to include both nongenetic test results and diagnostic imaging results in terms of the design, content, and functionality of the results presentation.
3. An additional study would be looking at optimizing results presentation and content for smartphones versus computers or tablets. There may be a way to optimize the presentation of the data so that patients could more easily see the data on the smartphone form factor. That is an area for future study.

Reference

1. Korngiebel DM, West KM. Patient recommendations for the content and design of electronic returns of genetic test results: Interview study among patients who accessed their genetic test results via the internet. JMIRx Med 2022;3(2):e29706 [FREE Full text]

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Peer-Review Report

Peer Review of "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study"

Haleh Ayatollahi[1], PhD

Iran University of Medical Sciences, Tehran, Iran

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(JMIRx Med 2022;3(2):e38872) doi:10.2196/38872

KEYWORDS

ophthalmologic surgical procedures; access to health care; ophthalmology; patient-centered care; ethnography; health knowledge; attitudes; practice

This is a peer-review report submitted for the paper "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study."

Round 1 Review

Major Comments

1. It is better to choose keywords that are MeSH terms.
2. It is better to integrate all sections before *Methods* as an *Introduction* section.
3. How did the researchers develop the interview guide?
4. The trustworthiness of the results and validity and reliability need to be discussed separately for each research method.
5. More details should be added to the *Document Review* section.
6. How many participants took part in the focus groups?
7. The *Results* section needs to be expanded.
8. In the *Discussion* section, the summary of results does not need to be supported by the participant's quotes.
9. The *Discussion* section needs to be revised to be more integrated.
10. Strengths and limitations of the study can be reported at the end of the discussion section.
11. Research implications can be reported before conclusions.

Round 2 Review

General Comments

I appreciate the authors [1] for their time and efforts to implement our suggestions. It seems that the manuscript has been improved; however, some issues are still remaining.

Specific Comments

Major Comments

1. The author response letter only includes the authors' responses without mentioning the reviewers' comments. For some comments, they just said "done" and I have no idea what the comments were and what they exactly did. So, a complete response letter needs to be uploaded.
2. The *Discussion* section needs to be integrated to show an integrated *Discussion* for the whole research. In the current format, it seems fragmented.
3. Also, the subsections under the *Conclusions* section need to be moved to the end of the *Discussion* section or be integrated with other existing subheadings in this section.

Conflicts of Interest

None declared.

Reference

1. Mbwogge M, Nkumbe HE. Exploring the reasons for low cataract surgery uptake among patients detected in a community outreach program in Cameroon: focused ethnographic mixed methods study. JMIRx Med 2022;3(2):e35044 [FREE Full text]

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Peer-Review Report

Peer Review of "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study"

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(JMIRx Med 2022;3(2):e38873) doi:10.2196/38873

KEYWORDS

ophthalmologic surgical procedures; access to health care; ophthalmology; patient-centered care; ethnography; health knowledge; attitudes; practice

This is a peer-review report submitted for the paper "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study."

Round 1 Review

General Comments

This is an interesting qualitative study assessing the current status and potential causes underlying the low uptake of cataract surgery among community-diagnosed patients with cataract in Cameroon [1]. The authors showed extensive knowledge about the context of the study and provided valuable suggestions on how health care professionals may help solve the problem. The interview was detailed, and the methodology was well designed and clearly explained.

While the topic has its merits and the discussion is quite comprehensive, I believe the manuscript can be further improved after some points are addressed or some questions are clarified.

Major Comments

1. The lengths of both the main text and the abstract are a bit long. We suggest the authors to further condense the paper or move some parts to Multimedia Appendices.

2. Although 29 subjects were interviewed, only 9 of them were direct subjects. We are unsure if this is a sufficient number for such qualitative analysis.

3. The influence of indirect subjects' opinions on the decision of the direct subjects was not particularly discussed.

4. Considering the potentially different weights of direct versus indirect subjects' opinions in the decision, whether the quotes were taken from direct subjects should be shown.

5. We are no experts of traditional medicine, but is there anything to be noted about these therapies? (Maybe certain therapies were helpful from the patients' perspectives?) We are unsure if these should be taken into consideration when assessing the "Knowledge and awareness" and "reasons of refusal."

6. The "poor outcome" of prior cataract surgeries was mentioned in the *Results* section. Can this be a possible reason for the "fear" of cataract surgery and the reason to choose traditional medicine instead?

Minor Comments

7. There are still some grammatical mistakes that should be checked and amended.

8. Please make sure to provide the full spellings of all abbreviated words at first use (eg, "MICEI" and "FGDs").

9. The table did not show the particular demographics of the direct subjects (which may help reveal other socioeconomic factors influencing the decision or limitation of the study).

10. How is the surgery acceptance or backlog situation for community cataract screening programs conducted in nearby countries with a similar socioeconomic status? While this is not the focus of the study, if there are available data, it would be good to include some general information (this will help justify the study aim and support the overall results).

Round 2 Review

General Comments

The authors have addressed most of the comments. While the scientific content is acceptable after the revision, it is still recommended that the authors shortened the article to <6500-7000 words. No further suggestions are enclosed.

Conflicts of Interest

None declared.

Reference

1. Mbwogge M, Nkumbe HE. Exploring the reasons for low cataract surgery uptake among patients detected in a community outreach program in Cameroon: focused ethnographic mixed methods study. JMIRx Med 2022;3(2):e35044 [FREE Full text]

Edited by E Meinert; submitted 19.04.22; this is a non–peer-reviewed article;accepted 19.04.22; published 09.06.22.

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Peer-Review Report

Peer Review of "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study"

Alexandros Argyriadis[1], PhD

Frederick University, Nicosia, Cyprus

Related Articles:

Companion article: https://preprints.jmir.org/preprint/35044

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Companion article: https://med.jmirx.org/2022/2/e35044/

(JMIRx Med 2022;3(2):e39041) doi:10.2196/39041

KEYWORDS

ophthalmologic surgical procedures; access to health care; ophthalmology; patient-centered care; ethnography; health knowledge; attitudes; practice

This is a peer-review report submitted for the paper "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study."

Round 1 Review

General Comments

This paper [1] studies the reasons for the low cataract surgical uptake among patients detected in a community outreach program in Cameroon, and it can be characterized as innovative as the research on that time-place context is limited. Moreover, this is an ethnographic approach that comes to fill the research gap in a huge database of quantitative data. There are some qualitative efforts that discuss the access of citizens in health care structures [2] but the issue of cataract has not been studied in terms of prevention and health promotion. However, the article contains both quantitative and qualitative data, and this is a positive aspect that endures the whole research project. It is evidence-based, and the authors offer the opportunity to the scientific community to have access to their database, if asked. The fact that this project is not only theoretical but also it can contribute to the quality of everyday life in Cameroon is evident by the funding that the research team received. They engaged the local community and institutions to the awareness of this issue and that is one of the main ingredients of the ethnographic methodology. This study has brought to light the potential of ethnography in uncovering the challenges faced by underprivileged populations in accessing cataract surgery and the related complexity that underpins the considerations in improving uptake of cataract surgery in low-resource and culturally inclined settings. It also shows that the patient-reported barriers to cataract surgery of those attending eye clinics (in this case for hospital-based studies) may not necessarily be the experience reflecting the communities they come from. Our results also provide useful insights regarding the planning of advocacy and other public health services.

Hence, on the one hand, in the case of the methodological selection and on the other hand in the selection of the specific topic to be investigated, we can say that this is a very successful project, which would be of great interest if it expands to other areas where similar difficulties are identified. In the Community Health Care context, one of the most important issues discussed among experts is health promotion and the prevention of diseases of specific population groups characterized by risk factors. As there has been such a huge outbreak of awareness programs for the COVID-19 pandemic crisis, it would be useful to extend similar programs to other diseases that affect the health of communities over time [3].

The article concludes with the results that cost and fear were the main barriers to cataract surgery compounded by a strong belief in traditional medicine and superstition. These results apply to settings reliant on hospital-based delivery models with a disintegrated eye care delivery from the public health strategy and with little or no health coverage. Finally, the authors recognize the research implications and they come up with recommendations for further research.

Specific Comments

Major Comments

1. There are no major amendments needed.

Minor Comments

1. It would be interesting if there are any other articles that mention this problem and can be added in the manuscript.

2. Moreover, the eye care delivery in Cameroon is presented only from the financial aspect. It would be interesting if the authors could add some other demographic or educational and cultural factors that affect the access to health care.

Conflicts of Interest

None declared.

References

1. Mbwogge M, Nkumbe HE. Exploring the reasons for low cataract surgery uptake among patients detected in a community outreach program in Cameroon: focused ethnographic mixed methods study. JMIRx Med 2022;3(2):e35044 [FREE Full text]
2. Ioannou K, Soteriou S, Mantzourani K, Argyriadis A. The lack of access citizens have to health care of Kenya. Cyprus Nursing Chronicles Journal 2020;20(1):38-42.
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Peer-Review Report

Peer Review of "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study"

Anonymous

Related Articles:

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Companion article: https://med.jmirx.org/2022/2/e35044/

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KEYWORDS

ophthalmologic surgical procedures; access to health care; ophthalmology; patient-centered care; ethnography; health knowledge; attitudes; practice

This is a peer-review report submitted for the paper "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study."

Round 1 Review

Dear Authors,

Thank you very much for this interesting paper [1] about cataract surgery uptake in Cameroon. I have nothing to add.

Kind regards!

Conflicts of Interest

None declared.

Reference

1. Mbwogge M, Nkumbe HE. Exploring the reasons for low cataract surgery uptake among patients detected in a community outreach program in Cameroon: focused ethnographic mixed methods study. JMIRx Med 2022;3(2):e35044 [FREE Full text]

Edited by E Meinert; submitted 28.04.22; this is a non–peer-reviewed article;accepted 28.04.22; published 09.06.22.

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study"

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Companion article: https://med.jmirx.org/2022/2/e37057/

Companion article: https://med.jmirx.org/2022/2/e37003/

Companion article: https://med.jmirx.org/2022/2/e30777/

Abstract

(JMIRx Med 2022;3(2):e37005) doi:10.2196/37005

KEYWORDS

patient readmission; quality assurance; health care; catchment area; health; community networks; regional medical programs

This is the authors' response to peer-review reports for "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study."

Round 1 Review

Reviewer BF [1]

General Comments

Thank you for the opportunity to review this study [2] of the association of shared care networks with heart failure (HF) excessive hospital readmissions. Hospital readmission is a very current topic. Nonetheless, several issues should be noted.

Authors' Comment

We appreciate the recognition that HF excessive hospital readmissions is a very current topic.

Specific Comments

Major Comments: Comment 1

1. In "study population and design" in "methods," the authors mentioned, "hospitals with less than 2 repeated measures of higher-than-expected HF readmission in the HRRP (Hospital Reduction Readmission Program) or without discharge data in the OSHPD (Office of Statewide Health Planning and Development) were excluded." Does this mean this study only considered hospitals with repeated higher-than-expected HF readmission? Ignoring hospitals without repeated higher-than-expected HF readmission may introduce bias to the analysis. Please clarify why you have chosen this data inclusion criterion.

Authors' Comment

We appreciate the comment about the exclusion of hospitals with less than 2 repeated measures and the bias such exclusion may produce. Given that the study design is longitudinal using generalized estimating equations (GEEs), repeated measures are required. Nevertheless, we rewrote this whole section, which is now as follows:

"Study Design, Study Setting, and Participants

This is an observational longitudinal study. The study setting was hospitals in California, US during the period from 2012 to 2017. Participants were all hospitals reported in the Hospital Readmissions Reduction Program (HRRP) (6). The eligibility criteria were as follows: At least 2 repeated measures of higher-than-expected HF readmission in the HRRP and availability of discharge data from the Office of Statewide Health Planning and Development (OSHPD) (16). These criteria enabled, respectively, carrying out a longitudinal study which requires repeated measures and linking data from the HRRP with date from OSHPD. Between 233 and 237 hospitals in California were included depending on the year. Ethical approval was unnecessary because all data was at the hospital-level and was already made publicly available from both HRRP and OSHPD. All code, processed data, built networks, and data analysis resulting from this work are available on the Open Science Framework (OSF) repository of this work (37)."

Major Comments: Comment 2

2. In "data sources" in "methods," the authors collected excessive readmission ratio (ERR) data from 2012 to 2017. In almost every year, the HRRP updated the inclusion criteria of HF readmission (eg, lists of eligible diagnosis codes and procedure codes in the planned readmission algorithm). In this case, how did you fairly compare the ERR across different years?

Authors' Comment

This is a very insightful comment and indeed requires extra discussion. The ERR is a risk-standardized 30-day readmission ratio. It is used by the HRRP to assess excess hospital readmissions and calculate hospital penalties [3]. The ERR has been used in longitudinal studies including the years of this study before [3-5].

The ERR is calculated by dividing the "predicted readmissions" (p) to "expected readmissions" (e). Using a hierarchical generalized linear model (HGLM), both "predicted" (p) and "expected" (e) readmissions are estimated using an "adjusted average intercept over all hospitals" (u), but the number of "predicted readmissions" (p), in addition, is estimated using a hospital-specific intercept deviation (a = u + w) from the "adjusted average intercept over all hospitals" (u). Such methodology, well documented in the Condition-Specific Readmission Measures Updates and Specifications Report from the Centers for Medicare & Medicaid Services (CMS) [6], makes the ERR an appropriate instrument for comparing hospitals within and between years.

The following text was included in "data sources" in "methods":

"The ERR is calculated dividing the predicted readmissions to expected readmissions. Using a hierarchical generalized linear model (HGLM), both predicted and expected readmissions are estimated using an adjusted average intercept over all hospitals, but predicted readmissions, in addition, is estimated using a hospital-specific intercept deviation from the adjusted average intercept over all hospitals. Such methodology, well documented in the Condition-Specific Readmission Measures Updates and Specifications Report from the Centers for Medicare & Medicaid Services (CMS) [7], makes the ERR an appropriate instrument for comparing hospitals within and between years."

Major Comments: Comment 3

3. Is the "Uncovering Shared Care Areas and Localization Index from Hospital-Patient Discharge Data" in "methods" a literature review of other studies or the method the authors used in this study? Please clarify. If it is a literature review, it should go in the "introduction."

Authors' Comment

Thank you for mentioning the methods in this subsection. Though it may appear to be a literature review, we are only specifying the parameters that were considered for each algorithm.

Reviewer BX [7]

Major Comments: Comment 1

- Title: For this study, please include the type of study in the title. If you are considering 30-day readmission, please specify it in the title.

Authors' Comment

We appreciate this comment, and following your suggestion, we changed the title to "Association of Shared Care Networks with 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study." We hope this new title is now appropriate.

Major Comments: Comment 2

- Abstract: Please move the objective section to the end of the background section, and it is recommended that it is written the same as in the study title.

Authors' Comment

Thank you very much. Following your suggestion, we changed the objective to "This study aimed to evaluate the association of shared care networks with 30-day heart failure excessive readmission rates using a longitudinal observational study" to be written the same as the study title. We would love to move it to the end of the background section, but it seems that the Objective section is mandatory.

Major Comments: Comment 3

- Methods: Please start this section with the study design. Study setting, study variables, and outcomes and their measurements should be mentioned, briefly. Eligibility criteria have not been provided.

Authors' Comment

Thank you for your suggestion. We rewrote the Methods section. Its first section is now "Study Design, Study Setting, and Participants."

Major Comments: Comment 4

- Methods: ERR: I think it is excessive readmission risk ratio because no person-year has been reported. Thus, to improve the reporting, please revise it in the whole document.

Authors' Comment

Thanks for the suggestion. We would rather use the same name used in the literature [6].

Major Comments: Comment 5

- Results: To facilitate the interpretation of the study results, please convert beta coefficients by exponentiating them.

Authors' Comment

We understand the need of converting beta coefficients when dependent variables are dichotomous (binary). In our case, the ERR is not dichotomous but a continuous variable that can be less than or greater than 1 such as 0.92 or 1.23 depending on the presence or absence of excessive hospital readmissions. Therefore, we used a GEE with a Gaussian family without a Logit link function. In this case, we understand that converting the beta coefficients would not be appropriate because in their current form they express, on average, a 1-unit of change in the predictor variable.

We modified the text to clarify potential misunderstandings.

We included the following text in "data sources" in "methods": "The ERR is calculated dividing the predicted readmissions to expected readmissions. Using a hierarchical generalized linear model (HGLM), both predicted and expected readmissions are estimated using an adjusted average intercept over all hospitals, but predicted readmissions, in addition, is estimated using a hospital-specific intercept deviation from the adjusted average intercept over all hospitals. Such methodology, well documented in the Condition-Specific Readmission Measures Updates and Specifications Report from the Centers for Medicare & Medicaid Services (CMS) [6], makes the ERR an appropriate instrument for comparing hospitals within and between years."

Major Comments: Comment 6

- Please use expanded forms of the abbreviations the first time they are mentioned. The expanded form of some abbreviations has not been provided.

Authors' Comment

We appreciate this comment from the reviewer. The paper was revised to use the expanded form of the abbreviations for the first time. Additionally, we included all abbreviations in the Abbreviations section in alphabetic order.

"Abbreviations

ACS: American Community Survey

CMS: Centers for Medicare & Medicaid Services

ED: emergency department

ERR: excessive readmission ratios

HF: heart failure

HGLM: hierarchical generalized linear model

HRRP: Hospital Reduction Readmission Program

GEE: generalized estimating equations

LI: localization index

LVAD: Left Ventricular Assisted Devices

OLS: ordinary least squares

OSHPD: Office of Statewide Health Planning and Development

SCA: shared care area

STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

OSF: Open Science Framework

UDS: Uniform Data System

ZCTA: ZIP Code Tabulation Area"

Major Comments: Comment 7

- Keywords: Please write these according to the Medical Subject Headings (MeSH) system.
- Introduction: The necessity of this study is not clear. Please provide a paragraph about the importance and necessity of this study and why you designed and conducted this study.

Authors' Comment

We appreciate the encouragement to write keywords according to the MeSH system. We changed all our keywords as follows: "Patient Readmission; Quality Assurance, Health Care; Catchment Area, Health; Community Networks; Regional Medical Programs."

Major Comments: Comment 8

- Methods: It is recommended to write this section according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) standard writing and refer to it in the first paragraph of the Methods section.

Authors' Comment

Thank you for your suggestion. The first paragraph of the Methods sections now includes:

"This methods section was written according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) standard writing."

Additionally, we changed the whole Methods section to include the following new subsections: Study Design, Study Setting, and Participants; Study Outcome; Study Variables; and Data Sources.

Major Comments: Comment 9

- Please start this section with the study design. A retrospective study is not a study design and refers to the type of data collection.

Authors' Comment

Thank you for your suggestion. We rewrote the Methods section. Its first section is now "Study Design, Study Setting, and Participants."

Major Comments: Comment 10

- Please provide information about institutional review board (IRB) approval of this study.

Authors' Comment

Thank you for your concern. As we stated in the text, ethical approval was not necessary because all data used in this work is made publicly available by the HRRP and OSHPD.

Major Comments: Comment 11

- Study variables and their measurement should be provided.

Authors' Comment

Thank you for your suggestion. The Methods section now has 3 new subsections: Study Design, Study Setting, and Participants; Study Outcome; and Study Variables, Data Sources.

Major Comments: Comment 12

- Statistical analysis: please use converted forms of beta coefficients.

Authors' Comment

We understand the need of converting beta coefficients when dependent variables are dichotomous (binary). In our case, the ERR is not dichotomous but a continuous variable that can be less than or greater than 1 such as 0.92 or 1.23 depending on the presence or absence of excessive hospitals readmission. Therefore, we used a GEE with a Gaussian family without a Logit link function. In this case, we understand that converting the beta coefficients would not be appropriate because in their current form they express, on average, a 1-unit of change in the predictor variable.

We modified the text to clarify potential misunderstandings.

We included the following text in "data sources" in "methods":

"The ERR is calculated dividing the predicted readmissions to expected readmissions. Using a hierarchical generalized linear model (HGLM), both predicted and expected readmissions are estimated using an adjusted average intercept over all hospitals, but predicted readmissions, in addition, is estimated using a hospital-specific intercept deviation from the adjusted average intercept over all hospitals. Such methodology, well documented in the Condition-Specific Readmission Measures Updates and Specifications Report from the Centers for Medicare & Medicaid Services (CMS) (17), makes the ERR an appropriate instrument for comparing hospitals within and between years."

Major Comments: Comment 13

- Results: The Results section is very long. Please avoid providing data both in the text and the table.

Authors' Comment

We understand the concern. The tables, however, contain more information than the text. In the text, we are providing some aspects of the results. We would prefer to keep the Results section without removing any text if possible.

Major Comments: Comment 14

- Please use converted forms of beta coefficients in the Results section.

Authors' Comment

We understand the need of converting beta coefficients when dependent variables are dichotomous (binary). In our case, the ERR is not dichotomous but a continuous variable that can be less than or greater than 1 such as 0.92 or 1.23 depending on the presence or absence of excessive hospitals readmission. Therefore, we used a GEE with a Gaussian family without a Logit link function. In this case, we understand that converting the beta coefficients would not be appropriate because in their current form they express, on average, a 1-unit of change in the predictor variable.

We modified the text to clarify potential misunderstandings.

We included the following text in "data sources" in "methods":

"The ERR is calculated dividing the predicted readmissions to expected readmissions. Using a hierarchical generalized linear model (HGLM), both predicted and expected readmissions are estimated using an adjusted average intercept over all hospitals, but predicted readmissions, in addition, is estimated using a hospital-specific intercept deviation from the adjusted average intercept over all hospitals. Such methodology, well documented in the Condition-Specific Readmission Measures Updates and Specifications Report from the Centers for Medicare & Medicaid

Services (CMS) (17), makes the ERR an appropriate instrument for comparing hospitals within and between years."

Major Comments: Comment 15

- Please identify adjusted and unadjusted beta coefficients in the Results section both in the Abstract and full text.

Authors' Comment

Thank you for your review. We reviewed the manuscript and identified the adjusted and unadjusted beta coefficients.

Major Comments: Comment 16

- I do not think there is a "perspective section" in the JMIR structure. You can add it to the Discussion and Conclusion section if it is necessary.

Authors' Comment

We apologize for including a perspective section. We moved it to the conclusion.

Major Comments: Comment 17

- Tables: They are not in the scientific form. Please revise them according to JMIR guidelines.

Authors' Comment

Thank you for your comment. We apologize for not following the appropriate table style according to JMIR manuscripts. All tables were revised and should comply with JMIR standards.

Round 2 Review

Reviewer BX

I would like to thank the authors for considering all the reviewers' comments.

However, there is no IRB or research ethics committee approval.

According to the authors' statement "all data used in this work is made publicly available by the Hospital Reduction Readmission Program (HRRP) and Office of Statewide Health Planning and Development (OSHPD)." It is recommended to mention it in the Acknowledgments section and the first paragraph of the study design.

Authors' Comment

We would like to thank the reviewer for all feedback provided. We agree with the reviewer. The current version of the manuscript now includes this sentence both in the Acknowledgments section and in the first paragraph of the study design.

Acknowledgments

RH is an independent researcher in Seattle, United States.

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1. Peng Z. Peer review of "The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study". JMIRx Med 2022;3(2):e37057 [FREE Full text]
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Abbreviations

CMS: Centers for Medicare & Medicaid Services
ERR: excessive readmission ratio
GEE: generalized estimating equation
HF: heart failure
HGLM: hierarchical generalized linear model

HRRP: Hospital Reduction Readmission Program
IRB: institutional review board
MeSH: Medical Subject Headings
OSF: Open Science Framework
OSHPD: Office of Statewide Health Planning and Development
REC: research ethics committee
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: A Scoping Review"

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KEYWORDS

COVID-19; pandemic; SARS-CoV-2; health care; hospitals; health care strategy; hospital resilience; interventions; crisis response; crisis preparedness; public health

This is the authors' response to peer-review reports for "Lessons Learned From the Resilience of Chinese Hospitals to the COVID-19 Pandemic: Scoping Review".

Round 1 Review

Reviewer Anonymous [1]

General Comment

1. This paper's [2] title mentions that the authors conducted a scoping review but used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method. The authors should clarify the difference between scoping review and systematic review.
   Response: We have added a phrase in the text to explain the difference in more detail. References 14-16 explain the PRISMA scoping methodology.
2. Provide a table of the studies that were selected for final analysis (study title, publishing year, research methods, main findings of each study).
   Response: Done; this is contained in a .xls file.
3. State the study exclusion reasons clearly with a subheading in the Methods section.
   Response: We feel that the study exclusion criteria are implicit in the inclusion criteria.
4. Revise your study limitations according to the study inclusion and exclusion criteria

Response: We have added two more sentences, which refer to the exclusion criteria.

5. Provide the list of all studies that were included at the initial stage without inclusion and exclusion limitations in a supplementary file.
Response: We have a list of articles attached as an .xls file.
6. English editing is required.
Response: Has been revised twice by native speakers.

Reviewer AY [3]

1. The authors refer to Table 4 three times in the manuscript; however, this table is not attached to the document. The same occurs with Table 3 that is referred to on page 7, second paragraph.
Response: These tables are within the supplementary files and are now labelled as such.
2. In relation to the PRISMA-ScR checklist, the eligibility criteria are not pointed out in the abstract section of the manuscript.
Response: This has been done in the Inclusion Criteria section.
3. The registration number of the scoping review's protocol is missing. The authors do not indicate if the protocol is available.
Response: Please find the protocol here [4]; there is a link in the references.
4. There are some typos in the manuscript, for example:
- Authors use the acronym PPE (personal protective equipment) several times in the manuscript. Please indicate its meaning the first time it appears in the manuscript (page 10).
- In the abstract section, the word "found" appears in a smaller size than the rest of the words.
Response: These issues have been resolved, and the manuscript was looked over again by a native speaker.

References

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Abbreviations

PPE: personal protective equipment
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model"

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Companion article: https://med.jmirx.org/2022/2/e38420/

Companion article: https://med.jmirx.org/2022/2/e30144/

(JMIRx Med 2022;3(2):e38008) doi:10.2196/38008

This is the author's response to peer-review reports for "Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model."

Review Round 1

Reviewer F [1]

General Comments

The paper [2] is very well written and is very timely. I believe that this model will be informative in that it shows how long-term solutions rather than short term are needed to avoid greater losses in the long term. However, as the authors say, the model is based on somewhat weaker empirical research, so I look forward to seeing this model validated with data.

Author response: As noted in the introduction of the paper, the data that I will explain in more detail below is largely for purposes of illustration. This is because the design of the study, for various reasons, simply does not allow for "validation with examples." One reason is that data on the socioeconomic profile of COVID-19 deaths is not available on a global scale. The other reason is that the years of life lost (YLL) due to loss of socioeconomic status (SES) are potential YLL. Whether these YLL will materialize in the future depends on current and future policy responses to the pandemic and whether they succeed at compensating for existing and containing future socioeconomic fallout. In other words, we can only hope that the model will be refuted in 10-20 years. The paper should therefore be seen as two things: a call for action based on a plausible estimate (not an empirical assessment) and an agenda to fill an important research gap. I did, however, try to insert more examples from individual countries into the conceptual discussion to clarify the approach.

Specific Comments

Major Comments

1. I think it should be made clearer that this model is applied to US and European scenarios.

2. I believe that the paper and research are well motivated and show a necessity for more research on the proportional impact of SES on YLL.

Author response: 1. The comment is based on a misunderstanding. The paper explicitly develops a global model. It is true that the main assumptions and parameters of the model necessarily rely on findings from studies on high-income countries, simply because this is the data that is available. However, for the model parameters to better suit the context of low- and middle-income countries, various adaptations are made plausible. Additionally, the study draws on the only current existing international cross-country data set on COVID-19 deaths spanning 81 countries from all income groups (see more details below).

Minor Comments

3. There are several cases where the authors should correct some typos (eg, the European [the European what?] and sill vs still).

Author response: Typos were corrected.

Anonymous [3]

This paper develops a model that compares the YLL due to COVID-19 and the potential YLL due to the socioeconomic consequences of its containment. The results highlight the importance of SES in evaluating the effect of nonpharmaceutical interventions (NPIs) during COVID-19. However, the methods, especially the empirical sample characteristics from which the life table is derived, are not clear.

Specific Comments

Major Comments

1. Needs to describe more about the data, study design, and study sample in more detail

2. Needs to discuss how the missing data was handled

3. It is important to consider a theoretical framework that can guide the selection of NPIs, indicators of SES, and the equivalent socioeconomic damages (on page 11). Right now, it is more arbitrary than scientific based.

4. The Discussion also needs to consider other factors (eg, pre-existing conditions, neighborhood resources, or occupation types). These are important social determinants of health factors.

Author response: 1. Concerning the study design [Anonymous] may have mistaken the paper for an empirical study whereas its main contribution is a conceptual innovation that is made plausible using existing data. As part of the revision, I further clarified that the data on YLL due to COVID-19 are taken from an existing study [4] and the life tables they use. Their data covers 81 countries across all income groups and is the most comprehensive global data set to date. Additional information about their sample can be obtained from the appendix of their study.

2. Missing data for low- and middle-income countries is indeed a major problem, both for the socioeconomic gap in life expectancy as well as the socioeconomic profile of COVID-19 deaths in these countries. The gap is documented in the study, and it was made plausible how assumptions from high-income country can be adapted to better suit the context of low- and middle-income countries. If there are concerns with their plausibility, I am happy to take more detailed and informative reviewer suggestions on how the assumption can be improved.

3. The comment is unclear. The paper does not aim at developing a theoretical framework for the selection of NPIs. Instead, it makes the assumption that the socioeconomic fallout in the pandemic is due to the NPIs. This is justified in the discussion section where issues of causality are taken up. The selection of SES indicators is also not arbitrary. With education and income, the two most important and widely used indicators of SES were used. It was made clear in the relevant text passages that SES corresponds to income quintiles (low 1, mid 2-4, high 5) and 3- to 4-year educational blocs following primary education (low primary, mid secondary, high tertiary). Furthermore, the paper only estimates how many more people and students would have to fall one SES group in the future due to income loss and foregone education.

4. The relevance of comorbidities is acknowledged in the COVID-19 YLL estimates but it is mainly argued that data on SES can partly proxy for comorbidities. Neighborhood resources and occupation type are indeed other important indicators of SES, but I would hope the reviewer could specify how these could be integrated in the analysis.

Minor Comments

1. The tables need to be adjusted in terms of the decimal points and more informative legends to guide readers.

Author response: Tables were adjusted to decimal points and more detailed descriptions of their content inserted in the main text.

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Abbreviations

NPI: nonpharmaceutical intervention
SES: socioeconomic status
YLL: years of life lost

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review"

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Companion article: https://med.jmirx.org/2022/2/e31019/

Abstract

(JMIRx Med 2022;3(2):e37114) doi:10.2196/37114

KEYWORDS

ventricular outflow obstruction; subarachnoid hemorrhage; vasospasm; intracranial; milrinone; hemorrhage; neurosurgery; neurology; surgery; pharmaceutical

This is the authors' response to peer review reports of "Left Ventricular Outflow Tract Obstruction in Patients Treated With Milrinone for Cerebral Vasospasm: Case Report and Literature Review."

Round 1 Review

Reviewer AA [1]

General Comments

This is an interesting paper [2]. Overall, the information is well presented. That said, there are some areas that need improvements.

Specific Comments

Major Comments

1. This type of left ventricular outflow tract obstruction (LVOTO) should be addressed as dynamic LVOTO.
   Response to the first comment: We will insist more on the difference between the fixed obstruction and the dynamic obstruction. Fixed LVOTO is due to anatomical features (excessive mitral tissue, mitro-aortic angle less than 120°, septal hypertrophy). Dynamic LVOTO is due to the addition of predisposing factors (decreased preload and afterload, increased inotropism).
2. LVOTO per se should be briefly explained in the "Introduction" for the benefit of noncardiology readers: what LVOTO means, types of LVOTO such as fixed and dynamic, and a brief and simple explanation of dynamic LVOTO.
   Response to the second comment: As you say, our introduction will include a paragraph briefly explaining LVOTO, its definition, and its mechanisms. It is a complex hemodynamic phenomenon in itself, and its description must be rigorous. To describe it exhaustively in the introduction would risk making this part of the manuscript too long, but a complete description will stay in a dedicated part of the manuscript.
3. For the second patient, pages 7 and 8 state "In view of the hemodynamic improvement and the good neurological course, treatment with milrinone was continued at the same dose." It looks like a repeat echo was done only after stopping milrinone. Was any echo repeated after hemodynamic improvement while the patient was continued on milrinone? How did you come to the conclusion that LVOTO is because of milrinone? He also had meningitis/sepsislike state (mentioned as an inflammatory syndrome in the manuscript), which in itself could predispose to LVOTO. Additionally, LVOTO can occur postoperatively after noncardiac surgery in patients with no known heart disease, and this patient also had a surgical procedure in the form of ventricular drain. These aspects are well discussed in reference 16 of the manuscript.
   Response to the second comment: Response to the third comment: For us, it is certain that the occurrence of LVOTO in our second patient was due to the addition of two predisposing factors: the use of milrinone and hypovolemia induced by sepsis. An echocardiogram in the presence of only one of the two elements could have made it possible to evaluate the dominance of one over the other. It is known that LVOTO is found in about 20% of patients in septic shock. However, this patient presented with a neurological infection with a state of relative hypovolemia, not being in shock. The systolic murmur persisted after punctual use of crystalloids, and only disappeared when the milrinone infusion was stopped. These elements support, in our opinion, the hypothesis that the use of milrinone was the main and triggering mechanism, sepsis being only an aggravating factor.
4. What is the explanation for unilateral left sided pulmonary edema for the first patient (as pulmonary edema is mostly bilateral in heart failure).
   Response to the fourth comment: Mitral regurgitation associated with LVOTO is most often eccentric and travels to the left pulmonary veins, resulting in unilateral acute pulmonary edema. We will incorporate this into the manuscript.

Minor Comments

1. The authors mention vasospasm was diagnosed using a computerized tomography (CT) scan. Plain CT scans are not used for the diagnosis of vasospasm, and they need to be more specific as to how vasospasm was diagnosed (eg, CT angio, Doppler study, or perfusion scan).
   Response to the fifth comment: We will specify in the manuscript that these were angio-CT

Reviewer AN [3]

This paper deals with a rare event on the occurrence of left ventricular outflow obstruction in a patient treated with milrinone for vasospasm following an aneurysmal bleed.

Major Comments

1. The rationale for radioembolization of aneurysms needs to be elaborated.
   Response: The treatment option chosen was the most suitable for the patient, after CT analysis of the aneurysm characteristics and a discussion between a neuroradiologist and neurosurgeon.
2. The probable differential diagnosis of stunned myocardium syndrome in the acute phase needs to be mentioned.
   Response: We will include a brief description of neurogenic myocardial stunning in the manuscript. It is a not-so-rare complication of aneurysmal meningeal hemorrhage. This occurs in the acute phase of subarachnoid hemorrhage. Unlike LVOTO, beta receptor overstimulation results in myocardial sideration. The common feature of the two conditions is the worsening with the use of catecholamines.

Round 2 Review

Reviewer AA

Specific Comments

Major Comments

1. Page 6, lines 10-12 states "Although milrinone was administered at a constant dosage of 1 µg/kg/min, the clinical presentation led to find the origin of the shock: an accidental bolus of a milrinone due to a plication of the central venous catheter line during nursing care". Would recommend clarifying this statement and explaining what exactly you mean by plication and how it resulted in an accidental bolus of milrinone.
   Response: The main hypothesis is that the catheter plicated when the patient was placed in a sitting position, the electric syringe did not stop, and the bolus of milrinone occurred when the obstruction was removed.
2. Bedside limited echocardiography is a routine practice to check the effect of various interventions in the intensive care unit. Therefore, it should be explained why echocardiography was not repeated in the second patient

after hemodynamic improvement while the patient was continued on milrinone. Just relying on "systolic murmur" is not enough. Moreover, a murmur is also not described in detail. The murmur description should include intensity, quality, radiation, timing (pan systolic/short systolic), etc.
Response: We have added a more specific description of the murmur in the manuscript. There was no follow-up echocardiography before discontinuation of milrinone therapy because the patient's hemodynamic status was subsequently stable.

3. "Mitral regurgitation associated with LVOTO is most often eccentric, and travels to the left pulmonary veins, resulting in unilateral acute pulmonary edema in this patient." Please provide a reference for this.
Response: We have added a bibliographic reference for this.

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Abbreviations

CT: computerized tomography
LVOTO: left ventricular outflow tract obstruction

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis"

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KEYWORDS

COVID-19; epidemiology; Google Trends; infodemiology; infoveillance; Italy; public health; SARS-CoV-2; vaccinations; vaccines; social media analysis; social media

The author's response to peer-review reports for "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis."

Round 1 Review

Reviewer M [1]

Comment: The subject of the brief paper [2] "Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: a Retrospective Infodemiological Analysis" is timely and valuable to the audience of JMIRx Med. Overall, the paper is well structured, reads exceptionally well, and covers the existing literature quite well. The analysis of the data is interesting and well documented.

The author of the paper has selected keywords used in the Google Search engine, which could reveal an intention to take a vaccine against COVID-19 in Italy and compared this interest with headlines in the second most read newspaper in Italy. The paper has a transparent and replicable procedure to collect data and do statistical tests.

The results show a marked and significant cross-correlation between web queries on vaccine reservations and actual vaccinations against COVID-19 in Italy. On the other hand, the cross-correlation between vaccine-related news and vaccine web searches is low.

Answer: I thank the reviewer for the comprehensive summary and positive comments regarding this paper.

Minor comment 1: I think that the limitations of this study are much broader than those listed in the work. There is a strong vaccine hesitation movement across different European countries, which could at least be mentioned in the work. The authors only noticed news in a newspaper on rare side effects of vaccination. This is what strongly influences, on the one hand, queries entered into a search engine and, on the other hand, a decrease in the number of vaccinations.

Answer 1: Dear Reviewer, I totally agree on the effects of vaccine hesitancy and the impact of mass media on web queries. In this regard, I have opted to introduce new results in the manuscript. Indeed, keywords related to not getting vaccinated and vaccine booking cancellations have been considered. In particular, it was shown that these keywords represented about 4% of the relative search volume (RSV) of the keyword "prenotazione vaccino" (vaccine reservation). Furthermore, the limitations section has been enriched.

Modified section: Introduction: "At present, monitoring of vaccine adherence is epidemiologically essential, especially considering the growing no-vax movement."

Modified section: Methods: Data Collection: "Following the previous methods, the keywords 'disdire vaccino + cancellare vaccino + evitare vaccino + non vaccinarsi + green pass falso + comprare green pass' (revoke vaccine + cancel vaccine + avoid vaccine + do not get vaccinated + fake green pass + buy green pass) were searched to investigate users' web interest in methods of not getting vaccinated. The first keyword searched was 'disdire vaccine.' The other terms have been selected by consulting various possible synonyms in the Treccani.it online dictionary and Google Trends related queries."

Modified section: Results: "The keywords related to the desire not to get vaccinated registered an average RSV of 4% compared to 'vaccine reservation.'"

Modified section: Discussion: Limitations: "Finally, although well targeted, there are no guarantees that all the keywords relating to the desire not to be vaccinated have been selected. In this regard, given the broad anti-vaccination movement, many users may not have expressed an online interest in not getting vaccinated."

Reviewer O [3]

Comment: The paper uses Google Trends (GT) to identify correlations between search queries and vaccinations. GT has been used previously by others for similar and other problems. The paper is well written. The Methods section can be improved. The Results section has a good explanation.

Answer: Dear Reviewer, thank you for your critical and positive evaluation of this paper.

Comment 1: The novelty of the paper is limited.

Answer 1: Dear Reviewer, I agree that some of the findings in this paper are intuitive. However, I believe that, as scientists, any analysis should not be prejudiced. For this reason, I found it helpful to provide more concrete evidence regarding the possible use of GT as a predictive tool for vaccinations. In particular, in some cases, GT's reliability has been compromised by spurious correlations with the media hype of related news. This paper provides evidence that well-targeted keywords can overcome such a problem.

Comment 2: The Introduction is short and can be extended to include more relevant studies.

Answer 2: Dear Reviewer, I agree and thank you for this criticism. I have enriched the introduction, trying to provide a thorough background on the topic. If further changes are required, I will be available to integrate them. However, I would like to try not lengthening this section too much to avoid violating the "short paper" structure (which I believe can be communicatively advantageous).

Comment 3: The Methods section needs more details. For instance, how GT works, especially when keywords are two words "vaccine reservation." Does it search for all queries that include both words vaccine and reservation or vaccine OR reservation, or does it search for an exact match ("vaccine reservation")? More search terms can be included, such as synonyms of reservation like an appointment or booking. Additionally, how was data normalized? What is lag week?

Answer 3: Dear Reviewer, I thank you very much for highlighting these fundamental issues. I propose the list of strategies I have adopted to solve these problems below.

- Queries: I have provided the URL of the search on GT to facilitate the reproducibility of the analysis. Additionally, I confirm that the Vaccine Reservation and "Vaccine Reservation" queries return highly similar results (proof [4]).
  Modified section: Methods: Data collection: "The final exact queries searched on Google Trends are reported as references."
- Queries synonyms: The synonyms have been searched on the Treccani.it online dictionary. However, the queries had a much lower RSV (proof [5]). Furthermore, even adding these queries with the "+" operator, the trends remained extremely similar (proof [6]). Since the combination of queries makes it more likely that anomalies will appear in the data sets, I have opted for a single query.
  Modified section: Methods: Data Collection: "Synonyms of the word 'prenotazione' (reservation) have been searched on the Treccani.it online dictionary. However, the synonyms queries had a much lower RSV. Besides, even adding them to the original keyword through the '+' operator, the trends remained highly similar. Since the combination of queries makes it more likely that anomalies will appear in the datasets, a single query was chosen."
- Data normalization: All data sets were normalized to 100 by multiplying individual values by the constant "100/data set maximum value."
  Modified section: Methods: Statistical Analysis: "All datasets were normalized to 100 by multiplying individual values by the constant '100/dataset maximum value.'"
- Lag week definition: The "lag week" was defined as the number of weeks by which a time series was shifted to obtain the maximum correlation with another time series. By doing so, it was possible to estimate the predictive power of one time series over another and the latency between the measurement of the first and the appearance of the second.
  Modified section: Methods: Statistical Analysis: "The 'Lag week' was defined as the number of weeks by which a time series was shifted to obtain the maximum correlation with another time series. By doing so, it was possible to estimate the predictive power of one time series over another and the latency between them."

Reviewer BL [7]

Comment: This brief paper examines the effective approach to investigating vaccine adherence against COVID-19 via GT. The topic is interesting and important to provide actionable data to the World Health Organization or other related health organizations to prioritize their risk communication efforts. The manuscript is nicely written and easy to understand. These data are of potential interest, but there are some concerns.

Answer: Dear Reviewer, I greatly appreciate the positive feedback and constructive criticism leveled at my paper.

Comments 1, 2, and 3:

1. The methodological strength is poor. It should discuss the overarching sampling method, measures, and procedures to justify the Google and news media content in this study.

2. In line with the methodology concern, the chosen keywords are questionable too.

3. Additionally, there is no rationale for sampling the historical archive of the newspaper "La Repubblica." Is this the second most read Italian newspaper online?

Answer 1, 2, and 3: Dear reviewer, I sincerely thank you for pointing out these essential points. In this regard, I have made numerous changes and clarifications in the manuscript. I have merged the answers since they are strongly correlated. In particular, thanks also to the previous reviewers' comments, I specified that all the keyword synonyms—found on the Treccani.it online dictionary—were searched on GT and showed very low RSVs compared to the final keyword chosen (proof [5]). The related queries were also consulted for this purpose. Now, I have also specified that "La Repubblica" has been selected as it was the second most read newspaper and, at the same time, the one that provides the most detailed news database. Furthermore, the choice of a single newspaper was based on the fact that previous articles found broad similarities between the news trends of the primary Italian mass media. Indeed, this is compatible with the theory of news competition and increasing returns-to-scale. The keyword used for the search on La Repubblica was chosen since it includes the generic and technical names of the vaccines administered in Italy in the investigated period.

Modified section: Methods: Data Collection: "Synonyms of the word 'prenotazione' (reservation) have been searched on the Treccani.it online dictionary. However, the synonyms queries had a much lower RSV. Besides, even adding them to the original keyword through the '+' operator, the trends remained highly similar. Since the combination of queries makes it more likely that anomalies will appear in the datasets, a single query was chosen. [...] In particular, this query includes the generic and proper names of the COVID-19 vaccines administered in Italy during the investigated period."

Modified section: Methods: Data Collection: "This newspaper was chosen since it represents the second most widely read newspaper in Italy and provides the most detailed news database online. Furthermore, a previous publication showed very similar news trends across primary Italian mass media during COVID-19. Such a result aligns with the theory of news competition and increasing returns-to-scale, which prompts profit-motivated media to publish on hot topics (as of interest to a broad audience). For these reasons, the author of this paper considered the source 'La Repubblica' sufficient to represent the Italian media clamor about vaccines."

Comments 4 and 5:

4. Confounding is a statistical concept that is important to all researchers. The concept of confounding is explained with the help of an amusing but true example. The methods to deal with confounding should be more detailed, with more applications and disadvantages to be examined.

5. The role of the mass media was considered as a confounding factor. Actually, confounding is said to exist when a third factor, known as the confounding variable, explains the association between two variables. One of the results indicated that vaccine reservation queries (VRQs) and news about COVID-19 vaccines have been low and characterized by lags. I am afraid this could be a failure to identify and control for confounding, which could result in the faulty interpretation of study outcomes. So, you really can't say for sure whether the lack of news influence (ie, from one specific website only) leads to the unwillingness of vaccination.

Answers 4 and 5: Dear Reviewer, I agree both with the importance of clarifying the concept of confounding and that this paper has not been able to analyze all the possible confounders. In this regard, I have substantially modified the manuscript to clarify the role of this research. In addition, to improve the quality of the evidence, I introduced Holm-Bonferroni correction and multiregression analysis. In particular, I kindly invite you to read the modified and new sections, which should be exhaustive from this point of view.

Modified section: Methods: Data Collection: "Following the previous methods, the keywords 'disdire vaccino + cancellare vaccino + evitare vaccino + non vaccinarsi + green pass falso + comprare green pass' (revoke vaccine + cancel vaccine + avoid vaccine + do not get vaccinated + fake green pass + buy green pass) were searched to investigate users' web interest in methods of not getting vaccinated. The first keyword searched was 'disdire vaccine.' The other terms have been selected by consulting various possible synonyms in the Treccani.it online dictionary and Google Trends related queries."

Modified section: Methods: Statistical Analysis. "Finally, a multiple regression was used to build the function Y=f(VRH, VRQ) to evaluate the impact of VRH and VRQ on V. Standard errors for the regression coefficients are reported after '±.' Based on previous literature, any causal correlations between the media clamor and web searches should be sought within a maximum of ±3 weeks (acceptability range) . Indeed, the web interest in a topic must arise around the media hype peak to be considered a direct consequence of the latter. Regarding the pairs (VRH, V) and (VRQ, V), the lag acceptability range was fixed at 0 – 8 weeks since it can take up to two months from vaccine booking to administration. Fisher r-to-z transformation (z) was used to compare Spearman coefficients. Since the search for cross-correlations is highly exploratory, the Holm-Bonferroni correction was adopted (m=50 hypotheses). The original *P*

values have been reported alongside the adjusted ones (P^*) – when $P^*>.001$ – to allow the reader to interpret the data independently."

New section: Methods: Mass Media Clamor as a Confounding Factor: "As discussed above, there is solid evidence that mass media can significantly impact users' web interests. This fact increases the probability of spurious correlations due to a so-called confounding factor, defined as a 'hidden' variable (or set of variables) capable of distorting the true relationship between other apparently (un)correlated variables. In this specific case, media hype can create highly confounding scenarios. For example, a COVID-19 outbreak can generate intense news fanfare, immediately followed by a growing users' web interest in the disease. After seven days, an increase in COVID-19 cases is registered. Examining the sole couple (user interest, COVID-19 cases), it could seem that online searches predicted the increase in infections. However, by introducing the 'media hype' variable, it is observed that users' web interest is much more correlated with the latter than with COVID-19 cases. For this reason, media coverage is introduced in this analysis as a possible confounding factor capable of distorting the relationship between V and VRQ. In this regard, it is fair to admit that other confounding factors not considered in this paper could alter such a relationship in complex ways. Nonetheless, at present, to the best of the author's knowledge, media influence is the only widely reported confounding factor in the literature regarding Google Trends. Furthermore, the main research hypothesis is well-targeted, thus reducing the likelihood of spurious correlations."

Modified section: Results: "The keywords related to the desire not to get vaccinated registered an average RSV of 4% compared to 'vaccine reservation.'"

Modified section: Discussion: Limitations: "Finally, although well targeted, there are no guarantees that all the keywords relating to the desire not to be vaccinated have been selected. In this regard, given the broad anti-vaccination movement, many users may not have expressed an online interest in not getting vaccinated."

Other changes: Old results have been modified, and new results have been added.

Comment 6: Another study outcome linked the VRQs and vaccinated for their positive linear relation. Instead of a valuable research question, it sounds like common sense that most laymen would agree with.

Answer 6: Dear Reviewer, I agree that the primary hypothesis is very intuitive. However, my thought is that scientists should not be limited by their own prejudices and that, when possible, even reasonable assumptions deserve to have supporting evidence. For this reason, I thought of writing this short paper to give further strength to such a hypothesis to be able to build more effective infoveillance systems in the future.

Comment 7: Following the abovementioned concern, it is not sustainable that the conclusion shows that GT is a surveillance and prediction tool for vaccine adherence against COVID-19 in Italy.

Answer 7: Dear Reviewer, I modified the conclusion by explicitly writing that the paper provides preliminary evidence. Additionally, I recommend using GT only as a complementary tool.

Modified section: Discussion: Conclusion: "This research provides preliminary evidence in favor of using Google Trends as a surveillance and prediction tool for vaccine adherence against COVID-19 in Italy. Further research is needed to establish appropriate use and limits of Google Trends for vaccination tracking."

Comment 8: Please list the ethics issue for this study if approved.

Answer 8: Thank you very much for this suggestion.

New section: Ethical Declaration: "This study does not involve human subjects and/or animals. All Google Trends data is anonymized. Therefore, the research does not require approval from a committee. No funding was received. The author declares that he has no conflicts of interest."

Comment 9: The first letters of a term should correspond to the initials, for example, "vaccine reservation query" (VRQ).

Answer 9: Thank you for having noticed it. I changed to "vaccine reservation query."

References

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Abbreviations

GT: Google Trends
RSV: relative search volume
VRQ: vaccination reservation query

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Authors' Response to Peer Reviews

Author's Responses to Peer Reviews of "Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach"

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Companion article: https://med.jmirx.org/2022/2/e33502/

(JMIRx Med 2022;3(2):e38587) doi:10.2196/38587

KEYWORDS

human behavior modeling; cognitive twins; human digital twins; cybersecurity; cognitive systems; digital twins; Metaverse; artificial intelligence

This is the author's response to peer-review reports for "Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach."

Round 1 Review

I am very grateful to the reviewers for their constructive comments regarding my paper [1]. I diligently considered the comments and made these key changes:

Reviewer Z [2]

1. The author states that this paper proposes an application of Digital Twins (DT) and Human Digital Twins (HDT) for the first time. This is not exact, as, in the last 2 years, there have been some approaches to the use of DT in cybersecurity.

The author should include some of these ideas in the literature review.[...]

Response: I removed the claim that Reviewer Z had mentioned for added clarity. I did not discuss the recommended literature that does not involve Human Digital Twins (HDT) or any cognitive feature. Instead, I discuss 5 papers about autonomous agents (cognitive twins) for cybersecurity in the *Prior Work* subsection. I also emphasized the differences between those autonomous agents and HDTs in the *Conclusions* section to refocus the audience's attention on HDTs for cybersecurity—the paper's main research topic.

2. In the literature review, the author should add a definition of DT and HDT, how HDT surges from the concept of DT, a comparison between both techniques, and finally a list of the main uses of DT and HDT.

Response: I made clearer the definitions of DT and HDT and added a brief definition of Metaverse in the *Introduction* section and the *Backgrounds on HDTs* subsection. I also point the

audience to the *Prior Work* subsection for a list of most relevant use cases for cognitive twins (autonomous agents).

3 and 4. In the literature review, the author claims that there is no grounded vision of the power of DT and HDT. In addition to the fact that, as I mentioned before, there are already applications of DT to cybersecurity, nothing is mentioned about proactive cyber defense existing techniques. What can DT and HDT add to the existing techniques?

The author states that the framework targets the cognitive process of a malicious actor as an HDT within a DT system. What is the purpose of this? The author must explain why these decisions were made.

Response: I added two paragraphs (the second and fourth paragraphs) in the *The General Landscape* subsection and discuss use cases of cognitive twins in the *Prior Work* section. Those details, the *Backgrounds on HDTs* and the Cybonto Conceptual Framework for a total of 15 related references should give the audience a good sense of the needs, benefits, and basic mechanisms of HDTs for cybersecurity vision.

5 and 6. Regarding Table 1, how was the total score calculated? There should be a description of every item. How was the score of every item calculated? An explanation is necessary.

Related to the above, it is good to have all the information in GitHub, but, at least a brief and clear description of the obtention of cybersecurity-related behavioral theories, and another description of the ontology should be provided in the manuscript or in a Multimedia Appendix.

Response: A paragraph was added for a brief explanation of table metrics calculations. I also added the Cybonto main hierarchies figure (Figure 1). Figure 1 and figure 2 should be able to convey the Cybonto core details. I emphasized the need of visiting the GitHub repository for the most up-to-date of all the artifacts at least two times in the paper. I believe it is the best way for the JMIR readership. For example, it is best to download the latest Cybonto and browse it interactively via Protégé.

7. An explanation of Figure 1 is needed.

Response: The original Figure 1 (Cybonto Conceptual Framework figure) was explained in the entire "Expanding the Vision With The Cybonto Conceptual Framework" subsection.

8. Without a clear description, the rest of the paper, although interesting, is difficult to follow.

Response: I added new sections and reformatted the entire paper per JMIR author guidelines. I hope that makes the paper easier to follow.

9. In broad terms, I understand the goal of the ontology, but it is so abstract that it is difficult for me how to apply it to proactive cyber defense. Some examples would be welcome.

Response: I added the "Prior Work" subsection and discuss interesting use cases of applying human-like agents (cognitive twins and autonomous agents) in the physical-cyber security domain.

10. Last, a general comment: this is the Journal of Medical Internet Research. Though other topics are welcome, and it is clear that security is capital in the medical field, some particular comments about cybersecurity in the medical field would be desirable.

Response: I reworked the "Conclusions" section with an emphasis on the potential use of Cybonto in virtual patients for applied psychology training, automatic behavioral annotations, and analysis of Electronic Health Records, and virtual agents for community psychology experiments.

11. In the introduction, the author states that "incredibly," HDT offers the capability of running large-scale simulations. Why "incredibly"?

Response: I removed "incredibly."

12. In the introduction, the author claims that "Analyzing the Cybonto ontology informed the Cybonto conceptual framework." I do not understand this sentence.

Response: I reworked the "Introduction" section and removed the confusing sentence.

13. The author defines the in-group environment acronym as IGE, but it appears as IEG in the rest of the paper.

Response: I corrected the typographical errors.

Round 2 Review

Reviewer Z

1. In Table 2, what are PR, EC, BC, and DC?

Response: PR stands for "Page Rank," EC stands for "Eigenvector centrality," BC stands for "betweenness centrality," and DC stands for "degree centrality." I added table footnotes to clarify this information.

References

1. Nguyen TN. Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach. JMIRx Med 2022;3(2):e33502 [FREE Full text]
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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"

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KEYWORDS

COVID-19; sport; injury; prevalence; cause; data; statistics; pain; training; practice; physiology; adaptation

This is the authors' responses to peer-review reports of "COVID-19 Return to Sport: NFL Injury Prevalence Analysis"

Round 1

Thank you for reviewing our paper [1]. We have provided response in regard to all editorial and reviewer comments.

Reviewer D [2]

General Comments

Thank you for your comments on our paper and for taking the time to review our research.

Specific Comments

1. Thank you for your comment. The data used in this study are publicly available data. As defined by United States Department of Health and Human Services policy 45 CFR 46.102, publicly available data do not qualify as human subjects research and do not require institutional review board approval. However, the authors of this research strive to uphold all principles of ethical research and principles of medical ethics.
2. Thank you for your comment; we have included in the introduction and methods that contact injuries are included in this study, as football is a contact sport, making contact a nonmodifiable risk factor.

Anonymous [3]

General Comments

Thank you for your comments and taking the time to review our paper. We have addressed the hours as a limitation, and we do not have access to the individuals or their specific training hours as we used a public data set. We also addressed the fact that there would be potential recall bias, as the research goes several years into the past and may not provide an accurate

number of hours per year if this were to be undertaken. We also have added support that there was a reduction in training among the majority of athletes across all levels of sport due to lockdown restrictions to mitigate the spread of COVID-19. We have also provided support that the National Football League training facilities were shut down between March 25, 2020, and May 19, 2020. We expanded on the conclusion as we have evidence of reduction in training across all levels of sport and facility closures due to COVID-19 precautions.

Specific Comments

1. Thank you for your comment. We have defined resistance exercise and changed the wording of “post-resistance exercise” to “after resistance exercise” in order to provide a clearer description.
2. Thank you for your comment, we have removed the cited figure from the abstract.
3. Thank you for your comment. We have provided rationale within the methods section as to why sick days were not included. Sick days were not included due to the fact that literature from other sports analyses have stated that it is best to report incidence of illness separate from injuries. In addition, sick days would not accurately represent the possibility of increased injuries due to less training and could potentially create a confounding variable.

Conflicts of Interest

None declared.

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study"

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Companion article: https://med.jmirx.org/2022/2/e22912/

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KEYWORDS

depression; diabetes; electronic health records; acute care; PLS-SEM; path analysis; equation modelling; accident; emergency care; emergency; structural equation modelling; clinical data

The author's response to peer-review reports for "Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study."

Round 1 Review

Thank you for the review of this submission [1] to the Journal of Medical Internet Research. We have considered the comments carefully and have revised the manuscript to address the issues raised. Our responses to the points made by the two reviewers [2,3] are detailed below.

We have submitted a revised version of the manuscript without tracked changes as requested. A copy of the manuscript with tracked changes has been included in the submission as a supplementary file.

Reviewer CJ [1]

General Comments

This paper takes structural equation modelling (SEM) and uses it in a novel way that could be beneficial for researchers and clinicians alike. The results and discussion are transparent, and do not overstate the findings. The researchers created a complex model that could demonstrate the benefits of use of this data analysis method in other health care contexts. The future directions and recommendations are realistic.

Specific Comments

Major Comments

1. Lacks a statement of the study design. SEM is the method of analysis, not the study design.

Response: We have now amended the Methods subsection "Data Source and Study Design" to include a statement indicating that this study was a cross-sectional observational cohort study (p4).

Minor Comments

1. Write out "A&E" in title and first mention in text of abstract.
   Response: Thank you for pointing this out. We have now amended the title and abstract.
2. In the Introduction and second section, you have 2 statements that are in close proximity and convey similar information. I would consider revising. Introduction statement: "Therefore, we sought to determine whether SEM could be used to make this data set more 'research friendly' by attempting to create clinical constructs and model some well-known clinical associations between depression and accident & emergency (A&E) use in patients with type 2 diabetes." Next section statement: "Therefore, we sought to test whether SEM could be applied to a large routine clinical data set from East London to model these associations between depression, diabetic care, diabetic control, and A&E utilization, while assessing the impact of current mental health care provision." Perhaps go with the second one.
   Response: Thank you for pointing this out. We agree it is somewhat repetitive and have amended the second statement so that it is now a development of the first statement (p3).
3. Measures of Mental Health Diagnosis and Care - The information on the AUDIT seems misplaced or excessive since other outcome measures are not explained in that amount of detail. Consider removing: "Scores on the AUDIT range from 0-40, with higher scores indicating higher risk of dependence. The AUDIT C consists of the three consumption questions from the AUDIT and scores can range from 0-12, with higher scores indicating higher risk."
   Response: We agree that we provide what seems to be an excessive description of the alcohol intake measures. This is because the variable itself was complex as the AUDIT and the AUDIT-C were combined in the data set (by the commissioning support unit), which led to two different scales being used to measure the same thing. For full transparency, we feel that we need to include this rather lengthy description in the paper. We believe it also reflects the complexity of using routine clinical data and data linkage.
4. I don't think you need to state this: "A full description of the adult mental health care cluster codes used by the NHS can be found here: (link)." Just state those are the clusters you chose, and why.
   Response: We agree and have now deleted the sentence and link.
5. Data Source: Consider explaining what the intended purpose of each data source/database is. These are largely unknown to anyone outside the UK health care context and will require more detail.
   Response: We agree that more detail is required for non-UK readers and have now provided a more detailed description of the data sources on page 4.
6. More explanation of what partial least squares (PLS) SEM is might be beneficial for the reader.
   Response: We have added some further explanation of PLS-SEM with appropriate introductory references for the nonstatistician on p3 of the manuscript as follows:
   "Structural equation modelling (SEM) is a statistical technique that allows for the inclusion of multiple variables and the creation of important constructs that cannot be observed directly. Partial least squares SEM (PLS-SEM) is a variant of SEM that poses no distributional assumptions (eg, normality, continuous/scale) upon data used for modelling but is frequently used for predictive approaches with an aim to understanding causal structures. Further, PLS-SEM can be effective with a relatively small sample: approximately 10 cases per regression or 'path' estimate leading to the most connected latent variable is considered adequate, although there has been some debate about the use of PLS-SEM with very small sample sizes."
7. May benefit from explanation of why PLS versus covariance-based (CB) and other SEM types since the sample size was large (PLS-SEM is a great choice in my mind, but others may want more justification).
   Response: We have added the following text to help explain our choice of approach on p7.
   "Given the nature of the data, which consisted mainly of dichotomous indicators (eg, diagnoses) and ordinal measures (eg, AUDIT drinking scores) with only a small number of continuous observed variables (eg, HbA1c reading), PLS-SEM was selected over other SEM approaches as it allows for the use of both continuous and discrete observed variables as indicators that measure unobservable latent variables. A covariance-based SEM approach (CB-SEM) would require continuous variables with some restrictions on distribution; Bayesian networks were also considered but are entirely probabilistic in outcome and would not have given the desired effect size coefficients for different pathways."
8. State whether the structural model is reflexive or formative and justification for this.
   Response: This is a reflective model—we have added the following text on p7:
   "Our modelling approach was reflective, in that we employed observed variables from the health care data set to measure pre-existing latent variables (eg, "A&E usage") and that, to use the typology proposed by Coltman et al, causality flows from latent construct to observed variable (eg, A&E usage [construct] causes increased spend on A&E services [observed])."
9. Discussion: there are 2 similar comments in close proximity: "This might be related to a problem with the data set, which will be described later in the Discussion" and "This is not in agreement with previous research, which has shown that improvement of depressive symptoms through the use of psychotherapy and pharmacotherapy is associated with improved glycemic control. The opposite association

reported in this study is likely related to issues with data quality, which will be outlined later."
Response: We agree this is somewhat repetitive and have removed the first comment from the Discussion as it did not add a huge amount to the interpretation of the data.

10. In the Limitations section, link those statements to the above issue (10) for clarity.
Response: In the original Limitations section of the Discussion, we do link back to the previous statement when we say the following:
"The problem with the IAPT data likely affected the mental health treatment latent variable in the SEM and might help to explain why mental health treatment was not associated with poor diabetic control."

11. A statement in Future Directions and Recommendations could address issues with the data set and what should/could be done to improve this.
Response: We have now added some extra recommendations about how the data set and data sets like it could be improved:
"Improvement of data flows (eg, information about use of IAPT services) and more years of data would address issues around lack of temporality and inaccurate findings."

Anonymous reviewer

Major comments

1. The general research hypothesis should be interpreted and clarified more in the introduction.
Response: We thank the reviewer for their suggestion and have now provided some clear research hypotheses in the Introduction (p3, p4):
"We hypothesised that depression would be associated with increased diabetic complications, poor diabetic control, and that both depression and poor diabetic control would be associated with increased utilisation of A&E. We predicted that the receipt of mental health treatment would improve diabetic control."

2. Please redesign Figure 1 with better quality and interpretations.
Response: After some thought, we decided to remove Figure 1 from the manuscript as we believe Figure 2 (now Figure 1 in current version) depicts the latent variables and associations between them sufficiently.

3. Recommendations and limitations are absent.
Response: In the original manuscript, we provided an extensive account of study limitations in the Discussion section (p13). We also provided a number of recommendations (p14).

Minor comments

1. Order keywords alphabetically.
Response: We have now amended this.

References

1. Ronaldson A, Freestone M, Zhang H, Marsh W, Bhui K. Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study. JMIRx Med 2022;3(2):e22912 [FREE Full text]
2. Jones C. Peer Review of "Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study". JMIRx Med 2022;3(2):e38007 [FREE Full text]
3. Anonymous. Peer Review of "Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study". JMIRx Med 2022;3(2):e38488 [FREE Full text]

Abbreviations

CB-SEM: covariance-based structural equation modelling
PLS-SEM: partial least squares structural equation modelling
SEM: structural equation modelling

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Authors' Response to Peer Reviews

Authors' Responses to Peer Reviews of "Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study"

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KEYWORDS

physical activity; university students; university; exercise; students; inactive; curricula; healthy lifestyle; higher education

This is the authors' response to peer-review reports for "Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study."

Round 1 Review

Reviewer E [1]

General Comments

It is very positive to see analysis of physical activity in different populations and different age groups, and this paper [2] is a very welcome study in terms of physical activity in India and in relation to students. This is an important area as, when trying to engender habits and physical activity across the life span, it is in the younger age groups where sustained impact can be made. However, I feel that this paper addresses the issue quite superficially and would benefit from more in-depth analysis.

Reply: Thanks for these encouraging remarks. We have tried our level best to address the issues you have pointed out.

Specific Comments

Major Comments

1. Throughout the paper, there is no point at which the categories of inactive, active, and highly active are defined—this is a major omission as it is impossible to gauge how this compares to, for example, World Health Organization or other national guidelines in terms of minutes physical activity per week or metabolic

equivalent minutes (apologies if this is indeed in the paper and I have missed it).

Reply: Thanks for pointing this out. We have now added a section that describes the categorical classification.

2. Demographics: although the authors should be commended for looking at differences between gender and age, there is no comment on socioeconomic status. For example, earlier in the paper, when describing the university, it would be useful to know what the demographics of the student population are (ie, do they represent general society or higher socioeconomic status?) This is important, as socioeconomic status (in the United Kingdom at least) is a major driver of physical activity. It would be useful for the reader as to how the subject population compares with the general population.

Reply: This has now been included, both in introduction and discussion sections. Word Health Organization suggests that economically developed regions are likely to show trends of physical inactivity. This seems to hold true in our case as the region is economically not a very developed one.

3. It is unclear to me how the metabolic equivalent minutes values of the subject population relate to that of the general population, and internationally. Over 4000 metabolic equivalent minutes per week is several times over World Health Organization guidance, and I would expect some analysis of how and why this might be the case.

Reply: A paragraph in discussion section has now been included that lists the limitations of the study and also points out other aspects that one needs to consider while interpreting our results.

4. In the discussion, there is a lot of description of the results from previous studies, and comparison with the current study, but without any analysis as to why there are similarities or differences. I also felt there was no real incorporation of the perceptions into the discussion, and no real analytical depth.

Reply: This analysis has now been added.

5. In the discussion, there is no real discussion of the limitations of the approach used, and no contextual framing of the findings.

Reply: New paragraphs have been added to address this.

Minor Comments

Abstract; objectives: Line beginning “the study also aims...” not quite clear: perhaps “This study also aims to capture student perceptions about the balance between curricular activities and leading a physically active lifestyle...”?

Reply: This has been corrected.

Introduction: “being overweight” rather than “overweight.”

Reply: This has been corrected.

It would be useful to describe briefly what the few studies regarding students show.

Methods: validation of the new tool—more information on this would be useful: does the Cronbach alpha number represent test-retest reliability? In which case, how was validity measured?

Reply: Thanks for pointing this out. Yes, we tested the tool for its reliability and did not validate it. We have corrected this.

Data collection and data entry: “written consent was obtained from each of the participants.”

Reply: This has been corrected.

How were outliers excluded? How did the authors define “erratic entries”? Is this according to International Physical Activity Questionnaire cleaning criteria?

Reply: Yes, this was done as per the guidelines of data processing available for International Physical Activity Questionnaire—Long Form tool. This has been clarified.

Views and opinions of the students: I would want more description of the items where there was discrepancy.

Reply: We have tried our level best to do this. However, since the items are now included in each of the tables directly, this description has become self-explanatory.

Table 8: There is a comment at the end of this section regarding why the authors feel students in different faculties are performing different levels of physical activity. This belongs in the discussion.

Reply: This sentence has now been moved to discussion section.

Discussion: the study on pooled data: was this from university students?

Reply: No. These pooled data are from population-based studies. We included them to have a comparative perspective.

Tables: Table 4—why was a Mann-Whitney test used if the data presented are in mean (SD) (ie, if the data are nonparametric, shouldn’t the median IQR be used?).

Reply: When the data do not follow normal distribution, then Mann-Whitney test may be used for intergroup comparison based on rank. Median and IQR are summary measures, which may also be given; however, they are not a test of significance, and in such case, test for median (sign test) may be calculated. We prefer giving the results based on Mann-Whitney test because significance can be inferred.

Table 6-8: it would be helpful to have the questions in the table to enable the reader to better see how they relate.

Reply: This has been done now. Each item has now been included in the table.

Reviewer F [3]

General Comments

This paper [2] was about the physical activity pattern of university students aiming at measuring this for the first time systematically as well as creating a new tool in order to have more accurate results. The authors collected a large body of data over several years, which gives an accurate and realistic perspective of the physical activity patterns of university student in India. It was an honour to read this remarkable job the authors did over the years.

Reply: Thanks for these encouraging remarks!

Specific Comments

Numbered Comments

1. I find the Introduction part quite short compared to the literature mentioned in Discussion. I learned more about the literature from Discussion than from the Introduction. I'd suggest writing a slightly longer introduction with details on activity patterns of different age groups. This could also point to the missing age group data this paper focuses on.

Reply: We appreciate your observation. We have now elaborated the introduction part.

2. The authors mention in the first paragraph of the introduction, "an increased engagement with video games, cell phones, television, computers, and social media are possibly some of the important contributing factors to this trend among youth." I'd write in more detail about this or have a bigger emphasis on this perspective in the paper as the manuscript was submitted to the Journal of Medical Internet Research both in the introduction and in the discussion.

Reply: Thanks for this suggestion. We have now elaborated on these aspects both in the introduction section and in discussion.

3. The authors mention in the methods, in the study design and sampling, "time and other limitations". I'd rather mention these in the limitations part of the discussion, and I'd explicitly say what are the other limitations not listed here. The authors write "approximately 4600 students" in this section. On the other hand, I read the exact number later. I'd suggest writing the exact number because it is accessible.

Reply: These issues have now been addressed accordingly.

4. In the "translation and revalidation" part, the authors mention a "professional" who did the translation and retranslation. I find it important what professional they were? Translators, interpreters, psychologists, English teachers? What profession did they have? You also mention "suitable corrections were made." What does this mean? Were certain items deleted based on certain criteria? I am not sure I understand the last sentence, "both the versions of the tool were used in the study to collect data based on student preference." I wonder if it would be possible to make it clear what two version were used?

Reply: Clarification on this aspect has now been provided in the manuscript.

5. In the "development of a new tool," I was wondering in what language did you state these questions? My understanding is that in Hindi. I'd suggest writing it explicitly. I also wonder why these 5 items were used? what was the process of creating these items? Were there possibly more, and then you deleted the ones that did not work? What did you base your decision on to use these exact 5 items?

Reply: The clarification has been now provided in the manuscript.

6. In the "validation of the new tool," you write "acceptable range." I suggest giving a literature reference on what you based your decision on, what is acceptable, and what is not. I read the manuscript, and you reported the Cronbach alpha. In my understanding, this means the tool is reliable; however, was not validated. For example, correlation with other tools.

Reply: Appropriate reference has now been added. As you have rightly pointed out, the tool was tested for reliability and was not validated. We have rectified this error.

7. The authors reported the data collection was between 2016 and 2019. This is a long stretch of time, and physical activity patterns can change in different groups year by year. I'd suggest for the authors to consider a statistical analysis on the data year by year. For example, people who filled out the questionnaire in 2016, the ones in 2017, and so on.

Reply: We did not address this as it would not give any additional inputs. However, a clarification to this effect has been included in the discussion section.

8. I read in the results you reported significant and not significant results. I'd consider writing a sentence about the direction of significant results. For example, "the difference between physical activity of students of different age groups was statistically significant." I'd find useful to read a sentence about which age group was more active and which one less active.

Reply: This has now been addressed suitably.

9. I'd find it useful if I could read the results in hour as well, beside reading it in minutes. As far as I understand, the tool used reports in minutes. However, it would be easier to read if I could read it also in hours.

Reply: We did not do this as International Physical Activity Questionnaire—Long Form questionnaire captures the activities in terms of minutes only. Conversion into hours is not usually recommended. Neither in the literature we find such reporting.

10.I'd suggest using the last sentence of the results in the discussion. "Hence, it ca be presumed that the students in these faculties get some or the other kind of motivation to lead a physically active lifestyle as a part of their curriculum."

Reply: Thanks! We have done this.

11. The authors write in the discussion, "this is possibly one of the first studies from India that looks at psychical activity…". I'd suggest not using the phrase "possibly." After having read the literature on India about psychical activity of students, it can be said if this is the first or one of the first papers reporting on the matter.

Reply: We have corrected this.

12. I'd find it useful to have a section for abbreviations.

Reply: This has been done now.

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study"

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KEYWORDS

pharmacogenomics; pain management; drug-drug interaction; DDI; pharmacy; prescriptions; genetics; genomics; drug-gene interaction; pain

This is the authors' response to peer-review reports for "Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study."

Round 1 Review

Reviewer AI [1]

General Comments

Authors of this manuscript [2] have determined the impact of pharmacogenetic (PGx) testing on pain medication prescribing. A retrospective analysis was conducted with 171 patients in a pain management clinic during 2016 to 2018 within the western United States. A novel deep sequencing (>1000X) PGx panel is described encompassing 23 genes combined with PGx dosing guidance, drug-gene interaction (DGI), and drug-drug interaction (DDI) reporting to prevent adverse drug reaction (ADR) events. This manuscript is interesting and well-written. However, the Methods and Discussion section of the manuscript could be improved for clarity. Please refer to my comments below.

Specific Comments

Major Comments

Abstract

1. What was the primary outcome of this study? Is it to report the number of cases where PGx information could be used to optimize drug dosing?

Response: Correct, but also to summarize the type of drugs altered and scenarios in a clinic that had never utilized PGx reports before, as much as possible based on urine drug toxicology (UDT) data and with limited access to patient progress notes, to better describe this:

Abstract: Objectives section was changed to "The following study summarizes an extended pharmacogenomic (PGx) sequencing panel intended for medication dosing and prescription guidance newly adopted in a pain management setting. The primary outcome of this retrospective study reports the number of cases and types of drugs covered, for which PGx

data appears to have assisted in optimal drug prescription and dosing."

The introduction sentence was changed to "The aim of this study is to evaluate the overall utilization and describe how PGx report recommendations (including genetic based dosing guidance (PGx), drug-gene interaction (DGI) and drug-drug interaction (DDI) based guidance) were applied to optimize drug dosing in a clinical setting which had not previously relied on pharmacogenetic test reports. Changes in prescription, patient compliance and drug usage were monitored based on updated medication lists and data in associated quantitative urine drug toxicology (UDT) reports, with limited access to patient progress reports."

2. "This study demonstrates a successful implementation of PGx testing utilizing an extended PGx panel combined with a customized, informational report to help improve clinical outcomes." Did authors develop a software platform to generate a customized, informational report to help improve clinical outcomes? I do not see any discussion on this matter.

Response: Yes, this may have not been described enough but was mentioned in the Methods section 2.6; the following has been added to section 2.6:

"Specifically, to accommodate reporting based on 23 genes, 141 SNPs or indels, and associated haplotypes newly combined in this panel (Supplementary Table 1), TSI bioinformaticians collaborated with Alcala Testing and Analysis Services (ATAS) scientists to include the most up-to-date guidance across 2 evidence levels for PGx dosing and drug-drug interactions (DDI) (Fig. 2). Recommendations from six different international pharmacogenetic consortia, professional societies or regulatory bodies (Clinical Pharmacogenetics Implementation Consortium - CPIC, Dutch Pharmacogenetics Working Group - DPWG, US Food and Drug Administration - FDA, European Medicines Agency - EMA, Canadian Pharmacogenomics Network for Drug Safety - CPNDA, American College of Medical Genetics and Genomics - ACMG) were incorporated in the reporting algorithm. The updated recommendations covered 13 drug categories and 198 drugs with a major emphasis on Pain, Psychiatry and Addiction Medicine drugs (Supplementary Table 3)."

What were the parameters of the effectiveness and safety of treatment in evaluated patients? Did you do any statistical testing to find an association between the presence of a polymorphic gene variant and the impact of pharmacotherapy? Did you have a control group?

Response: Changes in prescription, patient compliance, and drug use were monitored based on updated medication lists and data in associated quantitative UDT reports, with limited access to patient progress reports. Therefore, the effectiveness and safety of treatment could not be established through progress notes and on a limited basis for the 3 case studies (assuming routine clinical practice in a pain management setting). UDT reports were the primary source of information to monitor and evaluate if changes in prescriptions were made and if recommendations of the PGx report were followed. The evaluation could only focus on the PGx report recommendation given by consortia guidelines and could not determine prescription changes based off of polymorphic gene variants themselves. There was no control group to evaluate as this was data focused on patients (N=171) from one pain management clinic only.

Introduction

3. I would be interested in having a brief introduction to currently available PGx panels, and what the strengths of the panel in this study are.

Response: An excellent review of currently available PGx panels as of 2018 has been summarized in the Introduction section as follows: "In 2018, Fabbri et al. described 38 commercially available PGx test panels offering personalized medication prescription guidance in clinical settings. The only genes included in all of these panels are CYP2D6 and CYP2C19. Thirty-one out of the 38 panels (82%) include 8 genes or less (15). PGx testing as described in this study encompasses deep sequencing (>1000X) of 141 SNPs or indels across 23 genes by Next-Generation Sequencing."

Methods

4. "23 genes were selected based on having the most clinical utility in PGx at the time of design in April 2016 (ADRA2A, CES1, COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DRD1, DRD2, F2, F5, GNB3, HTR1A, HTR2A, HTR2C, MTHFR, OPRM1, SLC6A2, SCL6A4, SLCO1B1, VKORC1)." What were the criteria used to narrow down genes that authors considered of most clinical utility in PGx?

Response: Updated this paragraph to reference the process with Translational Software Inc (TSI) to select genes and haplotypes as updated in section 2.6: "23 genes were included in the described PGx panel at the time of design in April 2016 (ADRA2A, CES1, COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DRD1, DRD2, F2, F5, GNB3, HTR1A, HTR2A, HTR2C, MTHFR, OPRM1, SLC6A2, SCL6A4, SLCO1B1, VKORC1), to include the most up-to-date guidance covering 198 drugs with a major emphasis on Pain, Psychiatry and Addiction Medicine as described below in section 2.6."

5. "75 target regions were covered by 82 amplicons with an average amplicon size of 250 base pairs (bp)" Can you elaborate on 75 target regions? Did the authors have multiple target regions per gene? If so, details should be provided.

Response: Elaborated upon in changes in section 2.2, 75 is a typo, should be 79: "Unique reference single-nucleotide polymorphism cluster ID (rsID) numbers were assigned per target coordinate and region. 79 target regions (defined across Start and Stop coordinates, see Supplementary Table 1) covering 141 SNPs or indels were covered by 82 amplicons with an average amplicon size of 250 basepairs (bp) across 23 genes. Multiple target regions covering multiple rsIDs were targeted across each gene (e.g. 27 rsIDs within CYP2D6, see Supplementary Table 1)."

6. What were the medical conditions of patients with pain management in this study? Was it varied across patients in this cohort? I would like to see the authors' discussion on this.

Response: As previously described the full treatment history of outcomes, effectiveness, and safety of treatment could not be established through progress notes and only on a limited basis for the 3 case studies. The medical condition of each patient could not be established, as these were "snapshots" of patients' prescriptions during treatment based on UDT reports being the primary source of information to monitor and evaluate if changes in prescriptions were made and if recommendations of the PGx report were followed. A further result and discussion section on this would also exceed the length and focus of this manuscript.

7. "PGx reporting were obtained retrospectively from patients (n=171) in a pain management clinic representing an ethnically diverse patient population from 2016 to 2018 within the western United States." Although authors report that they have an ethnically diverse patient population, no descriptive statistics on demographics, age, and clinical information was provided.

Response: Essentially correct, the population within the western United States and San Diego area was assumed to be relatively ethnically diverse; while the age of patients was available, there were no demographic data available for this San Diego cohort (SDC) patient population from 2016 to 2018. However, Table 2 compared the SDC to 5 super populations from the 1000 Genomes Database. Additional statistics were now performed by the authors (see new Supplementary Table 6) to better characterize the SDC to the 1000 Genomes Database frequencies; therefore, the sentence in the Methods on page 4 has been changed to "...representing a patient population from 2016 to 2018 within the western United States. While no patient demographics data was available, Table 2 shows the genotype frequencies of the 'SDC' cohort of this study compared to 5 super populations from the 1000 Genomes Database: African (AFR), South Asian (SAS), Ad Mixed American (AMR), East Asian (EAS) and European (EUR). Pearson's correlation analysis (Supplementary Table 6) showed the 'SDC' cohort positively correlates to all allele frequencies in the 1000 Genomes Database (ALL=0.76, *P*=1.019 x 10-11). SDC cohort (n=171) closely correlates to the Ad Mixed American (AMR=0.77), European (EUR=0.78) and South Asian (SAS=0.78) super populations but is less representative of the East Asian (EAS=0.54) and African (AFR=0.55) population frequencies." Also see note in point 11 below.

8. What factors were tested on urine toxicology and progress report?

Response: Added "see sections 2.6 and 2.7" in Methods introduction paragraph. As per reviewers point 2 above, section 2.6 was elaborated on by adding: "Specifically, to accommodate reporting based on 23 genes, 141 SNPs or indels, and associated haplotypes newly combined in this panel (Supplementary Table 1), TSI bioinformaticians collaborated with Alcala Testing and Analysis Services (ATAS) scientists to include the most up-to-date guidance across 2 evidence levels for PGx dosing and drug-drug interactions (DDI) (Fig. 2). Recommendations from six different international pharmacogenetic consortia, professional societies or regulatory bodies (Clinical Pharmacogenetics Implementation Consortium - CPIC, Dutch Pharmacogenetics Working Group - DPWG, US Food and Drug Administration - FDA, European Medicines Agency - EMA, Canadian Pharmacogenomics Network for Drug Safety - CPNDA, American College of Medical Genetics and Genomics - ACMG) were incorporated in the reporting algorithm. Integrated recommendations covered 13 drug categories and 198 drugs with a major emphasis on Pain, Psychiatry and Addiction Medicine drugs (Supplementary Table 3)."

Section 2.7 specifies details on the drug adherence testing

"Urine toxicology reports reviewed by clinical laboratory scientists with ASCENT™ review software (IndigoBio Automation, Carmel, IN) (21) were made available by routine HPLC-MS/MS presumptive and confirmatory urine drug testing at ATAS from 2016-2018 (22)."

Results and Discussion

9. While the manuscript describes 3 patients (patient A, B, and C) who did not stick to the treatment regimen and drug response adversaries, did patients who stuck to treatment regimens based on PGx testing show any side effects or did they do any survey for reporting pain symptoms? For example, were they tested for ADRs or partial or complete response to treatments?

Response: As described above, the full treatments themselves and side effects could not be established through progress notes and only on a limited basis for the 3 case studies. The medical condition of all patients could not be established, as these were "snapshots" of patients' prescriptions during treatment based on UDT reports being the primary source of information to monitor and evaluate if changes in prescriptions were made and if recommendations of the PGx report were followed. A further Results and Discussion section on this would also exceed the length and focus of this manuscript.

10. I would like to see a discussion on key limitations of this study and further improvement on this study.

Response: Good point, the following paragraph has been added to the Discussion section: "Limitations within the retrospective study presented here include lack of detailed patient demographics associated with UDT and PGx reports, limited access to progress notes and long-term treatment outcomes. Rather than resorting to 1000 Genome Database population frequencies to characterize the SDC cohort, specific demographics and additional case studies as the three presented above would allow more comprehensive insights as to the combinatorial effect of prescription drugs among polypharmacy, pain management patients."

11. Have you looked into genotype frequencies of different ethnic populations in your study? What benefits do you anticipate by studying PGx-guided treatment interventions on diverse ethnic populations?

Response: As there are no descriptive statistics on demographics for this particular patient population from 2016 to 2018 and we changed the sentence to "...representing a patient population from 2016 to 2018 within the western United States...," this is a good point, and Table 2 does at least provide an overview of

population frequencies of relevant genotypes across 5 super populations (1000 Genomes Project). We think studying PGx-guided treatment interventions on diverse super populations show all populations are possibly affected for these serious ADRs, albeit at less frequency for certain metabolizer types. The authors have added more description in the Results section on page 8 as to how serious ADRs caused by PGx guidance based on only the genotype have been observed in this study (see Figure 3) affecting mainly CYP2D6 and CYP2C19 poor or rapid metabolizer types: "Phenotypes and associated genotypes were summarized in Table 2 with an overview of population frequencies compared to this 'SDC' cohort. As shown in Figure 3, 5.5% of 146 patients showed serious adverse drug reactions (ADRs) based on changes in either CYP2C19 (Poor, Intermediate to Rapid metabolizers), CYP2D6 (Poor or Ultra-Rapid Metabolizers) and one SLCO1B1 reduced function genotype. CYP2C19 genotype frequencies for 3 metabolizer types causing serious ADRs are spread across all 5 super populations ranging from 0.9 to 47.4% frequency (Table 2, CYP2C19 section). CYP2D6 genotype frequencies for Intermediate to Ultra-Rapid Metabolizers range from 1.2 to 57.1% frequency and SLCO1B1 Poor Function genotypes from 1.8 to 37% (Table 2, CYP2D6 and SLCO1B1 section). While South Asian (EAS) population frequencies for CYP2C19 Ultra-Rapid Metabolizers and CYP2D6 Poor Metabolizers are determined as non-existent in the 1000 Genome Database data, more recent studies show frequencies of 0.24% (23) and 0.84% (24) respectively, indicating possible occurrence within the EAS super population."

And in the Discussion section on page 11:

"Serious ADRs can occur based on incidences of these metabolizer types in all 5 super populations for prescriptions such as amitriptyline, citalopram or clopidogrel, metoprolol, paroxetine, simvastatin and tramadol."

Conclusion

12. "This study demonstrates the predictive value of PGx testing combined with a customized informational report to help improve clinical outcomes, which resulted in increased utilization on patients in a pain management setting." On what basis do the authors claim increased utilization on patients in a pain management setting? Did you do any statistical analysis to back up this statement?

Response: As described in the changes to the Abstract and Introduction, the clinical setting described had previously not relied on PGx testing and reports, and therefore, the utilization was studied, which showed changes in prescriptions based on PGx report recommendations. "Increased utilization" may have been the wrong wording, rather "successful application"; the discussion sentence was changed to:

"In summary, the effect of PGx reports newly made available to medical staff in this context seems quite significant as observed by the individual PGx dosing/metabolizer status, DGI and DDI recommendations showing a corresponding modification of the medication regimen for each patient. Preventative action was observed for all serious interactions and only moderate interactions were tolerated where there may not have been other alternatives. This study demonstrates the predictive value of PGx testing combined with a customized informational report to help improve clinical outcomes, which resulted in successful application on patients in a pain management setting."

Reviewer CK [3]

General Comments

This paper touches a very important and clinically relevant issue of adverse drug interactions with genetic variations and how these variants affect the patient's response to the specific drug. It focuses on utilizing pharmacogenetic (PGx) testing in clinical practice, which takes into account these relevant drug-genome interactions when prescribing drug therapy. They appropriately chose an acceptable sample size >150 and follow them for a significant period of time (>18 months). Importantly, they have performed retrospective studies, which makes a good case for the utility of PGx testing. They also lay a good background on what other technologies for PGx testing are being routinely used in current clinical settings.

Specific Comments

Major Comments

I have no negative comments for this paper; here are some positive comments:

1. I especially find it very impressive that various figures and tables were added to the paper, which shows their thorough work. Figure 1 clearly describes PGx testing compared to UDT reports. Figure 2 indicates the potential drug-gene and drug-drug interactions as provided by the PGx testing and suggests alternatives in case of serious and moderate interactions based on information from various regulatory bodies. Tables 1 and 2 are of significant interest because they focus on genotype, phenotype, and population frequencies for the genes in the panel. Figure 3 focuses on the importance of PGx testing in identifying moderate to serious drug-drug or DGIs.

Overall, I find this study very impactful especially with the advent of individualized drug therapy and targeted drug recommendations.

2. The results and discussion focus on how recommendations and dosage were changed based on PGx reports and resulted in favorable outcomes for the patients. This shows the utility of PGx in areas where health care professionals are not aware of these interferences or interactions between drug-gene and drug-drug.

3. I am not sure how many clinically relevant genes have changed or updated since April 2016, but this paper lays the groundwork for a more up-to-date gene panel to be used. I would be interested in seeing the outcome with a more up-to-date gene list but that does not necessarily have to be addressed in this paper.

Minor Comments

4. This was a very legibly worded paper, and I found no issues with the English or the scientific language that was used.

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Abbreviations

ADR: adverse drug reaction
AFR: African
AMR: Ad Mixed American
ATAS: Alcala Testing and Analysis Services
bp: basepairs
DDI: drug-drug interaction
DGI: drug-gene interaction
EAS: East Asian
EUR: European
PGx: pharmacogenomic
rsID: reference single-nucleotide polymorphism cluster ID
SAS: South Asian
SDC: San Diego cohort
TSI: Translational Software Inc
UDT: urine drug toxicology

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study"

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KEYWORDS

Extended Parallel Process Model; COVID-19; lockdown; public acceptance; nonpharmaceutical measures; Likert scale; France

This is the authors' response to peer-review reports for "Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study."

Round 1 Review

We are grateful to the reviewers [1,2] for the truly helpful comments they made when revising the previous manuscript. We did our best to be receptive when revising our paper [3]. Please find below a detailed point by point response. Please note that all changes are marked in bold in the revised manuscript.

Specific Comments

1. Your title needs to follow the guidelines of the journal to which you are submitting.

Response: We have revised the title to reflect the guidelines of the journal.

2. The "Background" and "Methods" subsections of your Abstract need to be improved.

Response: As recommended, the Background and Methods subsections of the Abstract have now been improved.

3. The specific objectives of the paper need to stand out as a subsection.

Response: We have added the specific objectives of the paper as a subsection.

4. Major subsections are missing in your introduction, methods, and the results.

Response: We have added the subsections in the different sections of the manuscript.

5. Some subsections in the Methods section warrant improvement.

Response: We have revised the subsections of the Methods section based on additional feedback from the Major comments section.

6. The structure of the Discussion section needs to align with the guidelines.

Response: We appreciate the suggestion and have aligned the Discussion section with the guidelines.

7. The in-text citations and references must comply with the journal's guidelines.

Response: The citations and references now comply with the journal's guidelines.

8. Tables and figures in the appendix need to be moved to the body of the text.

Response: We appreciate the suggestions and have revised the title and abstract in response to the specific comments.

Major Comments

1. Format your title to include the country and study design. Kindly refer to the guidelines for titles [4]. For instance, "Acceptance of COVID-19 preventive measures as a trade-off between health and social outcomes in France: Cross-sectional Study". By the way, I have not seen anywhere in the body of your paper where health and social outcomes mentioned in your title have been articulated.

Response: We have changed the title to reflect the recommendation and remove the health and social outcomes that are not mentioned in the paper.

2. The beginning of your background in the Abstract ("A better understanding of the factors underlying their acceptance may contribute greatly to the design of more effective public health programs during the current and future pandemics") does not make it clear to the reader to whom you are alluding. Kindly rephrase.

Response: As recommended, we have revised the sentence to clarify the point we aimed to make.

3. Your objectives need to be improved. I guess along the lines of (1) measure the public's acceptance of COVID-19 preventive measures and (2) assess the association of the public's acceptance of these measures and their perception of COVID-19.

Response: We are grateful for the suggestion on how to improve the objectives. We have revised the objectives accordingly.

4. In the "Methods" subsection of your Abstract, kindly add a summary of how data for each objective was analyzed and the statistical package that was used to perform the analysis. Please note that your Abstract (currently <250 words) can go up to a maximum of 450 words. Response: We have revised the Methods subsection accordingly to reflect how the data were collected and analyzed for each objective as shown below.

5. It would be good to include the following items under Introduction after the background: (1) study rationale, to justify your study and to present the Extended Parallel Process Model, and (2) specific objectives, to clearly outline your study objectives.

Response: We agree with the suggestion and have added the subsections under Introduction.

6. Kindly start your Methods section with a subsection "Study Design" and specify your study design.

Response: Study Design has been added as the first subsection in the Methods section.

7. The statement under Participants and Procedures—that is, "The objective of the research was to assess the emotional, cognitive, and behavioral responses of the French people to the COVID-19 epidemic during the full lockdown (wave 1) and thereafter (wave 2)"—should not be there. You might want to move this to the study aim or specific objectives.

Response: We agree and have made the revision.

8. The second to last statement under Participants and Procedures ("For this study, we analyzed data from a 2-week survey administered 6-8 weeks after the first lockdown between June 25 and July 5, 2020") does not fit quite well under this subsection. I suggest you rephrase as "This was a 2-week survey administered 6-8 weeks after the first lockdown of June 25 through July 5, 2020" and incorporate it into your Study Design subsection.

Response: We have added the suggestion to the Study Design subsection.

9. The last sentence under Participants and Procedures needs to be moved to a section entitled "Ethical Considerations" to be created at the end of the Methods section (just before the Results section).

Response: We agree and have moved the sentence to an "Ethical Considerations" subsection.

10. Kindly start your Results section with the subsection "Participant Characteristics" to give a summary of participant characteristics. Kindly move your Table 1 in the appendix to accompany your participant characteristics.

Response: As suggested, the Results section now starts with Participant Characteristics.

11. You need to move Tables 2-4 in the appendix to where they are first mentioned in the Results section for easy comprehension. It becomes easy to refer to the tables while reading. In addition, bear in mind that you are allowed to include up to a total of 5 tables in the body of your text.

Response: We have moved Tables 2 to 4 where they are first mentioned in the Results section.

12. Move Figure 1 to where it is first mentioned in your Results section.

Response: We have uploaded Figure 1 as a spare file, in accordance with journal guideline. It is indicated in the Results section where it should be inserted.

13. Kindly organize your Discussion into (1) Principal Results, (2) Comparison With Prior Studies, (3) Study Limitations, and (4) Conclusion.

Response: The Discussion is now organized as suggested.

14. The in-text citations and references must be in line with the AMA citation style, in accordance with the journal guidelines [5]. Kindly refer to the references accompanying this report.

Response: The in-text citations and references are now in accordance with the journal guidelines.

Minor Comments

15. Based on your title, I guess your study aimed to evaluate the acceptance of COVID-19 nonpharmaceutical measures. I suggest you add to your background (both in the Abstract and the Introduction) a study aim similar to the above and use the last sentence of your background in the Abstract to create a separate "Objectives" subsection before the Abstract's "Methods" subsection.

Response: We have revised the background in the Abstract and Introduction accordingly.

16. I suggest you rephrase sentence #2 in the methods subsection of your Abstract as "For objective 1, participants were asked the extent to which they supported 8 COVID-19 preventive measures using a 4-point Likert scale", and start the following sentence with "For objective 2, COVID-19 perceptions…"

Response: We have added the suggestions in the Methods subsection of the Abstract.

17. In the results subsection of the Abstract, could you please include figures for positive and negative associations and highlight if these were statistically significant or not?

Response: The results subsection of the Abstract now includes the figures for positive and negative associations and whether they were statistically significant or not.

18. Kindly include "Likert scale", "France" and "Nonpharmaceutical measures" in your keywords.

Response: We have added the suggestions to the keywords.

19. Under Measurements, kindly substantiate your use of the Likert scale with suitable references. You might want to use this link [6].

Response: The above reference is now inserted in the manuscript.

20. For your beginning statement under Data Analysis, I suggest you use "frequencies (N)" instead of "numbers (N)".

Response: The term "frequencies" is now used in the Data Analysis section.

21. I like the flow and harmony between Participants and Procedure, Measurements, and Data Analysis. You did well to have organized these by objective. In your Data Analysis, could you please highlight how you assessed the model fit (goodness of fit) of your multivariate model?

Response: The goodness of fit for each multivariate model (value/df for the deviance) is now indicated (revised Tables 3 and 4).

22. I suggest you organize your Results section, which already is in good shape, by study objective after "Participant Characteristics" so that it flows well in the measurements and data analysis subsections.

Response: We appreciate the suggestion and have organized the Results section by study objective.

23. Relating your study results to the title, readers might expect to see where you articulated the trade-off between health and social outcomes. This is not the case. It might be worthwhile to rephrase your title.

Response: We have revised the title.

24. Kindly format your tables and figures following the journal guidelines.

Response: The tables are now edited according to journal guidelines.

25. I suggest you start your Conclusion by highlighting the study objectives.

Response: As suggested, we have revised the Conclusion and highlighted the study objectives.

26. It is important to include citations from the journal to which you are submitting or its sister journals.

Response: We have inserted 8 additional citations from JMIRx Med or sister journals in the manuscript.

Round 2 Review

Again, we are grateful to the reviewer for the helpful comments and suggestions and believe that responding to them has resulted in an improved manuscript. Questions and concerns noted by the reviewer are addressed below.

Major Comments

1. The phrase "The aim of this study was to evaluate the acceptance of COVID-19 nonpharmaceutical prevention measures in France", in the Objectives subsection should be moved to be the last sentence of the Background subsection in your Abstract.

Response: The sentence was moved to be the last sentence of the Background subsection in the Abstract.

2. Under Rationale, I think you should start the second sentence as "This study was based on the Extended Parallel Process Model."

Response: The sentence was inserted in the text as recommended by the reviewer (page 4).

3. The last sentence of your Rationale is not suitable for this section, so I suggest removing it.

Response: This last sentence of the rationale was removed.

4. The starting sentence of your Specific Objectives should be part of your Rationale instead, so you may want to move that from there.

Response: The starting sentence of the Specific Objectives ("As nonpharmaceutical interventions play a considerable role…) was moved to the Rationale (page 4).

5. All weblinks in the body of your text should be cited as references. The journal to which this manuscript is submitted does not allow the use of weblinks in the body of the text.

Response: All weblinks were removed from the text.

6. The phrases "EPPM factors were estimated using an unweighted least-square factorial analysis, followed by a Promax rotation, and 5 factors were extracted accordingly" and "The raw scale scores were transformed to a 0-100 scale. Higher scores in the respective scales are indicative of greater perceived efficacy, lack of fear control, severity, susceptibility, or avoidance" should be moved to Data Analysis.

Response: These sentences were moved to the methods section (page 8).

7. Tables 1, 3, and 4 still need to be updated to comply with the journal guidelines. You will notice in this link [7] that item categories like "Age in years" and "Professional status" should be in their own row while the items under each category start on the next row.

Response: Tables 1, 3, and 4 now comply with the guidelines. Thank you for the guidance.

8. As part of the participant characteristics, kindly include the mean age of participants and if the mean age difference between men and women was statistically significant.

Response: It is now stated in the Results section that "The mean age (SD) was 46.9 (SD 15.9) years, and was similar between men (mean 46.4, SD 16.3 years) and women (mean 47.4, SD 15.5 years; *P*=.18)" (page 9). It is also stated in the Methods section that numerical data were compared with a 1-way ANOVA (page 8).

9. Regarding your statement "The raw scale scores were transformed to a 0-100 scale", there is a serious debate about calculating Likert scale scores from responses. Kindly be clear on how you converted the responses to scores.

Response: It is now stated in the method section that "EPPM raw scale scores were transformed to a 0-100 scale: ([raw score − lowest possible raw score]/possible raw score range) × 100" (page 8).

10. Kindly include your Figure 1 in the body of the text. All figures uploaded online must also be included in the body of the text, as per the guidelines.

Response: Figure 1 is now included in the body of the text (page 12).

11. Kindly move the first sentence of your Principal Results ("The aim of this study was to evaluate the acceptance of COVID-19 nonpharmaceutical measures and, more specifically, to measure the public's acceptance of these measures and their association with COVID-19 perceptions") to be the starting sentence of your Conclusion.

Response: The sentence was moved to be the starting sentence of the conclusion (page 17).

12. Kindly ensure that all percentages reported in the body of your text (apart from those from other studies) are expressed in absolute values in parentheses; for instance, 20% (5/25).

Response: All percentages (except for averages) are now expressed in absolute values (Results section, pages 9-10).

13. Evidence suggests that there are also issues around sex and gender reporting [8-10]. Since sex is biological, it will be good to make clear in your methods that the sex definition was based on self-reported sex [9].

Response: It is now mentioned in the Methods section that respondents had to report their gender (self-reported sex, page 7). Estimates for "female gender" are now reported in Tables 1, 3, and 4 for clarity.

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Authors' Response to Peer Reviews

Authors' Responses to Peer Reviews of "Supporting Technologies for COVID-19 Prevention: Systemized Review"

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Companion article: https://med.jmirx.org/2022/2/e30344/

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KEYWORDS

COVID-19; medical treatments; personal protective equipment; testing methods

This is the authors' response to peer-review reports for "Supporting Technologies for COVID-19 Prevention: Systemized Review".

Round 1 Review

Anonymous [1]

General Comments

The manuscript [2] talks about medical technologies during COVID-19. The review is nice to read. I could not find Table 2.

Specific Comments

Major Comments

1. My main concern is that several technologies are missing, so I am not sure if the review on Google search was carried out properly. There must definitely be over 90 technologies. If you check the Federal Drug Administration (FDA) In Vitro Diagnostics, there are over 240 test kits alone. Additionally, I am not sure how you reach to 38 items from 90, or are there so many unrelated items?

Authors' response: The title has been adjusted to narrow down the search range. Moreover, detailed selection criteria have been included.

2. The images in the figures, especially on company products, need actual permission from the original company or inventor. For example, the image citing reference 2 is a British Broadcasting Corporation (BBC) article, but the actual image is from a hospital whose permission is needed, rather than citing BBC.

Authors' response: Proper citation has been done through the company website.

3. Several topics are outdated as of now, such as personal protective equipment. The interest in smart or green personal protective equipment has declined dramatically as vaccination has picked up. Therefore, the text needs to be made aligned to current needs, such as low-temperature storage technologies to store vaccines, etc.The ventilators section is interesting, but such images have been shown before in many places. As such, it will be difficult to garner readership based on the sections.

Authors' response: The vaccine storage is very interesting. However, due to the length of this review paper, it is difficult to explore a whole new different topic.

4. Several points are repeated throughout the manuscript, such as lack of manpower and resources. The flow of the text could be made more fast paced by removing general statements and sticking to facts only.

Authors' response: The manuscript has been checked to avoid general statements.

5. New and interesting topics could be added based on the current status of the pandemic, such as technologies centering around vaccination or at-home testing.

Authors' response: At-home testing has been mentioned in the article.

Reviewer CM [3]

General Comments

The need for effective and rapid response mechanisms to the COVID-19 pandemic has seen the emergence of new technologies. The European Parliament has organized such technologies into 10 broad categories. Many studies have reported the emergence of new digital tools as a direct response to COVID-19. While some of the studies report that these technologies make a major impact in the management of COVID-19 despite some challenges in their real-life usage, others acknowledge that COVID-19 control is critical, which calls for regular stock-taking, given the rapid advances in the field. Following the above, the authors of the paper "Supporting Technologies for COVID-19 Prevention: Systemized Review," [2] in an attempt to stay on top of these advances, investigated the emerging technologies relating to the COVID-19 pandemic. The topic addressed in this paper is of interest to the journal's readership and the international community. Being an important topic, it would have been important to report the review based on specific reporting guidelines to make it more appealing. The paper does not comply with the journal guidelines. Apart from the lack of a research objective, the paper is lacking in its methodology due to the lack of use of reporting guidelines. As such, the results remain doubtful. The general structure and English warrant improvement. If this paper must be brought to standard, the following specific comments are worth considering;

Specific Comments

1. The title of the paper does not conform to the journal guidelines.

Authors' response: The title has been adjusted.

2. The Abstract of your paper needs to be structured following the recommended guidelines.

Authors' response: The abstract has been adjusted.

3. This paper neither has a research objective nor question to permit its evaluation.

Authors' response: research objective has been added.

4. You need to follow the guidelines of the journal to which you are submitting.

Authors' response: The guideline has been double-checked.

5. Kindly refer to the new PRISMA checklist to see how you can report your search results.

Authors' response: The PRISMA checklist has been double-checked.

6. You need to have a look at the reviews published in the journal you are submitting to.

Authors' response: The newly published work has been double-checked.

7. The English of your paper needs to be improved.

Authors' response: English has been checked thoroughly.

8. The Methods section lacks clarity and warrants improvement.

Authors' response: The method section has been improved.

9. Your references need to be in line with the journal guidelines.

Authors' response: The references have been edited.

The above specific comments are further divided into the below major and minor comments;

Major Comments

1. Firstly, you need to identify and report the type of review you conducted to help in the evaluation of your paper. If this is a narrative review, kindly indicate clearly in your paper

2. I suggest the following: (1) Emerging Medical Technologies for Fighting COVID-19: Systematic Review; or (2) Emerging Medical Technologies for Fighting COVID-19: Narrative Review

3. Your abstract needs to be structured in line with the journal guidelines, to include the Background, Objective, Methods, Results, and Conclusion subsections. Additionally, be aware that the PRISMA checklist also provides additional information that must appear in the Abstract section of systematic reviews.

Authors' response: The title has been changed to: Systematic Review of Supporting Technologies for COVID Prevention

3. Your abstract needs to be structured in line with the journal guidelines, to include the Background, Objective, Methods, Results, and Conclusion subsections. Additionally, be aware that the PRISMA checklist also provides additional information that must appear in the Abstract section of systematic reviews.

Authors' response: The abstract has been restructured.

4. Kindly restructure the manuscript using the IMRD format using the following word template;

Authors' response: The journal guideline has been checked.

5. It is absolutely important to read through the journal guidelines to which you are submitting.

Authors' response: The journal guideline has been checked.

6. Kindly put your study in context as part of your introduction. Use the provided reference if you need help with how to put your study in context.

Authors' response: The reference has been used to add more content to the introduction.

7. This study is without a research objective. State your research question and objectives.

Authors' response: The research objective has been added to the abstract.

8. Kindly report the Methods section using the subsections below:

- Study objectives
- Eligibility criteria for selected studies
- How literature was searched
- The method used to synthesize results
- Data management and analysis
- Quality assessment (including the risk of bias assessments)
- How missing data were handled
- Heterogeneity assessment
- The method used to present data and results

The above may vary depending on the type of review you undertook. A simple literature review of emerging technologies will normally not require some of the above subsections.

Authors' response: The Methods section has been restructured to include some of the bullet points above.

9. It is very important to indicate the guidelines used to report your review results.

Authors' response: The guideline PRISMA 2020 has been mentioned in the Methods section.

10. Your results section should be reported based on your research objectives (yet to be defined), and should include the following:

a. Search results: [a] flow diagram based on the new PRISMA flow chart and [b] characteristics of included studies (table and discussion).

b. Risk of bias assessment

c. Synthesis results (report results based on objectives and the different technology categories)

d. Overall assessment of the body of evidence

e. Heterogeneity

Again, as highlighted above, a literature review will not require some of the above points (assessment of overall evidence, and heterogeneity). That said, if you did a narrative review, I suggest using the following reported guidelines. I also find the structure of this referenced narrative review and systematic review more robust (use these as references in reporting your review). In reporting a narrative review, it is important to bear in mind how narrative reviews are evaluated. Moreover, be aware that review papers are expected to be submitted with a filled template of the guidelines used.

Authors' response: The research objectives have been defined in the Methods section. The new PRISMA flow chart has been added into the manuscript.

11. You need to have a look at studies that have reported on similar topics for inspiration.

Authors' response: The articles have been thoroughly read and cited in the manuscript.

12. See guidelines for the structure of the Discussion section. Present your Discussion into (1) Principal findings and (2) Comparison with prior studies.

Authors' response: The Discussion section has been reorganized.

13. Kindly include a subsection "study limitations" as part of the Discussion section.

Authors' response: The study limitation has been included as part of the Discussion section.

14. Your references have to be in line with the recommended journal guidelines. Set your reference manager to the AMA citation style and make sure to include a PubMed ID at the end of each reference. You can search the PubMed IDs of various articles at https://pubmed.ncbi.nlm.nih.gov/. In the absence of a PubMed ID, kindly include a DOI (verify your DOIs using https://www.doi.org/).

Authors' response: The reference has been checked.

15. Include a subsection "Author Contribution" after the Acknowledgments section to state the contribution of each author included in this paper.

Authors' response: The section has been added.

16. Include a subsection "Conflicts of Interest" after Author contributions to declare any conflict of interest.

Authors' response: The section has been added.

17. Kindly list all Multimedia Appendices before the References.

Authors' response: No Multimedia Appendices in this manuscript.

18. For referenced websites, ensure to make as much effort as possible to get and reference the pdf version of the article (ie, in the absence of a PMID and DOI).

Authors' response: PDF of the websites have been added.

19. Create a section “Abbreviations” after your references to list and expand all abbreviations in the text.

Authors’ response: The section “Abbreviations” has been added.

20. I suggest starting your Conclusion with a statement on the study objectives followed by a summary of findings, then lessons learned from your findings, and finally, suggested direction of future research.

Authors’ response: The conclusion has been restructured.

Minor Comments

1. Kindly include only the corresponding author in the manuscript and create or include all coauthors in the metadata section of the online manuscript management system (MMS) of your journal profile.

Authors’ response: The title page has been changed accordingly.

2. End your introduction with the aim of the study.

Authors’ response: The aim of the study has been added.

3. Kindly format your table following the journal guidelines.

Authors’ response: The table has been reformatted according to the guidelines.

4. You may want to start your Table 1 with study id, by merging columns 1, 2, and the last as 1 column. For instance, the first cell will be Rendeki et al (2020), followed by the “setting or country” in the second column, and then the description, etc.

Authors’ response: Table 1 has been restructured.

5. Following from (4) above, I recommend having (1) a table of characteristics of included studies for each category of technology or (2) present a single table of “Characteristics of included studies” under the Search Results subsection of the Results section, after the PRISMA flow diagram.

Authors’ response: The table of characteristics has been added for each category of technology.

6. I suggest attempting to format your Figure 1 following the new PRISMA diagram.

Authors’ response: Figure 1 has been reformatted.

7. Review all your figures and their captions in line with the guidelines. Apart from being uploaded as Multimedia Appendices, all figures must appear in the body of the text where they are first mentioned. Use a single sentence as the caption for each figure, which should appear at the bottom of the figure.

Authors’ response: The figures have been placed next to the paragraph where they were first mentioned. The figure caption has been checked and edited.

8. Following from (7) above, you may want to combine figures (a) to (i) to form a single figure as is the case with Figure 4.

Authors’ response: Figure 2-3 has been checked and ensured consistency with Figure 4.

9. I advise downloading Grammarly to assist you with the editing of your paper.

Authors’ response: Grammarly has been used.

10. There is a need to justify your outcome prioritization. I suggest organizing your technology categories in line with the European Parliament categorization.

Authors’ response: 3D printed facial mask has been prioritized in the manuscript.

11. Ensure that titles and subtitles of your “Comparison with Prior studies” subsection of the Discussion are the same as the titles and subtitles of your Results section (Prevention, Diagnosis, Treatment, etc), and as suggested in (30) above.

Authors’ response: The discussion section has been reorganized.

Round 2 Review

We would like to express our gratitude once again to the reviewer for detailed thoughts and feedback. We have carefully considered, responded to, and made changes to the manuscript based on the specific recommendations of the reviewers. We feel that the changes have greatly increased the overall quality of work, and we are very appreciative of the kind comments. Thank you. Our responses to the specific comments of the reviewers are listed as follows.

Reviewer CM [3]

General Comments

I acknowledge that the authors of the paper titled “Supporting Technologies for COVID-19 Prevention: Systemized Review”[2] have done well to improve on the overall structure and presentation of the paper, with a much better flow. Comments that were made in the previous round were based on the understanding that this was a standard “systematic review” type paper, but this is not the case. However, this paper still warrants some improvement. Kindly refer to the below major comments.

Specific Comments

Major Comments

1. Systematic reviews require a predefined robust search strategy that is exhaustive, an appraisal scheme for each type of study (both risk of bias and quality) with well-cited tools, a clearly outlined method for synthesizing results, a method of assessing all the evidence emanating from the literature and most especially, with a clearly stated guideline used in reporting the review. Given that this review does not formally appraise the included studies for risk of bias and quality, neither does it have a clearly outlined method of synthesis, It will be appropriate to identify your study either as a (1) literature review, (2) systemized review, (3) narrative review, or simply (4) overview, all of which do not forcefully require a comprehensive search, formal appraisal of studies and typically aimed at a narrative synthesis [1]. It is enough to note here that even “systematic reviews with narrative synthesis” and “rapid reviews” that may omit some aspects of a standard systematic review, follow specific citable guidelines in their methods and synthesis approach, to say the least.

Authors' response: The paper title has been changed to "Supporting Technologies for COVID-19 Prevention: Systemized Review."

2. It is absolutely important to bear in mind that reviews have their terminologies, as is the case with randomized controlled trials or other studies. You wrote I quote "In this paper, 150 news articles and scientific reports on COVID-19-related innovations during 2020-2021 were firstly checked, screened and shortlisted to form a pool of candidates yielding a total of 18 publications for review" and yet elsewhere I quote "After the initial candidates were selected, they were subjected to eliminating evaluations". I do not think the term "candidate" can be used to refer to records retrieved in reviews. You may want to rephrase those and elsewhere (Introduction and Methods sections) in the body of your text and use "records" or "articles" instead.

Authors' response: The word "candidate" has been rephrased to "article" throughout the manuscript.

3. Your "results" and "conclusions" subsections of the Abstract are not robust in a way that helps the reader understand what you found and what you learned or deduced from the findings and your recommendations. Kindly include a sentence or two each for personal protective equipment, testing methods, medical treatment, and other considerations in the "results" subsection.

Authors' response: A summary sentence has been added into each subsection of "results" so that "results" can be seen as more separate from "conclusion."

4. Kindly include this phrase in the "methods" subsection of your Abstract: "The keywords 'COVID-19 technology,' 'COVID-19 invention,' and 'COVID-19 equipment' were used in a Google search to generate related news articles and scientific reports." Moreover, indicate the date that the search was performed.

Authors' response: The sentence has been added into the abstract.

5. Regarding your PRISMA diagram, your numbers for records identified from other databases (websites) do not add up. You excluded 15 articles from 30 you sought to retrieve, and it follows that you apparently excluded all 15 articles you assessed for eligibility, but you contradictorily still included the 15 articles in this review. Kindly verify and correct your PRISMA chart.

Authors' response: The PRISMA chart has been updated.

6. Your PRISMA diagram shows that you searched other websites other than Google, it will be absolutely helpful and more robust to indicate these websites under your "Search strategy."

Authors' response: Another website has been included in the search strategy.

7. You did well to have included the PRISMA flow. Kindly substantiate your phrase I quote "The selection of the article followed the guideline of PRISMA 2020" with a suitable reference.

Authors' response: Two new references have been added to the manuscript.

8. Under "Testing methods" in your Results section, kindly also allude to "pooled" and "rapid testing (serology and antigen)" technologies as these are indispensable innovations to increasing the turnaround time and for timely detection. This updated Cochrane review as well as this list of 42 rapid testing technologies considered to be of acceptable performance by the UK government can help you identify suitable new technologies to add to this review. Regarding their pros and cons, it might be worthwhile to also look at the extent to which information provided by manufacturers is helpful for each technology considered if possible.

Authors' response: The section of "testing methods" has been edited, and more references including have been added to Table 2 of the manuscript. Additionally, an additional paragraph has been added to the manuscript.

9. Coming to your Study Limitations, your phrase, and I quote "Also, the paper only provides a quantitative comparison between the technologies" does not seem to be coherent with your synthesis approach. I think this should be a qualitative comparison since you made use of textual descriptions to draw similarities and dissimilarities between the data. Tabular presentations facilitate the narrative but do not make it quantitative. Kindly phrase and include the following in your Study Limitations as well;

a. The search strategy was not comprehensive as it was limited to one database (Google).

b. The fact that the protocol was not registered with PROSPERO might have affected the results in one way or the other.

c. Even though you unveiled some of the complexities regarding supporting technologies, a quantitative analysis would have also added value to the review results.

d. You did not do a formal appraisal of the included studies and the overall evidence from included studies. This must-have affected your results.

10. Your Table 1 through 3 make up 17 articles instead of 18 according to the number of retained articles. Kindly verify.

Authors' response: The study limitation has been edited. There are 23 articles in the manuscript.

Minor Comments

11. Your "Conflicts of Interest" should follow the journal guidelines. Kindly use "None declared."

Authors' response: The statement has been updated.

Round 3 Review

Reviewer CM [3]

Authors' response: We would like to express our gratitude again to the reviewers for their careful thoughts. We have carefully considered, responded to, and made changes to the manuscript based on the specific recommendations of the reviewers. We are very appreciative of the kind comments. Thank you.

Our point-by-point responses to the comments of the reviewers are listed as follows:

General Comments

Unfortunately, I still have the 3 following concerns.

Specific Comments

Major Comments

1. Recommendation #3: I am happy that the authors of this paper [3] improved on the results following the recommendation in Point 3, but this recommendation was primarily referring to the Results and Conclusion subsections in the Abstract. The current wordings in the Results of the Abstract should be moved to the Methods subsection of the Abstract. This means that you are yet to produce a summary of your findings (results) in the Abstract. Moreover, kindly word up the Conclusion subsection in the Abstract to reflect the main Conclusion of the paper.

Authors' response: The abstract section has been updated.

2. The authors have also done well to have deployed the current PRISMA flow chart. However, your flow diagram shows that you included 5 articles from a previous version of this review indicating this paper is about updating a previous review and I do not think it is the case [1]. Except otherwise, kindly leave this box empty and move this number (n=5) to either "Records identified from Databases" or "Records identified from Websites". My humble suggestion is that since you seem to have identified 200 records from Google search and ScienceDirect, under "Records identified from Databases (n=200)", kindly specify "Google=150", and "ScienceDirect=50" for readers to be clear about how many articles were retrieved from which database. Under "Records identified from Websites, kindly put "n=5, assuming that the 5 previously published reviews were identified from websites. If these were identified through Google search, ScienceDirect, or Cochrane, then kindly include under Records identified from Databases and leave "Records identified from Websites empty.

Authors' response: The flowchart has been improved according to the suggestions. The five review articles have been identified from Database, so the boxes of "identification of new studies via other methods" as well as "previous studies" has been removed according to the study by Page et al, "PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews." Please kindly see the manuscript.

3. You need to correct your statement "Three previous review papers were also included" as this seems to be 5 in the flow diagram.

Authors' response: The statement has been corrected.

References

1. Anonymous. Peer Review of "Supporting Technologies for COVID-19 Prevention: Systemized Review". JMIRx Med 2022;3(2):38728 [FREE Full text]
2. Zhao Z, Li R, Ma Y, Islam I, Rajper AMA, Song W, et al. Supporting Technologies for COVID-19 Prevention: Systemized Review. JMIRx Med 2022;3(2):30344 [FREE Full text]
3. Mbwogge M. Peer Review of "Supporting Technologies for COVID-19 Prevention: Systemized Review". JMIRx Med 2022;3(2):38606 [FREE Full text]

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Author's Response to Peer Reviews

Author's Responses to Peer Reviews of “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study”

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KEYWORDS

SARS-CoV-2; COVID-19; variants of concern; case-fatality rates; virulence; vaccine effectiveness; correlation study

This is the author’s response to peer-review reports for “The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study”

Round 1 Review

Anonymous [1]

General Comments

This paper [2] used ecological data to study the correlation between SARS-CoV-2 variants and the fatality rates. It introduced a new indicator to correct for the lagging of the reported death since the initial infection. When applying this indicator to different countries, it demonstrated that the spreading of variants coincided with the surge in death while also acknowledging the potential confounding factors such as vaccination rates. Although the conclusions drawn in this paper showed some inconsistency with other observational/community-based epidemiological studies, the paper also explored the correlation between disease risk factors and the reported death.

Response: Done

The revision makes extensive reference to the “ecological” nature of the data and has revised the analysis and text accordingly (see text in red on the attached PDF).

Specific Comments

Major Comments

1. The author should provide more characterizations of the proxy case-fatality rate (pCFR). For example, the author should

compare the pCFR and the case-fatality rate (CFR) while doing the analysis, such as correlation analysis.

Response: Done

2. The author mentioned "One could equally well average the infection rate over the period from 28 to 14 days," but no figure was also presented. Comparing different parameters used to construct the pCFR is essential for the reader to evaluate the robustness of the proposed indicator.

Response: Done. The comparison is included.

3. Related to the first point, the author should probably also compare the raw CFR 7-day rolling average and the pCFR 7-day rolling average.

Response: Done

Figure 1 already shows the time variation of the average CFR. Features are very slowly variable and not large in magnitude. Simply dividing the new deaths on day N by the new cases on day N is inappropriate, as those fatalities were from infections contracted several or more days in the past.

4. The death rate is also related to the capacity of the health care system, such as available intensive care unit (ICU) facilities or bed occupancy. Thus, the CFR on a particular day might also depend on the CFR (as an approximation to the ICU occupancy) the day before. While the author reported the absolute pCFR percentage in most of the figures, these results should also be confirmed by replotting the percentages as relative percentages. For example, one could report the daily pCFR as the percentage change to the previous day (or the previous 7-day rolling average).

Response: Done

Actually, the ratio suggested is a differential measurement that is much noisier than the reported time series of the pCFR. A comparison of noise level is easily made by making a Fourier transform of the time series and of the time series of the suggested ratio.

One finds no significant correlation between the pCFR throughout the pandemic versus the national per capita availability of hospital beds. The correlations are shown in Appendix B, Figure B.5.

5. By doing point 4 above, the relative pCFR can be used to compare different included countries that have daily CFRs that are highly variable.

Response: Done

The figure above is a comparison for the United Kingdom. The noise level in the ratio is far too large for this measure to be useful as an absolute measure of increased virulence during waves of diverse variants or to compare differing countries. This figure is reported in Appendix B.

6. The risk factor correlation analysis can be misleading. The author should state very clearly that ecological data were used for the analysis, both in the Introduction and Discussion sections. It has been shown that a population-based correlation provided little insight into understanding the disease pathology. (Portnov B, Dubnov J and Barchana M. On ecological fallacy, assessment errors stemming from misguided variable selection, and the effect of aggregation on the outcome of epidemiological study. J Expo Sci Environ Epidemiol 2007; 17:106-121).

Response: Done. This point has been discussed at length in the revised text. In addition, the "ecological" consideration is the reason for performing a detailed multivariate regression. Some insight into cross-correlations can be gained from a heat map of correlations of the independent variable shown in Appendix C.

7. It is unclear that the definitions of each of the variables (risk factors) are included in the correlation analysis. While I assume it is the same as those cited in the second reference, some of the analysis methodologies seem imprecise. For example, epidemiologists usually model the age as ordinary variables and test for the trend (eg, using ANOVA) but not by using the median age. The author might want to revisit some of the analyses performed.

Response: Done. The three metrics of the age of a country's population are not imprecise. They are the values given in standard demographic tabular data. These metrics are distinct from the ages of individual patients as analyzed in usual epidemiological data of patient populations. The issues related to the use of any of these age metrics were examined in detail in response to the referee's point 9.

8. As the author also pointed out, many of these risk factors are correlated with each other. A better way to adjust for these potential confounding effects is by modeling all these risk factors in a regression model.

Response: Done. The author has performed an in-depth correlation and regression analysis of the dependence of pCFR (or even the pandemic average CFR) against a set of 24 independent variables both for the case of the 99 countries of the full study and for the 32 European countries. The heat map of correlations is given in Appendix C. In no case could a model be produced with a P value for the independent variable less than .04. The best model included only coronary heart disease and national health expenditures as the independent variables. The P values for these variables were .04 and .046, respectively. That comment is provided in the text.

9. The author should explain the choice of "shift by 60 days" in Figure 12.

Response: Done. The text now reads "However, shifting the Peruvian distribution 60 days later in time (that is, Day 1 for Peru corresponds to Day 61 for Argentina), increases the correlation of daily new cases in the two countries to 0.86."

Minor Comments

10. The author should consider unifying the color scheme used in the manuscript. For example, some figures are plotted in grayscale, but similar figures can also appear in a colored version.

Response: Done

11. In equation 2, “Total cases on day (N-14) - Total cases on day (N-21),” the “-” between the two phrases can be misleading. The author should consider rewriting the “-” as “to.”

Response: Done

12. The author should also consider replotting the correlation analysis into heat maps. The author did not justify the use of a line plot for plotting each risk factor.

Response: Done. The author agrees that the use of the line chart in Figure 7 is inappropriate. That figure has been replaced with a rank ordered bar chart with separately clustered medical and socioeconomic independent variables.

13. Furthermore, the author should consider clustering the risk factor and plotting a dendrogram with the heat map. Therefore, it will give readers a better idea of the correlation among each risk factor and the correlation among each of the cutoff dates (in Figure 6>) or regions (in Figure 7).

Response: Done. A reduced heat map (Figure 6) emphasizing regional variation is replacing the original Figure 8. A global heat map is given in Appendix C, Figure C.6

Reviewer BT [3]

General Comments

Emerging variants of concern (VOCs) have increased the uncertainty about bringing the pandemic to an end [4]. Countries will not only have to focus on stepping up vaccination efforts but effective surveillance as well to monitor and characterize the more transmissible and deadly variants [5-8]. The most prominent confirmed cases include Alpha, Delta, Beta, Eta, and Kappa [9]. This, in addition to flagging the need for more sustainable measures, raises concerns over their impact on CFRs in different countries.

The authors of the paper “The influence of SARS-CoV-2 variants on national case fatality rates” attempted to investigate the impact of VOCs on (1) pCFRs and (2) the vulnerability of persons living with comorbidities, using open source data of reported daily cases. They found little variations in the association between World Health Organization data-driven factors and the average pCFR and concluded that the increase in the impact of VOCs may be attributed to the fact that those living with comorbidities are more susceptible to infection severity. Other studies that evaluated the impact of new variants found them to be associated with higher rates of hospitalization and death. In the United Kingdom for instance, studies among cohorts infected with the B.1.1.7 variant (VOC-202012/1) compared to those with normal infections found an increased risk of hospitalization [7] and deaths [8,10,11] in the intervention group, using the TaqPath assay. According to expert opinion on some of these results, patients with the Kent or Delta variant (B.1.1.7) were 64% more likely to die [12]. The CFR was higher among men than women and increased with age.

This paper has been structured in compliance with the IMRD approach. The authors capitalized on prior published data and the concept on which the analysis was based [13] to generate new data, which seems logical. The English used is simple enough for the readership but demands improvement.

Even though the paper’s methods and analysis are based on a published concept, the fact that this was done by the same authors and no other authors have been cited making use of the same concept makes the paper’s methods weak. The study rationale has not been well established, thereby making the study objectives and research questions less robust. Besides, not only is data about variants of concern lacking and the interpretation of the results not well articulated, but the conclusion also arrived at is not clear enough in relation to the defined objectives. Kindly refer to the following major and minor comments.

Specific Comments

Major Comments

1. Kindly refer to the journal guidelines to see how titles are formatted. Well-formatted titles should include the main outcome of interest, the subject matter, and the study design.

Response: Done

2. Your interest is to measure the influence of VOCs, not SARS-CoV-2 variants as reflected in your title. You may want to correct that.

Response: Done

3. Your abstract must include (1) Background, (2) Objective, (3) Methods, (4) Results, and (5) Conclusions. Kindly use this source to see how to structure your paper [14].

Response: Done

4. The phrase I quote “may increase the vulnerability of persons with certain comorbidities” in the Abstract is not an objective. Kindly rephrase together with the first objective that appears too long.

Response: Done

5. You need to include (1) Study Rationale and (2) Specific Objectives in your Introduction as subsections. The “Specific Objectives” subsection should normally be the last part of your Introduction.

Response: Done

6. In your Study Rationale, make efforts to trace other studies that have made use of similar methods in predicting the impact of VOCs. This section needs to at least include some basic data about VOCs (prevalence or impact on hospitalizations and mortality). You may want to make use of this reference [9].

Response: Done. The author has not found similar studies for direct comparison. However, the results of this study are compared with systematic and meta-analyses of clinical studies. As this study does not use characteristics of the structural biology of variants of concern such details would be out of place. However, those details are described in the references cited.

7. Given that this paper is based on VOCs, it would be sensible to include in your Introduction and as part of your background literature evidence of a literature review of the different VOCs (their characteristics and virulence). Readers will be keen to discover the new variants in circulation. The availability of data

on VOCs and variants under investigation is key because it flags the need for vaccination, increases uptake, and signals policy makers about the importance of modifying surveillance policies.

Response: Done

8. If you decide to include research questions or hypotheses to be tested in your paper, kindly associate these with your research objectives. This makes it easy for readers to see how you transformed each objective into a question, as well as the hypothesis to be tested.

Response: Done

9. Kindly start your Methods section with the subsection "Study Design" and clearly state your study design. This is particularly important not just for reviewers but for those undertaking systematic reviews.

Response: Done

Studies are often excluded or not simply traced as a result of a lack of a clearly stated research design. Besides, it is the place of the author to inform readers of the study design and not for readers to determine the design that was used. Authors making use of study designs that are new to the journal's readership always make an effort to cite articles making use of similar designs regarding the subject matter.

10. I suggest structuring your Methods section as follows:

10.1 Study design

10.2 Data sources and setting (including providing a brief description of each country being profiled and the triggers and specific reasons for choosing particular countries to include in your analysis)

10.3 Study variables/outcomes (kindly specify here, the comorbidities you were interested in together with definitions for outcomes like case fatality)

10.4 Data analysis (include equations here and specify any underlying assumptions). Clearly explain how you run the correlations and time series, and report any statistical program that was used.

Response: Done

11. Explain how adjustments for age, sex, ethnicity, type of VOC, seasonality, etc, in the correlations were made. For instance, the impact on the national CFR may be contingent on the type of variant [15]. Comorbidities may exacerbate during winter and make it difficult to attribute increased mortality among those with comorbidities to VOCs [12].

Response: Done. Although the author agrees that the use of sex-disaggregated data would be preferable, a sex-disaggregated and ethnicity-disaggregated data set for COVID-19 has not been reported or is not publicly available in a consistent form for all the countries included in the analysis. The focus on the time series of pCFR and daily infections allows one to observe and, if possible, adjust for seasonal variations. The grouping by region serves as a quasi-proxy for ethnicity data. That explanation is added to the text.

12. In your data analysis, kindly explain how you arrived at using the Pearson product moment correlation. Kindly justify if your data was linear and report the values of normality tests that were performed prior to choosing the approach of analysis.

Response: Done

13. Kindly report how the different linearity assumptions were verified (for linear data).

Response: Done

14. In your data analysis, kindly report how you determined the strength of association between the proxy national CFRs and the different covariates.

Response: Done

15. The Results section seems to be a mix of data analysis, results, and discussion. Kindly move texts relating to the above to their respective subsections. For instance, readers will not expect to see any explanations in the Results section as this should normally appear under discussion, where you normally should explain why results appear the way they are. Additionally, equations relating to data analysis should not appear under results.

Results: Done

16. A look at your study results shows that this paper has 3 objectives I state (1) to assess the fluctuations in the daily proxy national CFRs, (2) to investigate the correlation between average national proxy CFRs and potential cofactors/comorbidities, and (3) to describe the correlation between proxy national CFRs of country pairs by region. You might want to amend your study objectives accordingly.

Response: Done

17. I suggest you organize and report your results by objective (1, 2, and 3) for a better flow.

Response: Done

18. You reported to have made use of the Pearson correlation coefficient but have not reported the coefficients obtained from the correlation anywhere. Kindly clarify.

Response: Done. These correlations among all variables are reported in Figure 5 and in the heat map Figure C.6 in Supplementary Appendix section C.

19. Kindly structure the Discussion section following the journal guidelines. I suggest:

19.1 Summary Findings

19.2 Strength and Limitations

19.3 Interpretation of Results

19.3.1 Fluctuations in the daily proxy national CFRs

19.3.2 Linear correlation of the averaged CFR and potential cofactors

19.3.3 linear correlation between proxy CFRs for country pairs by region

19.4 Implications for Policy and Research

19.5 Conclusion

Response: Done. This section has been restructured.

20. Your need to compare your results with those of other studies in your "Interpretation of Results" in your discussion, by citing other studies on the same subject matter and preferably undertaken in the same countries being profiled. This helps to situate the study within the existing literature. I understand this might be challenging for some objectives. Kindly provide explanations for the results in the event of a lack of suitable studies.

Response: Done where possible

21. Your conclusion needs to state your results within the context of your study objectives and give the significance and implications to future research, surveillance, and policy.

Response: Done

22. Kindly refer to the guidelines for referencing or have a look at published articles in the journal to which this work is submitted. Your references need to follow the AMA citation style. Please refer to the references of this report.

Response: Done

Minor Comments

23. The Methods subsection of your Abstract needs to summarize your study design, data sources, and how data was analyzed including any statistical packages.

Response: Done

24. Kindly ensure that the conclusion of your paper is under the subtitle "Conclusion."

Response: Done

25. Move all abbreviations to the end or as the last section of your paper.

Response: Done

26. Please be aware that you are not allowed to include more than 8 figures in your paper. You may want to merge some and move others to multimedia appendices. I did not find Figure 2 very necessary and you might want to move that.

Response: Done. Figure 2 does illustrate the concept of waves of infection associated with different variants of concern.

27. All figures to be published in the body of your paper must also be uploaded online. Kindly refer to the journal guidelines.

Response: Done

28. I suggest moving Table A to the "Data Sources and Setting" subsection and labeling it as Table 1.

Response: The author considers that including the table in the text would only serve to lengthen the main text while adding little to the description of its contents, which has been added.

Not adopted. This change would enlarge the main text while adding little content.

29. You need to cite more papers including those from the journal to which you submitted.

Response: Done

30. Kindly include a PubMed ID at the end, for each reference (searchable at crossref.org). Kindly refer to the references in this peer-review report.

Response: Done. Included where available.

31. Endeavor to cite the PDF version of articles for all web links if possible.

Response: Done. The DOI of all open access manuscripts cited do include a link to download the PDF of the paper.

Reviewer CI [16]

General Comments

This paper presents the changes in the CFR due to COVID-19 variants in different countries.

Specific Comments

Major Comments

1. Abstract

1.1. Should include a conclusion section

Response: Done

1.2. Results: A summary of the results in terms of variation in CFR according to the variants needs to be mentioned.

Response: Done

Main Manuscript

2. Objective

2.1. Specify the year for November 1

Response: Done

2.2. Figure 2: What do the different shades indicate? It should be clarified in the footnote. November spelling.

Response: Done

3. Methods of Analysis

3.1. Data sources should be specified for the different countries. The analysis should also mention the methods used for data analysis and presentation in the tables. The data on the infected case load should be used along with the CFR/pCFR.

Response: Done

3.2. pCFR: Full form when used first. The proxy CFR or pCFR should be used consistently in the text.

Response: Done

4. Results

4.1. Figure 7: What was the source of the data for the cofactors in these countries? It should be specified.

Response: Done

4.2. Correlation between regional CFRs

The pairing of the countries should be mentioned in the Methods.

Response: Done

Which statistical test was used for this correlation analysis? This should be mentioned in the Methods

Response: Done

5. Discussions and Conclusions

Discussion and Conclusion should be separated.

Response: Done

Reviewer CK [17]

I would like to appreciate the author for this study addressing the influence of SARS-CoV-2 variants on national CFRs. The manuscript is concise and well written, and is recommended for possible consideration in its current form. Before publishing the manuscript, I suggest the author presents an Appendix with (a) data with absolute numbers.

Response: Done. Figure 5> and Figure C.6 and Table C.1

(b) Illustration for smoothed values of the pCFR for at least one country (Figures 8-11)

Response: Done. Figures 2, 3, 7, and 8

(c) Discussion on the analytical framework in detail in the Method of Analysis section

Response: Done. The discussion appears in the main text and is extended in the appendix

In conclusion, the subject addressed in this manuscript is worth investigation, and the manuscript is recommended for possible consideration after addressing the above minor concerns.

Round 2 Review

Anonymous

This draft has been greatly improved but the author should still consider the following:

1. Rewrite the denominator of equation 11 using the summation sign

Response: Done

2. In the current manuscript, equation 2 appeared before equation 1.

Response: Done. Corrected.

3. There were multiple equation 2s. Equation 1 also appeared twice: in the main text and in the supplementary text.

Response: Done. Corrected.

4. It is better to always mention the year for the date/period that was referenced in the manuscript (eg, “B.1.1.7 (Alpha) and B.1.351 (Beta) strains dated from mid-October and mid-May respectively” and “that could be due to masking by the fraction of Delta cases peaking in Argentina in mid-May” in the Result section).

Response: Done

5. The meaning of the statement “The positive aspect of that limitation is that trends in pCFR can spot burn through cases in unvaccinated of less than vigilant groups” is unclear.

Response: Done. Corrected. The new text reads, “The positive aspect of the sensitivity of the pCFR when case numbers are small is that highly variable trends in pCFR can spot surges of cases in clusters of unvaccinated persons or in less than vigilant groups.”

6. The author mentioned “The red points are due to anomalous entries in the tables of (13)” in the Result section. It would be better to clean the data for the suspected anomalous entries mentioned in the Methods section while plotting the smoothened graph.

Response: Done

Additional smoothing was applied for the April data. All graphs have been updated and improved for clarity.

7. Regression results should be listed in tables that show (at least) effect size and P value.

Response: Done

P values plus the size of effects are now shown for global data in the heat map of Figure 6 and Figure C.5 in the appendix

Reviewer BT

General Comments

I am happy that the authors of the paper titled “SARS-CoV-2 variants of concern: Influences on national case fatality rates” have addressed all concerns raised in the previous round, thereby giving the paper a new and improved outlook. However, these have not been addressed in a manner satisfactory enough. The study title even though modified from “The influence of SARS-CoV-2 variants on national case fatality rates” still needs to comply with the journal guidelines [18]. The study objectives are not consistent across the different sections. Some sections need to be reorganized for a better flow. The English used for reporting warrants improvement. Kindly refer to the below minor comments to improve the paper further.

Specific Comments

Minor Comments

1. Could you please identify this study as a “Correlation Study” [19]? For instance “The influence of SARS-CoV-2 variants on national case-fatality rates: Correlation and Validation Study”

Response: Done

2. The current text in the Results subsection of the Abstract should be part of the Methods subsection of the Abstract. Kindly move it to the start of your Methods subsection.

Respond: Done

Could you please summarize your findings into say 5 to 10 lines in the Results section of your Abstract? One will expect to see some figures reported from the main results in this subsection. You may want to ensure that your word count for the Abstract

is not above 450 by decreasing the word count in your Methods and Conclusions subsections.

Response: Done

3. The discoverability of your paper can be improved by including SARS-CoV-2, COVID-19, and 2019-nCoV in your keywords. Kindly modify "Country correlation" to "Correlation study."

Response: Done

4. The Objectives section of your Introduction seems to include the study background information; otherwise, I do not understand why it should be that lengthy. Kindly move the subtitle "Objectives" (better phrased as "Specific Objectives") to the end of your Introduction and state your specific objectives. The Objectives subsection should not be more than a paragraph. All other text should either be part of your study background literature or rationale. The Specific Objectives subsection should be formatted as follows:

Specific Objectives

The principal objectives of this study are to (1) establish a valid proxy national CFR and assess its daily fluctuations, (2) investigate the correlation between average national proxy CFRs and potential cofactors/comorbidities on a global and regional basis, and (3) describe the correlation between proxy national CFRs of country pairs by region.

Response: Done

Please do not include any other text before the Methods section. Additionally, kindly ensure that the above specific objectives and those in your Abstract are the same for consistency.

Response: Done

5. The use of the word "reference" in most of your statements (eg, "To evaluate any changes in the susceptibility to co-factors, one can follow the method introduced in reference") may not be appropriate. I suggest you state author names instead of using "reference" when referring to a particular research work. Kindly rephrase these all through the body of the manuscript.

Response: Done

6. For standard reporting and to be in line with the journal guidelines, I suggest replacing the title "Method of Analysis" with "Methods." It will be good to identify this study as a "Correlation and Validation" study under your "Study Design" subsection. This should be a single statement or at most 5 lines if you need to explain why you used the design and make reference to other papers.

Response: Done

7. Regarding your analysis approach in the study methods, it will be good to provide a few lines on how each of the assumptions for running a Pearson product moment correlation was satisfied [20].

Response: Done

This is described in steps B through D of the methodology.

8. Kindly change the title "Discussion and Conclusion" to "Discussion." I still suggest you structure your Discussion in line with the journal guidelines [21]. You may want to refer to papers published in JMIR to help you with how to structure the Discussion section. Based on journal guidelines, well organized and standard Discussion sections will bring out the subtitles (not as paragraphs) "Summary of Findings," Study Limitations," "Comparison With Prior Studies," and the "Conclusion." Even in a situation where you do not have enough papers to cite under "Comparison With Prior Studies," the subsection will still include your reasons and explanations of why results appear the way they do.

Response: Done

9. I guess your current Conclusion that appears quite lengthy includes materials for the Discussion section. Kindly size down and move a majority of the material to the Discussion section (specifically to the "Comparison With Prior Studies" subsection).

Response: Done

10. I note that the "Summary of Findings" in the Discussion should be a carbon print in terms of length and text of the "Results" subsection in the Abstract. For coherence and consistency, the more you can make these the same, the better. The same should be the case with the "Objectives" subsection in the Abstract and the "Specific Objectives" subsection at the end of your Introduction.

Response: Done

11. Kindly define a study aim in one sentence based on your 3 specific objectives and start your Conclusion with this study aim. This reminds readers of what you set out to do and helps them marry it with what you found. This should be followed by the main findings in just a few lines, lessons learned, what the findings mean for public health, and future research.

Response: Done

12. Just like the "Summary of findings," it is common practice not to expect the Conclusion of a paper to be lengthy since all explanations relating to the results should be part of your "Comparison With Prior Studies" subsection in the Discussion.

Response: Done

13. As per the journal guidelines, kindly move your Abbreviations subsection to after the references.

Response: Done

14. Ensure you follow the journal guidelines to report your P values.

Response: Done

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Abbreviations

CFR: variant of concern
ICU: intensive care unit
pCFR: proxy case-fatality rate
VOC:

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers' Perspectives"

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KEYWORDS

pediatrics; caregivers; health care services; public hospital; Malaysia; public-private-partnership; children

This is the authors' response to peer-review reports for "Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers' Perspectives."

Reviewer Anonymous [1]

Round 1 Review

General Comments

Thanks for the opportunity to review this manuscript [2] entitled "Caregivers' Perspective—Satisfaction With Healthcare Services at the Paediatric Specialist Clinic of the National Referral Centre in Malaysia." The authors report on an important topic, and their research work will contribute to the existing literature. Overall, the manuscript is well written with enough details in different sections. The tables are informative. The following are comments/concerns for the authors to consider.

Specific Comments

1. Abstract: include data/numbers in the Results section rather than general summary statements

Response: Amendment done with relevant data/numbers

2. Introduction: include any a priori hypotheses

3. Introduction: to support the rationale for the review, the authors should include additional recent promising evidence that supports the feasibility, acceptability, and efficacy of digital health interventions in different chronic medical conditions to provide context for the applicability of lessons learned in the study across other fields [3-8].

Response: The sample articles provided focus on the use of mobile health (mHealth)/digital health/technology/telemedicine, whereas this paper is on caregiver satisfaction by simply using the SERVQUAL questionnaire.

"Many studies conducted at public health care facilities in Malaysia have shown a high level of patient satisfaction with the services provided (19). However, to our best knowledge, no studies have been conducted on caregivers' satisfaction in MoH pediatric outpatient clinics or facilities. This study, therefore, aims to ascertain the prevalence and factors influencing satisfaction and to identify areas of dissatisfaction among caregivers at the Paediatric Specialist Clinic of Tunku Azizah Hospital."

4. Discussion: two recent reviews focused on pediatric/adolescent care and COVID-19 with mHealth/eHealth and adolescent/children psychosocial well-being, both worth discussing [9,10]

5. Discussion: the authors could consider including a paragraph on study strengths.

6. Discussion: it is critical to discuss the value of including direct patient input in the development of mHealth interventions, and other key considerations for end users should be sought early on in the process of app or digital health intervention design to ensure long- and short-term engagement [11-14].

Response: The instances given here are speaking from an angle of mHealth, which does not correlate with our paper.

7. Discussion: the authors should expand and elaborate more on how their findings support or contrast available literature and provide suggestions for future research directions that would address existing knowledge gaps.

8. Discussion: the authors should also acknowledge the lack of economic data to support the use of digital health interventions to date [15,16].

Response: Mentioned at the end of the Discussion section:

"Routine satisfaction assessments should be conducted using improvised questionnaires or other tried-and-true methods to identify unsatisfactory domains that require substantial improvements. These measures will ensure that the services provided are in line with the Ministry of Health's mission of providing quality integrated, people-centered health care to the masses. Future studies may be able to compare additional hospitals that use the PFI model, as well as provide more information about the variations discovered in this study."

Round 2 Review

No additional comments.

Reviewer BX [17]

Round 1 Review

General Comments

This paper describes interesting research about factors affecting the satisfaction of caregivers at a national referral center. I really liked the research performed and the article. Nevertheless, I think that there are some minor aspects that perhaps could be better described so the readers can better understand the results and their external validity. The authors do explain the limitations adequately, but perhaps some aspects could be clarified within the main text of the article.

Specific Comments

Major Comments

1. In Methods, the authors write that "This cross-sectional study was conducted at the Tunku Azizah Hospital, Kuala Lumpur, Malaysia. Subjects were caregivers to children seen with an appointment at the clinic." They also write that "This study was conducted at the hospital's Paediatric Specialist Clinic by convenience sampling. Self-administered, structured questionnaires were distributed to consenting participants. Subjects who agreed to participate were given questionnaires after seeing the doctor and while waiting for the date of their next consultation."

Selection bias is probably the most important limitation of this research. Selection bias is almost unavoidable, so the authors must make a considerable effort to clearly describe where they obtain the sample from, so the readers can have a clear idea of the main features of that sample, which also should be described. To better understand the results (and therefore the conclusions), it would be very interesting to know, in more detail, how the patients were chosen, the attrition rate, or other factors related to the sample selection. Therefore, I would propose that the authors better describe where the sample is obtained from and how they were chosen.

Response: Mentioned in the Data Collection section:

"This study was conducted at the hospital's Paediatric Specialist Clinic by convenience sampling using a self-administered structured questionnaire. Every third registering caregiver was identified and given the questionnaires after seeing the doctor and while waiting for the date of their next consultation. Upon completing the questionnaire, participants were instructed to put it into an enclosed envelope. The sealed envelope is then passed to the nurse at the clinic counter."

2. In that same section, the authors write that "A total of 600 questionnaires distributed to the clinic, and we received 502 responses, giving a rate of 83.7%. Of these 502 responses, 43 were unusable and were excluded from this study, and the remaining 459 (91.4%) questionnaires were analysed. Some 2,238 patients were registered for an appointment at the clinic during this data collection period."

It would be interesting if they describe in the article if they performed any sample size estimation and which method did they employ, in that case.

Response: Mentioned in the Methods (Participants) section:

"The minimum sample size required is 364, which was calculated using the Raosoft (2004) online sample size calculator with a 95% confidence level, 0.5 SD, margin of error (CI) of 5%, and population size of 6714 (the monthly patient average)."

3. The authors write that "This was part of a hospital-level survey assessing satisfaction among caregivers attending the clinic using the SERVQUAL instrument."

They properly describe the dimensions of the questionnaire, but perhaps it would be useful to know if this tool has been validated (or has required transcultural adaptation) to be used with this specific sample.

Response: Mentioned in the Data Collection section:

"The analysis of gaps is based on the difference between service quality expectations and perception. It was modified, translated, and validated in line with the Malaysian health care setting (22)."

4. Despite these aspects, which are easily solvable, I think that this is a very interesting article that can be useful for other researchers.

Minor Comments

Some sentences and some paragraphs are perhaps a bit too long, and therefore, they are a bit confusing to read, but overall, the article is very well written.

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Abbreviations

mHealth: mobile health

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study"

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KEYWORDS

mask; protection; COVID-19; influenza; transmission; intervention; infectious disease; respiratory; simulation; model; prevalence; efficacy

This is a peer-review report submitted for the paper "Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study."

Round 1 Review

Anonymous [1]

Major Comments

1. An additional introductory paragraph on the susceptible-exposed-infected-recovered (SEIR) model would strengthen the manuscript [2] and open it up to a wider audience, as this topic is of interest to many.

Response: To address this, an introductory paragraph about the basic underworking of SEIR models has been added to the Methods section under the SEIR Model and Parameters subsection.

2. An additional 1 to 3 paragraphs in the Discussion are needed, comparing this study to similar studies.

Response: At the time of this write up, there have not been any similar studies, at least with comparable parameters with which we could compare.

3. I suggest the authors use color-blind–friendly colors for the figures.

Response: The colors in the figures are yellow and green combinations as well as red and blue combinations to be color-blind–friendly.

Minor Comments

4. This statement needs rewording: "vaccines of course only have to be administered once while face masks need to be worn continuously." I suggest separating this away from the rest of the sentence and making it a cleaner statement.

Response: The statement has been separated and has now been changed to "Nevertheless, vaccines only have to be administered once per year while face masks would need to be worn continuously."

5. The last sentence of the Discussion is a run-on sentence. Please fix.

Response: The sentence has been broken down into different sentences to address the suggestion.

Reviewer AL [3]

1. The final sentence of the Abstract needs to be completed or reworked to explain “other practical aspects.”

Response: The statement has been deleted. Other practical masks have been explained.

2. I’m assuming that this is all focused on solely the United States since it is using Centers for Disease Control and Prevention (CDC) data. However, noting that this is US-centric and giving a brief description of how the CDC acquires this data will help the reader understand the data set, especially with many of the CDC data sets being underrepresentative of actual case rates because they are highly dependent on medical reports. In the case of the flu, how many people get the flu but never report to the CDC or see a doctor to get treatment because symptoms are mild?

Response: A brief discussion of how the CDC obtains flu data through the National Notifiable Diseases Surveillance System has been added to the SEIR parameters subsection. We also address the issue of underreporting. The CDC acknowledges that since flu cases are heavily based on reports from hospitals, it is prone to underreporting as the reviewer suggested. This is why it undergoes further analysis to correct for this phenomenon. Details of the arithmetic and statistical manipulations are addressed in the revision paper.

3. A creation of a table of or explicitly stating the variables and values used in the model is important for understanding. Especially when it comes to the calculated variables like B(t). Is that the same for each of those curves or is it changing with the different curves? If so, how much does it vary?

Response: Since the values are temporal, we have referenced the source of the data set. A table of the values and model has been added to the SEIR parameters subsection of the paper; the calculated variables like B(t) remain constant.

Minor Comments

4. How much does the virulence of the flu strains for that year versus the efficacy of the vaccine that year affect the data you are working with? Are there years that you think the masks would have helped substantially more than other years because the vaccine efficacy was lower than expected?

Response: For concerns of overcomplexity, we did not consider variance in infection of different flu strains in this paper. Data used in all out work was extrapolated from the CDC combined influenza data.

On masks and vaccines, the primary objective was to highlight how masks could have helped. Surely, in times when vaccine efficacy was lower, masks could have been a reasonable option, but with the rate of flu transmission, it would also depend on the percentage of mask wearers.

5. What is the typical mask efficacy for respiratory viruses? How does this “real-world” efficacy rate compare to the efficacy rates that you are using in your model?

Response: We were very considerate of real-world efficacy rates, especially considering the political and social pushback against mask mandates. As such, we used a generous mask efficacy rate to account for shortcomings and other real-life issues that may arise outside of a controlled environment.

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Abbreviations

CDC: Centers for Disease Control and Prevention
SEIR: susceptible-exposed-infected-recovered

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet"

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KEYWORDS

user-centered design; genomic medicine; patient portals; electronic health records; return of results; bioethics; EHR; genetics; genetic testing; patient preferences; design; human factors

This is the authors' response to peer-review reports for "Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet."

Round 1 Review

Anonymous [1]

Introduction

A1. The actual purpose and study rationale/goal of the study [2] was not described until the middle of the *Methods* section (minus the abstract). At the end of the *Introduction*, no information about the study was provided, and so, I was a little lost when transitioning from the *Introduction* to the *Methods* section for a study that hadn't been mentioned at all. The second sentence in the *Data Collection* section could be moved up as the last sentence of the *Introduction*.

Response: We have stated the purpose in the *Introduction* and moved the second sentence in *Data Collection* to the last sentence in the *Introduction* and revised it for clarity.

A2. Toward the end of the *Introduction*, the inclusion about barriers to the utilization of patient portals is very broad and not specific to genetics. I would suggest limiting it to genetic test results.

Response: Regarding the suggestion on patient portal use to return genetic test results, the literature does not focus on such a use for patient portals but rather on patient portal use in general. The authors suspect that this may be due in part to the history of all genetic test results being deemed especially fraught and complicated to return by default, and thus many genetics professionals do not support electronic return or only support very limited electronic return.

Methods

A3. Perhaps include a *Study Overview* section before *Participant Recruitment* if you do not wish to introduce the study in the *Introduction*.

Response: We have introduced the study in the *Introduction*.

A4. Either provide the semistructured interview guide or provide more detail about the content and structure (eg, funnel approach?).

Response: We have selected sample questions from the semistructured interview protocols and have included them in Table 2.

A5. There is no mention of the analysis of content-related themes in the *Data Analysis* section.

Response: We have added details about our analytic process in the *Data Analysis* section, including the specific direct content analysis approach we applied to identify the details of the design elements.

Results

A6. Confirm whether the patient demographics were the same for both study groups. Perhaps redo the table to include a breakdown of demographics between the two groups.

Response: We have reworked the demographics table to depict the study groups separately.

A7. Clarify if the content recommendations came from the group that was asked to compare their experiences receiving genetic vs nongenetic test results through a patient portal.

Response: We can confirm that the quotations presented as exemplars were from the sections of the protocol where genetic test results were being discussed. That being said, participants frequently switched back and forth when discussing genetic and nongenetic test results. That level of fluidity is a finding that will be reported in another paper on thresholds for the electronic return of genetic and other test results.

A8. Did you conduct any analysis to factor in patients' background (eg, education, gender, age) or the specific type of experience with genetic testing to provide some context of their responses?

Response: We did not do an additional analysis, as the overall topics seemed similar across participants, and as the reviewers have indicated, the study is small and exploratory.

A9. Without a better understanding of what the questions were, it is not totally clear if the questions were totally open-ended or if you asked them to provide feedback on specific suggestions (like the summary sheet). I assume the questions were more open-ended, given the data analysis description, but the results appear to be narrowly confined.

Response: We have included Table 2, which presents sample questions. One of the strengths of a semistructured protocol is that it allows interviewers to organically adjust questions both in real time and when moving forward with future interviews. Many design-related data from participants, such as the suggestion to include a summary, were collected this way.

A10. It seems to me that design recommendation #3 about smartphone functionality is not specific to genetics and should not be reported as a recommendation.

Response: We think it is important to include smartphone functionality, despite the fact that smartphone access to test results would apply to all types of tests available online. It is crucial that report template designers understand that many patient users will be accessing those results on smartphones to, for example, share their genetic variant information with a new medical provider outside of their system.

A11. Some confusion about recommendations—is a simple coversheet (design recommendation #1) the same as an electronic summary (design recommendation #2) and a patient-friendly results summary (domain 2 subheading, content recommendations #2-#4)

Response: The summary is the same as the coversheet. We have changed the language we use to be consistent in conveying this.

Discussion

A12. Include some discussion of the implementation of the recommendations. Many would take considerable time to complete for multiple testing vendors/lab reports. Are they really feasible? Do you anticipate that the laboratories will do some of this work or will it fall to test orderer?

Response: Although we understand that there will be challenges regarding the implementation of any templates and processes for the electronic return of genetic (and other) test results, the focus of this study was on gathering patient user feedback and advice. We acknowledge this limitation on page 17: "We acknowledge that a patient-centered approach may elicit suggestions for content and design that might not be easily accommodated by available patient portal software (such as that available through Electronic Health Record software) or by the clinical workflow of healthcare systems or preferences of individual providers. These issues are beyond the scope of our study but must be considered in the final decisions regarding portal-based return of genetic results."

A13. In the section *Comparison to Prior Work*, I would suggest including more discussion about the format and design of current lab reports. Many are made available through labs on their websites. It is difficult to generalize lab reports for different indications/purposes and come up with a best fit with respect to design/formatting. Certainly, patient feedback will be valuable for learning how to improve the comprehension of genetic testing lab reports. Many results cannot be analyzed without the consideration of more clinical information. Test reports are intended for health providers and thus the style, jargon, and information will understandably differ for patients. The authors should consider reviewing reports intended for patients (eg, 23andMe), which are delivered electronically.

Response: Comparisons of industry methods and content for the return of results would be useful but are beyond this study. That being said, as authors who work in academic settings, we are aware that academic medical centers and health care organizations likely do not have the bandwidth to provide the type of test report and test report technical support that for-profit companies can.

Minor Comments

A14. Remove the extra numbers outside at the bottom of table.

Response: The number that follows Table 1 is a footnote relevant to the table. We have replaced the number with an asterisk.

Anonymous [3]

Major Comments

B1. In the final paper, I would recommend not including the quoted comments from the qualitative interviews. I would put those in the supplemental materials, as they are interesting, but they do not add that much to the paper itself.

Response: While we understand that removing quotations is economical, these exemplars are the “figures” of qualitative research that allow others to judge some of our interpretations of the data. We prefer to leave them in the main body of the text rather than move them to a supplementary file, so that readers can more easily judge our work. We have kept the number of our exemplar quotations to a minimum.

Minor Comments

B2. One area that is mentioned but not emphasized is the extension of the results of this qualitative study to the communication of nongenetic tests to patients. The same sort of principles should apply in terms of the cover sheet and the detailed explanation. Some of us already do this with our patients, but an extension of this study would allow some evidence to support that practice.

B3. It would be nice to expand the study to include both nongenetic test results and diagnostic imaging results in terms of the design, content, and functionality of the results presentation.

B4. An additional study would be looking at optimizing results presentation and content for smartphones versus computers or tablets. There may be a way to optimize the presentation of the data so that patients could more easily see the data on the smartphone form factor. That is an area for future study.

Response: We cannot actually expand the study at this point, but we agree with the reviewer that there are other relevant areas of application where more research needs to be done.

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3. Anonymous. Peer review of "Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet". JMIRx Med 2022;3(2):e38486 [FREE Full text]

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Authors' Response to Peer Reviewsr

Authors' Response to Peer Reviews of "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study"

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KEYWORDS

ophthalmologic surgical procedures; access to health care; ophthalmology; patient-centered care; ethnography; health knowledge; attitudes; practice

This is the authors' response to peer-review reports for "Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study."

Round 1 Review

Dear Editor and Reviewers,

We note with pleasure that your review comments were quite useful in helping us take a closer look and improve our work [1] further. We carefully observed and addressed all the comments as required and hope that the paper is in much better shape for the journal's readership. Kindly find below our answers to all the editorial and reviewer comments. We will be happy to address any comments you may have further to the reviewed version of the manuscript.

Reviewer P [2]

General Comments

Dear Reviewer P,

Thank you very much for the time you took to critically elaborate on the subject matter and for the compliments. We are grateful to you for indicating to us that this is an innovative paper. We also hold your views of extending our approach to

other areas in which similar challenges are faced. Kindly find our answers to your comments below.

Minor Comments

1. It would be interesting if there are any other articles that mention this problem and can be added in the manuscript.

Response: We thank the reviewer for this suggestion. We took time to explore a journal database of community eye health [3] of articles dealing with barriers to the uptake of eye care services in similar settings published within the last 30 years. We found no article that fell within the last decade. However, we alluded to similar programs run in other countries in the second-to-last paragraph of the *Introduction* section (highlighted in yellow), and we carried out a comparison with similar studies in the *Discussion* section.

2. Moreover, the eye care delivery in Cameroon is presented only from the financial aspect. It would be interesting if the authors could add some other demographic or educational and cultural factors that affect the access to health care.

Response: We appreciate your concern. Apart from financial challenges, we also highlighted other factors that limit access to health care, which have now been substantiated. We also added a couple of lines, all of which have been highlighted in yellow.

Reviewer Q [4]

General Comments

Dear Reviewer Q,

We are very grateful for the suggestions in improving our paper. We carefully considered and addressed all points as shown below.

Major Comments

1. It is better to choose keywords that are MeSH terms.

Response: We have modified the keywords to address this concern.

2. It is better to integrate all sections before *Methods* as an *Introduction* section.

Response: Done.

3. How did the researchers develop the interview guide?

Response: This has been clarified under *Data Collection Procedure* and highlighted in green.

4. The trustworthiness of the results and validity and reliability need to be discussed separately for each research method.

Response: We appreciate this suggestion. We did discuss the above under the subsection *Data Credibility*, which has been renamed as *Trustworthiness, Validity, and Reliability*. We have also made a few modifications.

5. More details should be added to the *Document Review* section.

Response: Done.

6. How many participants took part in the focus groups?

Response: All 29 subjects took part in the focus group discussions as highlighted in the table of participant characteristics. We have also rephrased the first sentence of the *FGDs* subsection to make this clearer.

7. The *Results* section needs to be expanded.

Response: Thank you for this. We were not able to expand the *Results* section owing to the editorial recommendation to reduce the length of the paper.

8. In the *Discussion* section, the summary of results does not need to be supported by the participant's quotes.

Response: This has been removed.

9. The *Discussion* section needs to be revised to be more integrated.

Response: We have gone through the paper again and made corrections where necessary.

10. Strengths and limitations of the study can be reported at the end of the discussion section.

Response: Done.

11. Research implications can be reported before conclusions.

Response: Done.

Reviewer BJ [5]

General Comments

Dear Reviewer BJ,

Thank you for taking the time to review our paper and for the recommendations. We considered all suggestions in improving the paper further. Kindly find below our responses to your comments.

Major Comments

1. The lengths of both the main text and the abstract are a bit long. We suggest the authors to further condense the paper or move some parts to Multimedia Appendices.

Response: We have removed some text from the *Abstract* and the body and maintained the word count in line with the guidelines [6].

2. Although 29 subjects were interviewed, only 9 of them were direct subjects. We are unsure if this is a sufficient number for such qualitative analysis.

Response: Thank you for raising this concern. In the context of this study, decisions regarding the uptake of cataract surgery to a greater extent are not made by blind patients with cataract themselves but rather by the breadwinner, if not the entire family, and often in consultation with other villagers who have been in similar situations, which sometimes may even extend to seeking advice from traditional healers or spiritualists about the success of the surgery. We wanted a sample that will represent the decision-making mechanism as highlighted under the *Ethnographic Rationale* subsection. This was discussed in a panel with colleagues, and it was determined that each subject category included in the sample played a key role in the uptake of cataract surgery.

There is evidence that data saturation in qualitative studies can be reached with a minimum sample of 13 [7-9]. The operated patients and blind patients with cataract together with their family members made up 15 subjects. According to Hennink and Kaiser [10], saturation can equally be reached with 9 subjects.

3. The influence of indirect subjects' opinions on the decision of the direct subjects was not particularly discussed.

Response: Thank you again for raising this. Following our explanation in point #2 above, it is a fact that direct patients to a lesser extent decide for themselves what they need. We have highlighted and underscored the fact that the decision-making mechanism in cataract surgery uptake is a social construct [11], with the family to a greater extent and the community to a lesser extent assuming major roles [12]. Kindly refer to the second-to-last paragraph of the *Conclusions* subsection (in pink).

4. Considering the potentially different weights of direct versus indirect subjects' opinions in the decision, whether the quotes were taken from direct subjects should be shown.

Response: Done.

5. We are no experts of traditional medicine, but is there anything to be noted about these therapies? (Maybe certain therapies were helpful from the patients' perspectives?) We are unsure if these should be taken into consideration when assessing the “Knowledge and awareness” and “reasons of refusal.”

Response: We have now added some text in the *Discussion* section to reflect this point (highlighted in pink).

6. The “poor outcome” of prior cataract surgeries was mentioned in the *Results* section. Can this be a possible reason for the “fear” of cataract surgery and the reason to choose traditional medicine instead?

Response: We have equally added a phrase under the *Perceived Reasons for Refusing Cataract Surgery* subsection in the *Discussion* section to reflect this.

Minor Comments

7. There are still some grammatical mistakes that should be checked and amended.

Response: We have read through and made some corrections.

8. Please make sure to provide the full spellings of all abbreviated words at first use (eg, “MICEI” and “FGDs”).

Response: Done

9. The table did not show the particular demographics of the direct subjects (which may help reveal other socioeconomic factors influencing the decision or limitation of the study).

Response: Done.

10. How is the surgery acceptance or backlog situation for community cataract screening programs conducted in nearby countries with a similar socioeconomic status? While this is not the focus of the study, if there are available data, it would be good to include some general information (this will help justify the study aim and support the overall results).

Response: Thank you for bringing this up. This has now been included in the second-to-last paragraph of the *Conclusions* subsection and highlighted in yellow.

Round 2 Review

Dear Editor and Reviewers,

We thank you for pointing out the outstanding concerns which we have now carefully considered and addressed accordingly. We have now integrated our responses in the review comments for both rounds 1 and 2 as recommended by some of the reviewers.

Reviewer Q

General Comments

Dear Reviewer Q,

We are thankful for the additional concerns. Kindly find our responses to your concerns below.

Major Comments

1. The author response letter only includes the authors’ responses without mentioning the reviewers' comments. For some comments, they just said “done” and I have no idea what the comments were and what they exactly did. So, a complete response letter needs to be uploaded.

Response: Our understanding in round 1 was that the reviewers had a copy of their comments. Additionally, we uploaded a copy of the response letter bearing the reviewer comments and our responses (as a supplementary file) and made it visible to the reviewers. We equally uploaded a version of the revised manuscript with track changes and made it visible to the reviewers as well. To address your concerns, we have included the responses for round 1 in this letter. We have also uploaded the revised manuscript with track changes.

2. The *Discussion* section needs to be integrated to show an integrated *Discussion* for the whole research. In the current format, it seems fragmented.

Response: We have now integrated the *Discussion* such that the former *Comparison With Prior Studies* is combined with the *Interpretation of Results* subsection, and we integrated the *Public Health Implications* subsection with the *Conclusions* subsection; we have made sure that our paper is in line with the journal guidelines with regard to the Discussion section [13].

3. Also, the subsections under the *Conclusions* section need to be moved to the end of the *Discussion* section or be integrated with other existing subheadings in this section.

Response: We have deleted the *Study Usefulness* subsection and integrated the *Recommendations* subsection with the *Conclusions* subsection as we think that the recommendations will better flow with the conclusion.

Reviewer BJ

Dear Reviewer BJ,

Thank you for taking the time to review our paper and for the recommendations. We considered all suggestions in improving the paper further. Kindly find below our responses to your comments.

1. The authors have addressed most of the comments. While the scientific content is acceptable after the revision, it is still recommended that the authors shortened the article to <6500-7000 words. No further suggestions are enclosed.

Response: We thank the reviewer for raising this concern. While we are not against cutting down the word count, we wish to reiterate that the word count is in line with the journal guidelines [6] that were updated 2 days ago. That notwithstanding, we have now down-worded the main body and abstract to 7329 words excluding the title, author information, multimedia appendices, references, and abbreviations. This is as opposed to a maximum of 10,000 words recommended [6].

Acknowledgments

MM is an independent researcher and can be reached via Alumni Relations, London School of Hygiene & Tropical Medicine.

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Original Paper

Using Structural Equation Modelling in Routine Clinical Data on Diabetes and Depression: Observational Cohort Study

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Abstract

Background: Large data sets comprising routine clinical data are becoming increasingly available for use in health research. These data sets contain many clinical variables that might not lend themselves to use in research. Structural equation modelling (SEM) is a statistical technique that might allow for the creation of “research-friendly” clinical constructs from these routine clinical variables and therefore could be an appropriate analytic method to apply more widely to routine clinical data.

Objective: SEM was applied to a large data set of routine clinical data developed in East London to model well-established clinical associations. Depression is common among patients with type 2 diabetes, and is associated with poor diabetic control, increased diabetic complications, increased health service utilization, and increased health care costs. Evidence from trial data suggests that integrating psychological treatment into diabetes care can improve health status and reduce costs. Attempting to model these known associations using SEM will test the utility of this technique in routine clinical data sets.

Methods: Data were cleaned extensively prior to analysis. SEM was used to investigate associations between depression, diabetic control, diabetic care, mental health treatment, and Accident & Emergency (A&E) use in patients with type 2 diabetes. The creation of the latent variables and the direction of association between latent variables in the model was based upon established clinical knowledge.

Results: The results provided partial support for the application of SEM to routine clinical data. Overall, 19% (3106/16,353) of patients with type 2 diabetes had received a diagnosis of depression. In line with known clinical associations, depression was associated with worse diabetic control (β=.034, *P*<.001) and increased A&E use (β=.071, *P*<.001). However, contrary to expectation, worse diabetic control was associated with lower A&E use (β=–.055, *P*<.001) and receipt of mental health treatment

did not impact upon diabetic control (*P*=.39). Receipt of diabetes care was associated with better diabetic control (β=–.072, *P*<.001), having depression (β=.018, *P*=.007), and receiving mental health treatment (β=.046, *P*<.001), which might suggest that comprehensive integrated care packages are being delivered in East London.

Conclusions: Some established clinical associations were successfully modelled in a sample of patients with type 2 diabetes in a way that made clinical sense, providing partial evidence for the utility of SEM in routine clinical data. Several issues relating to data quality emerged. Data improvement would have likely enhanced the utility of SEM in this data set.

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KEYWORDS

depression; diabetes; electronic health records; acute care; PLS-SEM; path analysis; equation modelling; accident; emergency care; emergency; structural equation modelling; clinical data

Introduction

Background

Currently, large amounts of routinely collected clinical data are becoming increasingly available for use in health research. The main advantages of these large-scale data sets are their comprehensive nature, and their large patient numbers [1]. Large clinical databases can improve clinical care by providing population characteristics, identifying risk factors, and allowing for the development of predictive models using vast amounts of historical data [1,2]. To date, several large data sets comprising routine clinical data have been developed in the United Kingdom and are being used to inform clinical guidance and health care delivery [3-5]. These data sets provide a rich research resource, but there are considerable limitations associated with the use of routine clinical data, particularly surrounding the completeness and accuracy of the data. Routine clinical data are subject to data entry errors, as well as systematic inconsistencies and coding errors, which can lead to inaccurate findings.

Structural equation modelling (SEM) is a statistical technique that allows for the inclusion of multiple variables and the creation of important constructs that cannot be observed directly [6]. Partial least squares SEM (PLS-SEM) is a variant of SEM that poses no distributional assumptions (eg, normality, continuous/scale) upon data used for modelling but is frequently used for predictive approaches with an aim to understanding causal structures [7]. Further, PLS-SEM can be effective with a relatively small sample: approximately 10 cases per regression or "path" estimate leading to the most connected latent variable is considered adequate, although there has been some debate about the use of PLS-SEM with very small sample sizes [7,8].

Routine clinical data contains many clinical variables that might not be directly appropriate for answering research questions. SEM could allow for the creation of clinical constructs from the routinely collected clinical variables that are more suitable for use in research. To the best of our knowledge, SEM has not yet been applied to routine clinical data. A large integrated data set has recently been developed in East London; it contains routine clinical data from both primary and secondary care [9]. This data set was developed to support commissioning decisions within health care trusts in East London, meaning that its primary purpose was not for research. Therefore, we sought to determine whether SEM could be used to make this data set more "research friendly" by attempting to create clinical constructs and model some well-known clinical associations between depression and accident & emergency (A&E) use in patients with type 2 diabetes.

Depression, Type 2 Diabetes, and A&E Use: A Case Study

Depression has been shown to occur approximately twice as frequently in type 2 diabetes than would be predicted by chance alone [10], and is associated with increased diabetic complications and poor diabetic control [11]. Patients with comorbid depression and type 2 diabetes have been shown to have increased health care utilization [12]; for example, they are more likely to present at A&E departments [13] and have increased health care costs (up to 70%) compared to patients with type 2 diabetes without depression [14]. This is particularly marked in those with poorly controlled diabetes [15]. Successful management of depressive symptoms through the use of psychotherapy and pharmacotherapy has been found to improve diabetic control [16] and to reduce health care service use and associated costs [17,18]. The evidence cited above comes from trial data and observational studies designed specifically for research purposes. We sought to replicate these findings using large-scale routine clinical data. More specifically, we aimed to model associations between depression, diabetic care, diabetic control, and A&E utilization, while assessing the impact of current mental health care provision. We hypothesized that depression would be associated with increased diabetic complications and poor diabetic control, and that both depression and poor diabetic control would be associated with increased utilization of A&E. We predicted that the receipt of mental health treatment would improve diabetic control. We also hoped to include relevant demographic, behavioral, and clinical factors in the model that are likely associated with pathways to care for people with depression and type 2 diabetes.

Methods

Study Setting

We used a large patient-linked data set from the borough of Tower Hamlets, an inner-city area located in the East End of London, United Kingdom. Tower Hamlets is unique as it has a diverse population and is home to the largest Bangladeshi community in England [19]. Tower Hamlets has the highest rate of poverty, child poverty, and unemployment of any London borough [20].

Data Source and Study Design

The patient-linked data set was developed by the Tower Hamlets Clinical Commissioning Group (CCG) and contains routinely collected clinical data from several sources: (1) Secondary Uses Service database, a secure data warehouse that stores patient-level information for management and clinical purposes other than direct patient care, and supports commissioning and the delivery of health services; (2) a primary care data set generated by North East London Commissioning Support Unit; (3) Improving Access to Psychological Therapies (IAPT) data sets (IAPT is a talking therapy service used for the treatment of adult anxiety and depression in England); and (4) clustered and nonclustered mental health care data sets (within the National Health Service [NHS], mental health care clusters provide a framework for planning and organizing mental health services and patient support).

The data set comprises data for the general practitioner–registered population in Tower Hamlets. A detailed description of the data set has been published elsewhere [9]. In this observational cohort study, routinely collected cross-sectional clinical and health service utilization data from Tower Hamlets were collated over one financial year (2017/2018). Variables of interest were selected and extracted from linked relational data sets. All data were pseudonymized and stored in a secure network database at Tower Hamlets CCG, Mile End Hospital. All data were accessed and analyzed on-site at Tower Hamlets CCG.

Ethical Considerations

As this study was examining the utility of a statistical method, it was deemed to not be defined as research and therefore required no ethical approval. All the necessary approvals were obtained from Tower Hamlets CCG to perform the analysis on the data set.

Participants

The sample to be analyzed included patients aged ≥18 years who were registered with a general practitioner in Tower Hamlets and had a diagnosis of type 2 diabetes recorded in their primary care records. Type 2 diabetes is deemed to be a difficult disease to reverse [21]. Therefore, all patients who ever had a type 2 diabetes diagnosis recorded were included.

Demographic and Clinical Factors

Demographic and clinical information included age, sex, ethnicity, deprivation index, smoking status, and BMI. Information about age and sex came from primary care records. Age was treated as a continuous variable. Ethnicity was also obtained from primary care records. Patients were classified into nine ethnic groups: White, or not stated; Indian; Pakistani; Bangladeshi; other Asian; Black Caribbean; Black African; Chinese; other ethnic group. For the purposes of the analysis, patients were reclassified into two groups: White or not stated and non-White. Deprivation index was based on Census data using Lower Layer Super Output Areas. Deprivation scores ranged from 1-10, with lower deciles being indicative of higher deprivation. Information relating to BMI and smoking status came from primary care records.

Measures of Mental Health Diagnoses and Care

Mental health variables included in the analyses were from primary care records, IAPT data, clustered mental health data sets, and nonclustered mental health data sets. Information about whether a patient had ever received a diagnosis of depression, anxiety, severe mental illness (SMI), alcohol use, or personality disorder was obtained from primary care records. The variable used for alcohol intake was generated by North East London Commissioning Support Unit. This variable contained collapsed scores for both the Alcohol Use Disorders Identification Test (AUDIT) and the AUDIT for consumption (AUDIT C) and was treated as a continuous variable in the analyses. Scores on the AUDIT range from 0-40, with higher scores indicating higher risk of dependence. The AUDIT C consists of the 3 consumption questions from the AUDIT and scores can range from 0-12, with higher scores indicating higher risk.

As the analysis was mainly concerned with depression, availing of clustered mental health care relating to depression was included in the model as well. The following NHS mental health clusters were deemed likely to be associated with depression: care cluster 1 (common mental health problems, low severity); care cluster 2 (common mental health problems, low severity with greater need); care cluster 3 (nonpsychotic, moderate severity); care cluster 4 (nonpsychotic, severe); care cluster 5 (nonpsychotic, very severe); and care cluster 15 (severe psychotic depression).

Variables that may be markers for the treatment of depression were also included in the analyses. These included whether a patient had received an antidepressant prescription from their general practitioner within that financial year, whether the patient had accessed IAPT services, and whether the patient had been admitted to a psychiatric inpatient ward. Although these variables are not necessarily specific to depression, the use of these services are increased among patients in the Tower Hamlets data set who have received depression diagnoses. Therefore, they are deemed to be an acceptable proxy for depression treatment in this case.

There was no variable relating to the use of psychiatric inpatient services readily available in the patient-linked data set. Therefore, this variable had to be constructed using information from the nonclustered mental health services data set. Within Tower Hamlets, there are six psychiatric inpatient wards: Brick Lane ward, Globe ward, Lea ward, Millharbour ward, Roman ward, and Rosebank ward. If a patient had been admitted to any of these wards within financial year 2017/2018, they were recorded as having been a psychiatric inpatient. However, the reason why the patient was admitted to a psychiatric ward was unknown.

Measures of Diabetes Care

We included several variables relating to diabetes care and diabetic control. The diabetes care variables were taken from primary care records and comprised whether a patient had been assigned a diabetes care plan, received a diabetic retinal exam, or received a diabetic foot exam. As specified in the National Institute for Health and Care Excellence (NICE) 2019 guidelines for the treatment of type 2 diabetes in adults, when a patient

receives a diagnosis of type 2 diabetes, a diabetes care plan is usually agreed between the patient and their general practitioner [1,22]. This care plan allows the patient to take responsibility for their own well-being through increasing understanding about their condition, implementing healthy lifestyle changes, and being proactive about seeking care. Receiving routine retinal and foot exams is a standard part of type 2 diabetes care used to detect any associated retinopathy or diabetic foot problems [22]. Variables pertaining to diabetic control included the patients' latest glycated hemoglobin (HbA_{1c}) levels. In this study, HbA_{1c} is measured in mmol/mol as per the International Federation of Clinical Chemistry units. HbA_{1c} is measured to determine the patient's average blood sugar level, with higher levels being associated with more diabetic complications [23]. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also included as variables associated with diabetic control. Blood pressure is known to be associated with increased vascular risk in patients with type 2 diabetes and maintaining a healthy blood pressure is associated with better clinical outcomes for these patients [24].

A&E Use

Variables used to measure A&E use related to the number of A&E attendances per patient within financial year 2017/2018 and the A&E spend associated with that patient for the same time period. This data came from the Secondary Uses Service database.

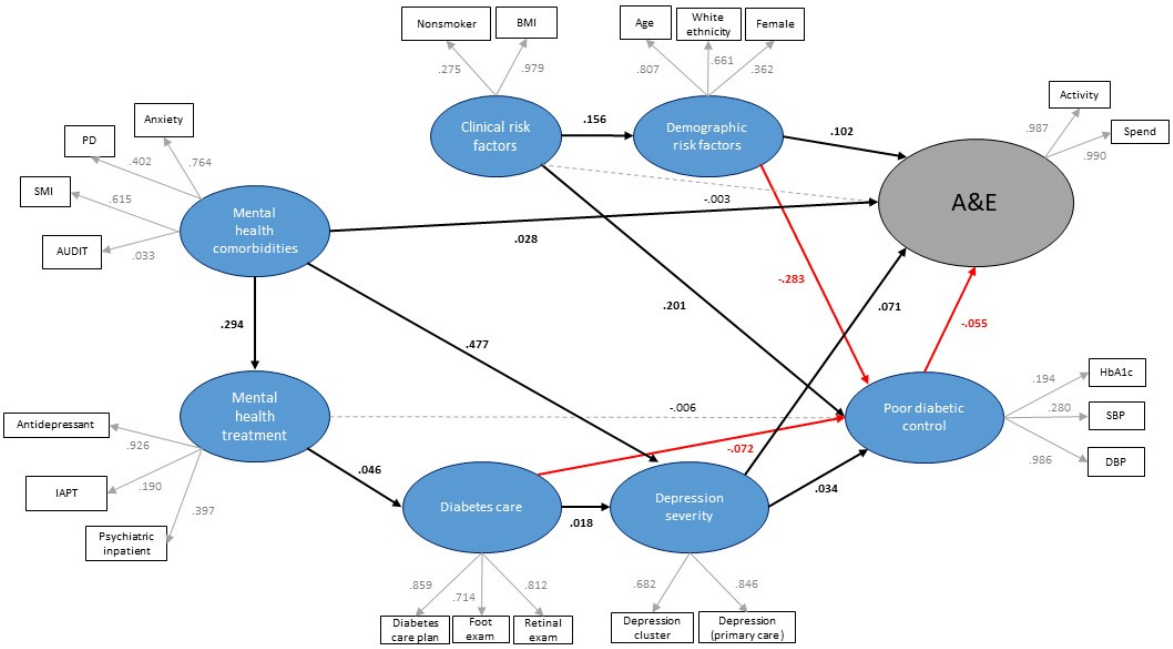
Data Preparation and Cleaning

The data were cleaned prior to statistical analysis. In many cases, patients who had been assigned to a mental health cluster code in that year had been assigned to several cluster codes, leading to the same individual appearing in the data set numerous times. In cases where assigned cluster codes were the same, all duplicates were removed. If the assigned cluster codes were different for an individual patient, the most severe cluster code was retained, and the less severe cluster code was removed from the data set. All patients aged <18 years were removed from the data set to ensure that the analyses were being carried out on an adult sample. All variables were complete apart from AUDIT (alcohol intake) data, cholesterol data, and deprivation level. Missing AUDIT and cholesterol data were resolved using mean imputation (ie, missing values were replaced by the mean of the available cases). As less than 50 patients were missing data pertaining to deprivation level, these patients were removed from the data set. Frequency analysis revealed that there were a number of data entries well out of clinical range for HbA_{1c} values (20-100 mmol/mol), SBP (90-200 mm Hg), DBP (50-120 mm Hg), and BMI (15-55 kg/m^2). These cases were removed from the data set.

Structural Model

As the purpose of this research was to test the role of mental health service use on A&E use in patients diagnosed with type 2 diabetes, we constructed a model of latent variables that reflected existing knowledge on this subject (Figure 1). Within this model, for example, we recreated the links observed between depression and poor diabetes control [11] and that the comorbidity of the two conditions increases A&E attendance [13]. We also included latent variables representing mental health comorbidity and clinical risk factors for diabetes that may confound the relationship between diabetes care, depression, and A&E admission.

Figure 1. Fitted partial least squares structural equation model of factors associated with A&E use among patients with type 2 diabetes living in Tower Hamlets. A&E: Accident & Emergency; AUDIT: Alcohol Use Disorders Identification Test; DBP: diastolic blood pressure; HbA_{1c}: glycated hemoglobin; IAPT: Improving Access to Psychological Therapies; PD: personality disorder; SBP: systolic blood pressure; SMI: severe mental illness.



Statistical Analyses

Independent *t* tests and chi-square analyses were used to measure differences between patients with type 2 diabetes with and without depression. To investigate the relationships between depression, diabetic care, diabetic control, mental health treatment, and A&E use, PLS-SEM was carried out. Given the nature of the data, which consisted mainly of dichotomous indicators (eg, diagnoses) and ordinal measures (eg, AUDIT drinking scores) with only a small number of continuous observed variables (eg, HbA_{1c} reading), PLS-SEM was selected over other SEM approaches as it allows for the use of both continuous and discrete observed variables as indicators that measure unobservable latent variables. A covariance-based SEM approach would require continuous variables with some restrictions on distribution; Bayesian networks were also considered but are entirely probabilistic in outcome and would not have given the desired effect size coefficients for different pathways.

Our modelling approach was reflective, in that we employed observed variables from the health care data set to measure pre-existing latent variables (eg, "A&E usage") and that, to use the typology proposed by Coltman et al [25], causality flows from latent construct to observed variable (eg, A&E usage [construct] causes increased spend on A&E services [observed]). We created 8 latent variables with multiple indicators for A&E use, poor diabetic control, diabetes care, depression severity, mental health treatment, mental health comorbidities, demographic risk factors, and clinical risk factors. PLS-SEM allowed for multiple linear equations between these 8 latent variables to be carried out simultaneously, which is not possible using traditional regression methods. The latent variables were created and connected using prior clinical and research knowledge and discussed with a clinical reference group to ensure that the proposed pathways made clinical sense.

All analyses were carried out using R software (version 3.51 for Windows x64; R Foundation for Statistical Computing) [26]; SEM analysis within R was conducted using the *plspm* package [27]. A *P* value of <.05 was considered significant.

Results

Patient Characteristics

Prior to data cleaning, the data set contained 20,088 patients with type 2 diabetes. Once duplicates based on mental health cluster codes were removed, the sample size was reduced to 18,092. Removal of patients under 18 years of age resulted in a sample size of 18,067 adult patients with type 2 diabetes in Tower Hamlets. Removing HbA_{1c} values (n=1382), BMI values (n=175), SBP values (n=55), and DBP values (n=55) outside of clinical range further decreased the overall sample size to 16,400. In addition, 47 patients did not have deprivation level recorded so were removed from the data set, leading to a final sample of 16,353 patients with type 2 diabetes.

Sample characteristics for the overall sample and for type 2 diabetic patients with and without depression are provided in Table 1. The overall sample comprised 7862 (48.1%) women and had a mean age of 59.5 years. The sample were on average overweight (mean BMI of 28.8) and living in areas of high deprivation (12,145/16,353, 74.3%). A considerable proportion of patients were recorded as smokers (n=4595, 28.1%), but mean AUDIT scores were low (mean 0.5), which is indicative of lower-risk drinking. In addition, 19% (n=3106) of patients with type 2 diabetes had a diagnosis of depression recorded in their primary care records, and 84.3% (n=2619) of these patients had received prescriptions for antidepressants. Very few patients with depression had been referred to local therapy services (IAPT; 1.4%) but this might reflect issues with certain data flows. Very few patients with depression had been admitted to a psychiatric ward (39/3106, 1.3%) within the study period and a greater proportion of psychiatric inpatients did not have a primary care diagnosis of depression. Overall, the majority of patients with type 2 diabetes had an agreed diabetes care plan (15,271/16,353, 93.4%) and had both a retinal (n=15,521, 94.9%) and foot (n=16,005, 97.9%) exam in the last year.

Comparisons between type 2 diabetic patients with and without depression revealed a number of significant differences in terms of demographic, clinical, and health service use factors (Table 1). Patients with and without diagnoses of depression did not differ in age but more female patients tended to have depression (*P*<.001). The majority of patients were of non-White ethnicity (12,528/16,353, 76.6%) but patients of non-White ethnicity were less likely to have a recorded diagnosis of depression (*P*<.001).

Patients with depression were more likely to be overweight (*P*<.001), more likely to smoke (*P*<.001), and scored higher on the AUDIT, indicating higher alcohol intake (*P*<.001). Patients with depression did not differ from patients without depression in terms of receiving retinal (*P*=.17) or foot (*P*=.88) exams. However, patients with type 2 diabetes and depression were more likely to have an agreed diabetes care plan (*P*=.02). Depression did not have a significant impact on HbA_{1c} levels (*P*=.46). However, patients with depression had significantly lower SBP (*P*=.004) but significantly higher DBP (*P*=.02) than patients without depression. In terms of health service utilization, patients with type 2 diabetes and depression attended A&E more in the 12-month study period than those with type 2 diabetes and no depression (*P*<.001) and incurred higher spend per head (*P*<.001). Spend, on average, for patients with type 2 diabetes with depression was £37.80 (US $49.84) more per year in A&E than for patients with type 2 diabetes without depression.

Table 1. Sample characteristics.

Characteristics	Overall sample (N=16,353)	Depressed (n=3106)	Not depressed (n=13,247)	*P* value[a]
Age (years), mean (SD)	59.5 (16.6)	59.5 (14.6)	59.5 (17.1)	.94
Gender				
Female, n (%)	7862 (48.1)	1877 (60.4)	5985 (45.2)	<.001
Male, n (%)	8491 (51.9)	1229 (39.6)	7262 (54.8)	N/A[b]
Non-White ethnicity, n (%)	12,528 (76.6)	1964 (63.2)	10,564 (79.7)	<.001
High deprivation[c], n (%)	12,145 (74.3)	2297 (74)	9848 (74.4)	.30
BMI (kg/m^2), mean (SD)	28.8 (6.2)	30.0 (6.9)	28.5 (5.9)	<.001
Smokers, n (%)	4595 (28.1)	1064 (34.3)	3531 (26.7)	<.001
Depression, n (%)	3106 (19)	N/A	N/A	N/A
Anxiety, n (%)	2498 (15.3)	1453 (46.8)	1045 (7.9)	<.001
Severe mental illness, n (%)	731 (4.5)	338 (10.9)	393 (3)	<.001
Personality disorder, n (%)	131 (0.8)	97 (3.1)	34 (0.3)	<.001
Alcohol Use Disorders Identification Test score, mean (SD)	0.5 (0.9)	0.7 (1.3)	0.5 (0.9)	<.001
Antidepressant prescribing, n (%)	7600 (46.5)	2619 (84.3)	4981 (37.6)	<.001
Improving Access to Psychological Therapies activity, n (%)	80 (0.5)	45 (1.4)	35 (0.3)	<.001
Psychiatric inpatient, n (%)	82 (0.5)	39 (1.3)	43 (0.3)	<.001
Depression cluster code[d], n (%)	95 (0.6)	84 (2.7)	11 (0.1)	<.001
Diabetes care plan, n (%)	15,271 (93.4)	2930 (94.3)	12,341 (93.2)	.02
Retinal exam, n (%)	15,521 (94.9)	2963 (95.4)	12,558 (94.8)	.17
Foot exam, n (%)	16,005 (97.9)	3041 (97.9)	12,964 (97.9)	.88
HbA_{1c}, mmol/mol (International Federation of Clinical Chemistry units), mean (SD)	57.8 (15.4)	58.0 (16.3)	57.8 (15.2)	.46
Systolic blood pressure (mm Hg), mean (SD)	127.6 (15.0)	127.0 (14.9)	127.8 (15.0)	.004
Diastolic blood pressure (mm Hg), mean (SD)	74.8 (9.6)	75.2 (9.5)	74.8 (9.6)	.02
Accident & Emergency attendances, mean (SD)	0.6 (0.9)	0.8 (1.2)	0.6 (0.9)	<.001
Accident & Emergency spend (£; US $), mean (SD)	103.80 (170.20); 136.87 (224.42)	134.50 (210.70); 177.35 (277.83)	96.70 (160); 127.51 (210.98)	<.001

[a]*P* value calculated by comparing the depressed with the nondepressed cohorts. For gender, those listed as male were compared with those listed as female.

[b]N/A: not applicable.

[c]High deprivation: combination of deciles 1 and 2.

[d]Depression cluster codes include 1, 2, 3, 4, 5, and 15.

Structural Equation Modelling

The SEM diagram in Figure 1 depicts the relationships between the latent variables and their indicators (outer model) and the relationships among the latent variables (inner model) that make up the SEM. Latent variables are shown as ellipses and observed variables are shown as squares. Arrows show the hypothesized direction of effect between variables and each arrow is accompanied by a path coefficient, which can be interpreted as standardized beta coefficients in a regression model. Statistically significant associations between variables are shown using bold arrows. Black arrows depict positive associations whereas red arrows depict negative associations. Associations that are not statistically significant are illustrated using dashed lines.

In the final inner model, coefficients were estimated simultaneously for all 8 latent variables as depicted in Figure 1. Path coefficients are provided in Table 2 and shown in Figure 1. When checking the model, it was decided to omit deprivation index from the model as this indicator did not load on to the latent variable for demographic factors significantly.

Table 2. Parameter estimates from final structural equation modelling.

Parameter	Coefficient (SE)	*t* value (*df*=240)	*P* value
Accident & Emergency on			
Demographic risk factors	0.102 (0.008)	12.50	<.001
Clinical risk factors	–0.003 (0.008)	–0.448	.65
Mental health comorbidities	0.028 (0.009)	3.18	.001
Depression severity	0.071 (0.009)	7.97	<.001
Poor diabetic control	–0.055 (0.008)	–6.72	<.001
Poor diabetic control on			
Demographic risk factors	–0.283 (0.007)	–37.50	<.001
Clinical risk factors	0.201 (0.007)	26.80	<.001
Mental health treatment	–0.006 (0.008)	–0.856	.39
Diabetes care	–0.072 (0.007)	–9.68	<.001
Depression severity	0.034 (0.008)	4.27	<.001
Depression severity on			
Mental health comorbidities	0.477 (0.007)	69.4	<.001
Diabetes care	0.018 (0.007)	2.68	.007
Diabetes care on mental health treatment	0.046 (0.008)	5.89	<.001
Mental health treatment on mental health comorbidities	0.294 (0.007)	39.3	<.001
Clinical risk factors on demographic risk factors	0.156 (0.008)	20.2	<.001

In the final model, depression severity was associated with worse diabetic control (β=.034, *P*<.001) and higher A&E use (β=.071, *P*<.001). However, poor diabetic control was associated with lower A&E use (β=–.055, *P*<.001). Mental health treatment was not significantly associated with poor diabetic control (*P*=.39). Receipt of diabetes care was negatively associated with poor diabetic control (β=–.072, *P*<.001). Receipt of diabetes care was also associated with depression severity (β=.018, *P*=.007) and receipt of mental health treatment (β=.046, *P*<.001).

Demographic risk factors associated with A&E use (β=.102, *P*<.001) included being older, female, and of White ethnicity. These same factors were negatively associated with poor diabetic control (β=–.283, *P*<.001), meaning that being older, female, and of White ethnicity is associated with better diabetic control. Smoking and having a higher BMI were associated with worse diabetic control (β=.201, *P*<.001).

Discussion

Principal Findings

In this study, we sought to test whether SEM could be applied to a large routine clinical data set from East London to model known associations between depression, diabetic care, diabetic control, A&E utilization, and mental health care provision in patients with type 2 diabetes.

The model showed that depression severity was associated with worse diabetic control among patients with type 2 diabetes. This is in keeping with previous epidemiological evidence that has shown that depression is associated with increased diabetic complications and poor diabetic control [11]. Depression was associated with increased A&E utilization among patients with type 2 diabetes, which is in line with previous research [12-14]. What this suggests is that the application of SEM to this routine clinical data set enabled us to model associations in a way that made clinical sense and was in agreement with existing research. However, poor diabetic control was associated with lower A&E utilization, which is not consistent with existing evidence [15]. It is possible that this association is valid and reasons for type 2 diabetic patients with depression presenting at A&E are related to factors not associated with diabetic control. In fact, the presence of hypertension and obesity in patients with type 2 diabetes has been associated with increased A&E visits [25]. It is also possible that poor diabetic control results in greater utilization of primary care services, as well as inpatient and outpatient services. Future attempts to model associations between depression and A&E usage in type 2 diabetic patients should include relevant physical comorbidities (eg, coronary heart disease, hypertension, obesity), examine the reasons for A&E attendance, and include use of other health services in the model.

We predicted that receiving mental health treatment would be associated with improved diabetic control, thereby impacting upon health service use. However, receipt of mental health treatment was not associated with poor diabetic control in this study. This is not in agreement with previous research, which has shown that improvement of depressive symptoms through the use of psychotherapy and pharmacotherapy is associated with improved glycemic control [16]. The opposite association reported in the current study is likely related to issues with data quality, which will be outlined later. We found that better diabetic control was associated with receipt of diabetes care

within primary care settings. Moreover, receiving diabetes care was also associated with depression and receipt of mental health treatment. This indicates that patients with type 2 diabetes and comorbid depression might be receiving better overall care, suggesting that comprehensive integrated care packages are being delivered in East London.

Taken together, these results provide partial support for the use of SEM in large routine clinical data sets. The data allowed us to model some associations within a sample of patients with type 2 diabetes that made clinical sense. Counterintuitive results are likely related to issues with the data set, rather than with the use of SEM. This implies that this methodology could be adapted and applied to data sets of this nature to understand pathways to health service use in other comorbid patient groups.

Limitations

Large-scale routinely collected clinical data can have some significant limitations, particularly surrounding data completeness and accuracy [1]. In this study, the data needed to undergo considerable cleaning before analysis could take place. The removal of duplicate cases, cases where variables were way out of clinical range, and cases where data were missing and could not be imputed led to a decrease in sample size of almost 19%. These issues are mainly attributable to data entry errors and are largely unavoidable, but errors in coding and recording need improvement to support wider use of routine data in health research.

There were also suspect flaws in the data set, which may account for some of the unexpected findings we report. IAPT referrals seem suspiciously low (1.4%) in the patients with recorded diagnoses of depression. In Tower Hamlets, about 29% of patients with anxiety or depression access IAPT services [28]. This discrepancy probably reflects an issue with the flow of data. The problem with the IAPT data likely affected the mental health treatment latent variable in the SEM and might help to explain why mental health treatment was not associated with poor diabetic control.

We were unable to generate any robust goodness-of-fit statistics for the specified SEM model into the data (eg, normed fit index, standardized root mean squared residual) as these are not implemented in the *plspm* package, and data protection restrictions in place on the analysis environment meant that we could not install external software packages (eg, SmartPLS) designed to generate such statistics. The goodness-of-fit statistic generated by this package is not standardized and does not represent a "fit" measure [29]. Therefore, we could not be sure that our model was a good or a poor fit to the data; however, this was not our original intention.

A final significant limitation of this study is the cross-sectional nature of the data, meaning that causality could not be attributed in the SEM we report. Although the data we analyzed were collected over one financial year, we had no temporal information about the data, meaning that prospective analyses were not possible. This was problematic for the direction of effect we report in this study. For example, we could not tell when the latest HbA_{1c} or blood pressure measurement was taken, and we did not know the date on which A&E attendances took place. This means that the measure of diabetic control might have been taken after the A&E attendances took place within that financial year, making the attribution of causality difficult. This also might have explained the counterintuitive result seen in the SEM. Moreover, we could not tell how long a person had diabetes or depression for, which would have provided a good proxy for disease severity, and we also did not have information about how long a person had been receiving treatment for diabetes and/or depression. Despite these shortcomings, a lot of the results we report make clinical sense, supporting the application of SEM in routine clinical data. The quality of the data will determine the utility of the SEM.

Future Directions and Recommendations

To confirm the validity of this study, it would be prudent to apply SEM to another London-based routine clinical data set in this same patient group. This would help to overcome some of the limitations outlined above and provide further evidence for utility of SEM in routine clinical data sets. Future analyses should seek to use temporal data so that prospective analysis is possible. This would allow the direction of association within the SEM to be confirmed and causality attributed to the model, overcoming some of the significant limitations outlined above. Temporal information surrounding receipt of treatment and duration of disease would also allow for the construction and inclusion of latent variables that are more clinically valid. Improvement of data flows (eg, information about use of IAPT services) and more years of data would address issues around lack of temporality and inaccurate findings.

Conclusions

In conclusion, our results indicate that, despite the significant limitations of the data set, we were still able to successfully model associations between depression and A&E use in a sample of diabetic patients in a way that made clinical sense using SEM. This demonstrates the utility of this statistical technique in routine clinical data, and this model can be refined and retested as more data become available and prospective analyses can be carried out. Results also suggest that SEM could be adapted and applied to routine clinical data for use in other patient groups to model health care pathways.

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Conflicts of Interest

None declared.

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Abbreviations

A&E: Accident & Emergency
AUDIT: Alcohol Use Disorders Identification Test
AUDIT C: Alcohol Use Disorders Identification Test for consumption
CCG: Clinical Commissioning Group
DBP: diastolic blood pressure
HbA_{1c}: glycated hemoglobin
IAPT: Improving Access to Psychological Therapies
PLS-SEM: partial least squares structural equation modelling
NHS: National Health Service
SBP: systolic blood pressure
SEM: structural equation modelling
SMI: severe mental illness

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Original Paper

Effects of Pharmacogenomic Testing in Clinical Pain Management: Retrospective Study

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Abstract

Background: The availability of pharmacogenomic (PGx) methods to determine the right drug and dosage for individualized patient treatment has increased over the past decade. Adoption of the resulting PGx reports in a clinical setting and monitoring of clinical outcomes is a challenging and long-term commitment.

Objective: This study summarizes an extended PGx deep sequencing panel intended for medication dosing and prescription guidance newly adopted in a pain management clinic. The primary outcome of this retrospective study reports the number of cases and types of drugs covered, for which PGx data appears to have assisted in optimal drug prescription and dosing.

Methods: A PGx panel is described, encompassing 23 genes and 141 single-nucleotide polymorphisms or indels, combined with PGx dosing guidance and drug-gene interaction (DGI) and drug-drug interaction (DDI) reporting to prevent adverse drug reactions (ADRs). During a 2-year period, patients (N=171) were monitored in a pain management clinic. Urine toxicology, PGx reports, and progress notes were studied retrospectively for changes in prescription regimens before and after the PGx report was made available to the provider. An additional algorithm provided DGIs and DDIs to prevent ADRs.

Results: Among patient PGx reports with medication lists provided (n=146), 57.5% (n=84) showed one or more moderate and 5.5% (n=8) at least one serious PGx interaction. A total of 96 (65.8%) patients showed at least one moderate and 15.1% (n=22) one or more serious DGIs or DDIs. A significant number of active changes in prescriptions based on the 102 PGx/DGI/DDI report results provided was observed for 85 (83.3%) patients for which a specific drug was either discontinued or switched within the defined drug classes of the report, or a new drug was added.

Conclusions: Preventative action was observed for all serious interactions, and only moderate interactions were tolerated for the lack of other alternatives. This study demonstrates the application of an extended PGx panel combined with a customized informational report to prevent ADRs and improve patient care.

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KEYWORDS

pharmacogenomics; pain management; drug-drug interaction; DDI; pharmacy; prescriptions; genetics; genomics; drug-gene interaction; pain

Introduction

Over the last decades, there has been considerable growth in the use of pharmacogenomic (PGx) testing due to increased awareness of patients developing moderate to serious adverse drug reactions (ADRs) attributed to individual genetic variation. The US Food and Drug Administration (FDA) "Table of Pharmacogenomic Biomarkers in Drug Labeling" contains 457 entries (status March 2021) relating to dosage and administration, warnings, precautions, drug interactions, adverse reactions, or clinical pharmacology [1]. For example, codeine, a frequently prescribed opiate present in Tylenol #3 (acetaminophen with codeine), contains the boxed warning:

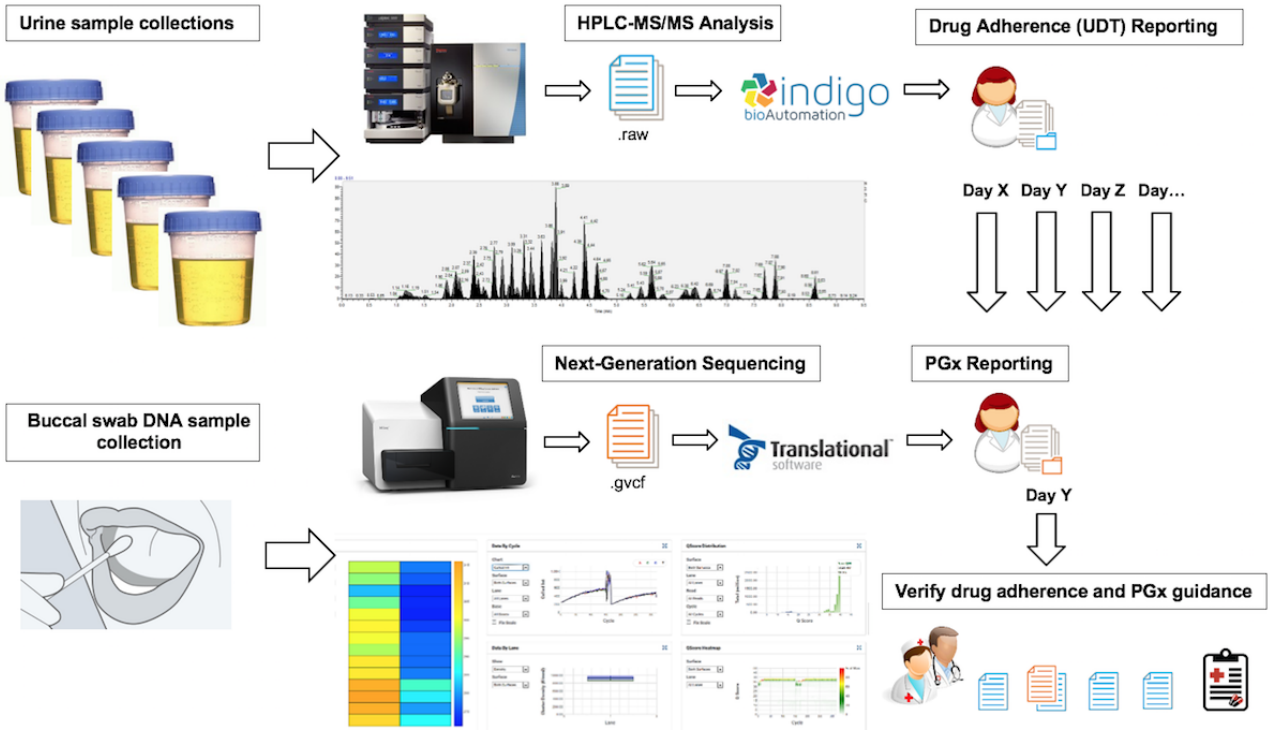
> *Death Related to Ultra-Rapid Metabolism of Codeine to Morphine. Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. (...) For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. (...) Nursing Mothers: At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Codeine Sulfate Tablets.*

A survey involving clinicians from academic medical centers showed 99% agreed that PGx variants would influence a patients' response to drug therapy and should be acted upon when a clinically significant drug-genome interaction was present (92%) [2]. Previous studies have shown that over 80% of patients can carry at least one functional gene variant influencing one of the 100 most prescribed medications in the United States, and the rate of rehospitalization can be significantly reduced by implementation of PGx test recommendations [3-7].

Recommendations for actionable prescribing decisions are routinely based on clearly defined, peer-reviewed guidelines with different evidence levels (levels 1-4) issued by international pharmacogenetic consortia and professional societies such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and maintained in high-quality public and expert-curated databases, including PharmGKB [8-11]. Currently, most laboratories conducting PGx testing use targeted genotyping technologies to screen for specific variants to determine ADRs. Examples of these technologies include single or multiplexed polymerase chain reaction (PCR) assays combined with Taqman hydrolysis probe chemistry, microarrays (ThermoFisher Scientific), mass spectrometry (Agena Biosciences), bead-based molecular assays (Luminex), or next-generation sequencing (NGS) assays (Illumina) [12-14]. In 2018, Fabbri et al [15] described 38 commercially available PGx test panels offering personalized medication prescription guidance in clinical settings. The only genes included in all of these panels were *CYP2D6* and *CYP2C19*. Of the 38 panels, 31 (82%) included 8 genes or less [15]. PGx testing as described in this study encompasses deep sequencing (>1000X) of 141 single-nucleotide polymorphisms (SNPs) or indels across 23 genes by NGS.

The aim of this study is to evaluate the overall use and to describe how PGx report recommendations, including genetic-based dosing guidance (PGx), drug-gene interaction (DGI)–based guidance, and drug-drug interaction (DDI)–based guidance, were applied to optimize drug dosing in a clinical setting that had not previously relied on pharmacogenetic test reports. Changes in prescription, patient compliance, and drug use were monitored based on updated medication lists and data in associated quantitative urine drug toxicology (UDT) reports, with limited access to patient progress reports. UDT reports were evaluated in a pain management setting before and after application of PGx panels to prevent ADR events (Figure 1).

Figure 1. Overview of this study to determine the implementation of PGx report recommendations as compared to urine drug adherence reports in a pain management setting after application of a deep sequencing PGx panel. PGx: pharmacogenetic; UDT: urine drug toxicology.



Methods

Overview

This study was conducted in accordance with the Declaration of Helsinki with written informed consent from each patient. Patient data collection and summaries at Alcala Testing and Analysis Services (ATAS) were approved by the Alcala Pharmaceutical Inc Institutional Review Board (IORG0010127, IRB00012026, #R003). All test samples derived from human patients were deidentified of their health information as defined by Health Insurance Portability and Accountability Act guidelines. Patient data for comparison of urine drug adherence testing before and after PGx reporting, with limited access to patient progress notes, were obtained retrospectively from patients (n=171) in a pain management clinic representing a patient population from 2016 to 2018 within the western United States. While no patient demographics data were available, the Results section shows the genotype frequencies of the "San Diego cohort" (SDC) of this study compared to 5 super populations from the 1000 Genomes Database: African (AFR), South Asian (SAS), Ad Mixed American (AMR), East Asian (EAS), and European (EUR). Pearson correlation analysis (Multimedia Appendix 1) showed the "SDC" positively correlates to all allele frequencies in the 1000 Genomes Database (ALL=0.76; P=1.019 × 10^{-11}). SDC (n=171) closely correlates to the AMR (0.77), EUR (0.78), and SAS (0.78) super populations but is less representative of the EAS (0.54) and AFR (0.55) population frequencies. Other available data included deidentified pre- and post-PGx medication lists, PGx, and urine drug adherence data (see sections PGx Dosing/DGI/DDI Data Interpretation and Reporting, and Drug Adherence Testing).

Genes

A total of 23 genes were included in the described PGx panel at the time of design in April 2016 (*ADRA2A*, *CES1*, *COMT*, *CYP1A2*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *DRD1*, *DRD2*, *F2*, *F5*, *GNB3*, *HTR1A*, *HTR2A*, *HTR2C*, *MTHFR*, *OPRM1*, *SLC6A2*, *SCL6A4*, *SLCO1B1*, and *VKORC1*) to include the most up-to-date guidance covering 198 drugs with a major emphasis on pain, psychiatry, and addiction medicine as described in the section PGx Dosing/DGI/DDI Data Interpretation and Reporting.

Selection of Target Regions

The online probe design was performed by entering target regions into Design Studio software (Illumina) [16]. Unique reference SNP cluster ID (rsID) numbers were assigned per target coordinate and region. A total of 79 target regions (defined across start and stop coordinates, see Multimedia Appendix 2) covering 141 SNPs or indels were covered by 82 amplicons with an average amplicon size of 250 base pairs (bp) across 23 genes. Multiple target regions covering multiple rsIDs were targeted across each gene (eg, 27 rsIDs within *CYP2D6*; see Multimedia Appendix 2). Possible gaps in target coverages, repeats, and GC-rich regions that could interfere with optimal amplification of all desired regions were identified in 3 iterations (design 32844, 32865, and 98659) and optimized for TruSeq Custom Amplicon Low Input (TSCA-LI) assay technology (*Homo sapiens* [UCSC hg19]; variant source: 1000 Genomes). Predicted coverage of the full region of interest was 100% with all amplicons showing scores at 100%. Oligonucleotide probes were synthesized and pooled at Illumina (San Diego, CA) into a Custom Amplicon Tube.

DNA Isolation and Genotyping

Genomic DNA (gDNA) was isolated from up to 4 buccal swab specimens provided by the pain management clinic using PureLink Genomic DNA Isolation (ThermoFisher Scientific, Carlsbad, CA) and Agencourt DNAdvance Genomic DNA Isolation kits (Beckman Coulter, Indianapolis, IN). Quality and concentration of gDNA were determined using Qubit 3.0 Fluorometric Quantitation (ThermoFisher Scientific). NGS was carried out on a MiSeq system (Illumina, San Diego, CA) with 2 × 150 bp paired-end reads using the TruSeq Custom Amplicon v1.5 Targeted Resequencing workflow (Illumina) for up to 24 samples per plate. HYB and EXT_LIG programs were as described in the TSCA-LI protocol. Amplification was carried out at 32 cycles (<96 amplicon plexity). After cleanup and normalization by AMPure XP magnetic beads, pooled libraries were denatured at 98 °C for 2 minutes and cooled on ice for 5 minutes. Denatured PhiX control (12.5 pmol/L) was spiked into the library pool at 1% and loaded onto an Illumina MiSeq instrument at 7 pmol/L for automated cluster generation and sequencing according to the manufacturer's instructions. All targets and 50 bp flanking regions were sequenced, the capture region totaled approximately 20 kb.

Data Analysis

The TruSeq Amplicon workflow version 1.0.0.61 on the MiSeq instrument was used to perform primary analysis by Real Time Analysis (RTA; version 1.18.54) during the sequencing run. Base calls of indexed raw sequence reads and demultiplexing were performed using bcl2fastq. MiSeq Reporter version 2.6.2.3 performed secondary analysis on base calls and quality scores generated on-instrument by the RTA software and evaluated short regions of amplified DNA for variants. Clusters from each sample were aligned against amplicon sequences from the provided manifest file (Design 98659). The first read was evaluated against the probe sequence for each amplicon in the manifest, which is the reverse complement of the downstream locus-specific oligo (DLSO). If the start of the read matches (with at most 1 mismatch) a probe sequence, the read was aligned against the target or targets for that probe sequence. If no such match was found for the read, MiSeq Reporter checked for any probe sequence that was matched with fewer than six mismatches and attempted to align against these amplicons. For paired-end data, the second read was handled similarly, except that read 2 was compared to upstream locus-specific oligo (ULSO) sequences. After the probe sequence (ULSO or DLSO) was matched, adapter sequences were removed, and trimmed reads were mapped to the human reference genome (GRCh37 hg19) using banded Smith-Waterman alignment generated in the .bam file format. The maximum indel length is normally 10 bp but was overridden using the sample sheet setting CustomAmpliconAlignerMaxIndelSize set to 250 (higher values improve indel sensitivity but impact workflow speed). Other sample sheet settings included IndelRepeatFilterCutoff set to 1, MinimumCoverageDepth=1, VariantMinimumGQCutoff=1, VariantFilterQualityCutoff=1, VariantCaller=GATK, VariantAnnotation=MARS, and outputgenomevcf=TRUE. Genome Analysis Toolkit (GATK, Broad Institute) identifies variants and writes .vcf and .gvcf output files to the Alignment folder. SNPs and short indels were identified using GATK for each sample, and false discovery rates for each variant were evaluated using coverage (read depth), the Qscore (quality), and the GQX value (a conservative measure of genotype quality derived from the minimum of the GQ and QUAL values listed in the .vcf file). The Qscore predicts probability of an erroneous base call (Q20 represents the probability to call an erroneous base out of 100, reflecting an accuracy of the sequenced base at 99%, Q30=99.9%, Q40=99.99%, etc). Coverage for a defined region is the total number of reads passing quality filters at this position representing a given nucleotide. Only variants showing Qscores and GQX values >30 and coverage >100X were considered in this study. The average coverage per target exceeded 2000X. Two positive gDNA controls (PC1 and Coriell cell line NA19920 gDNA) and one negative (RS1 buffer) control were sequenced per plate (up to 48 samples). All 167 mutation sites covering 141 SNPs, 2 sex probes, and 1 indel (43-44 bp insertion in the *SLC6A4* promoter region—short [S] or long [L] form—see Multimedia Appendix 2) within the 23 genes identified by MiSeq Reporter were reviewed for each sample in VariantStudio software (Illumina) assisted by the PASS filter function. Gender (SRY) probes were matched to the provided gender in the sample requisition.

Copy Number Variation and Indel Assays

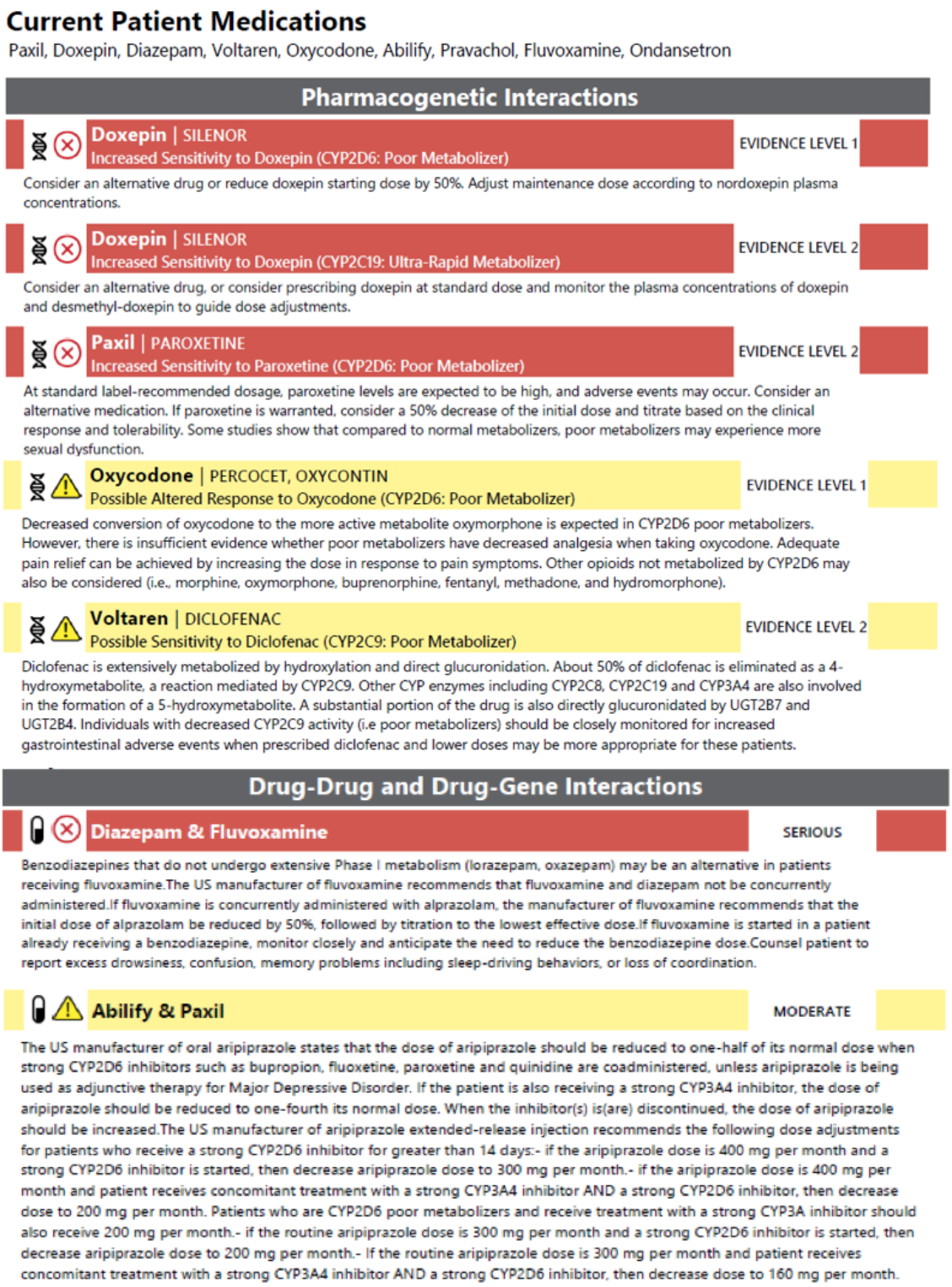
Copy number variations (CNVs) of *CYP2D6* were identified with two different PCRs for detection of *CYP2D6**XN duplication or *CYP2D6**5 deletion events by long-range PCR as previously described [17,18]. A total of 10 nanograms of input gDNA was used with Takara LA *Taq* polymerase (Takara Bio USA, San Diego, CA) carried out according to the manufacturer's instructions. The long-range PCR conditions for duplication testing were as follows: initiation at 94 °C for 2 minutes, 27 cycles of 98 °C for 20 seconds, 61.4 °C for 20 seconds and 68 °C for 10 minutes, and termination at 72 °C for 10 minutes. PCR conditions for deletion tests were the same except annealing was at 65 °C for 25 seconds and extension at 68 °C for 5 minutes with 25 cycles and termination at 72 °C for 6 minutes. Long-range PCR products were analyzed by 1% agarose gel electrophoresis. The presence of a 10 kB fragment (by primers CY_DUP_5 and CY_DUP_3) indicated duplicated or multicopy *CYP2D6* alleles and a 3.5 kb product (by primers CY_DEL_5 and CY_DEL_3) was indicative of the deletion (*CYP2D6**5 allele). Amplification of the S and L variant of the 5-HTT gene-linked polymorphic region (5-HTTLPR) of *SLC6A4* was accomplished with oligonucleotide 5-HTTF, corresponding to nucleotide positions −1346 to −1324 and 5-HTTR (positions from −910 to −888) as previously described [19,20], except amplification was performed in 25 µl containing 10 ng of gDNA, 1.5 mM $MgCl_2$, 200 µM dNTPs, 1X Colorless GoTaq Flexi buffer, 0.4 µM of each primer, and 1 U of Hot Start GoTaq DNA polymerase (Promega Biosciences, San Luis Obispo, CA). Initial denaturation was performed at 98 °C for 3 minutes, followed by 35 cycles at 94 °C for 1 minute, 64 °C for 30 seconds, and 72 °C for 2 minutes. PCR products were resolved by 2% agarose gel electrophoresis. A total of 458 and 415 bp fragments indicated the L/S genotype for *SLC6A4*; single 415 bp bands or 458 bp bands (no double band profile) indicated the S/S and L/L genotypes, respectively. All primer sequences are listed in Multimedia Appendix 3.

PGx Dosing/DGI/DDI Data Interpretation and Reporting

All samples and positive controls were imported as .gvcf files into a customized portal through Translational Software Inc (TSI, Bellevue, WA) [21]. Specifically, to accommodate reporting based on 23 genes, 141 SNPs or indels, and associated haplotypes newly combined in this panel (Multimedia Appendix 2), TSI bioinformaticians collaborated with ATAS scientists to include the most up-to-date guidance across 2 evidence levels for PGx dosing and DDIs (Figure 2). Recommendations from six different international pharmacogenetic consortia, professional societies, or regulatory bodies (CPIC, Dutch Pharmacogenetics Working Group, FDA, European Medicines Agency, Canadian Pharmacogenomics Network for Drug Safety, and American College of Medical Genetics and Genomics) were incorporated in the reporting algorithm. Integrated recommendations covered 13 drug categories and 198 drugs with a major emphasis on pain, psychiatry, and addiction medicine drugs (Multimedia Appendix 4).

After portal entry of *SLC6A4* indel S/S, La/La, La/Lg, or Lg/Lg variants and *CYP2D6* deletion or duplication, data transfer of all variants and phenotype calls were reviewed for samples and quality controls prior to medical report generation for each patient. Translational Software provides interpretations of specific variants for "PGx DOSING" guidance (ie, based solely on genetic metabolizer status categories: "Normal Metabolizer," "Poor Metabolizer," "Intermediate Metabolizer," or "Ultra-rapid Metabolizer") and DGI or DDI warnings provided by a third-party agreement with First Databank (FDB). Control gDNA from NA18861, NA18868, NA19920, and NA19226 purchased from Coriell Cell Biorepositories and internal positive controls were used for validation of the TSCA-LI workflow with design 98659, CNV/indel assay validations, and for the evaluation of the data interpretation software by TSI.

Figure 2. Example of pharmacogenetic (PGx) report results showing PGx dosing guidance (ie, based solely on genetic metabolizer status categories: "Normal Metabolizer," "Poor Metabolizer," "Intermediate Metabolizer," and "Ultra-rapid Metabolizer"), as well as drug-gene interactions (DGIs) and drug-drug interactions (DDIs). Evidence level 1 descriptions were actionable with established evidence-based clinical guidelines issued by international PGx consortia, professional societies, or regulatory bodies (Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group, Food and Drug Administration, European Medicines Agency, Canadian Pharmacogenomics Network for Drug Safety, American College of Medical Genetics and Genomics). Evidence level 2 descriptions were informative, requiring further investigations. PGx dosing guidance, DGIs, and DDIs were further marked as either yellow (moderate) or red (serious) interactions (also see Multimedia Appendix 4).



Drug Adherence Testing

All PGx reports were compared to urine toxicology reports generated before or after clinicians received the PGX report. Urine toxicology reports reviewed by clinical laboratory scientists with ASCENT review software (IndigoBio Automation) [22] were made available by routine HPLC-MS/MS

presumptive and confirmatory urine drug testing at ATAS from 2016 to 2018 [23].

Results

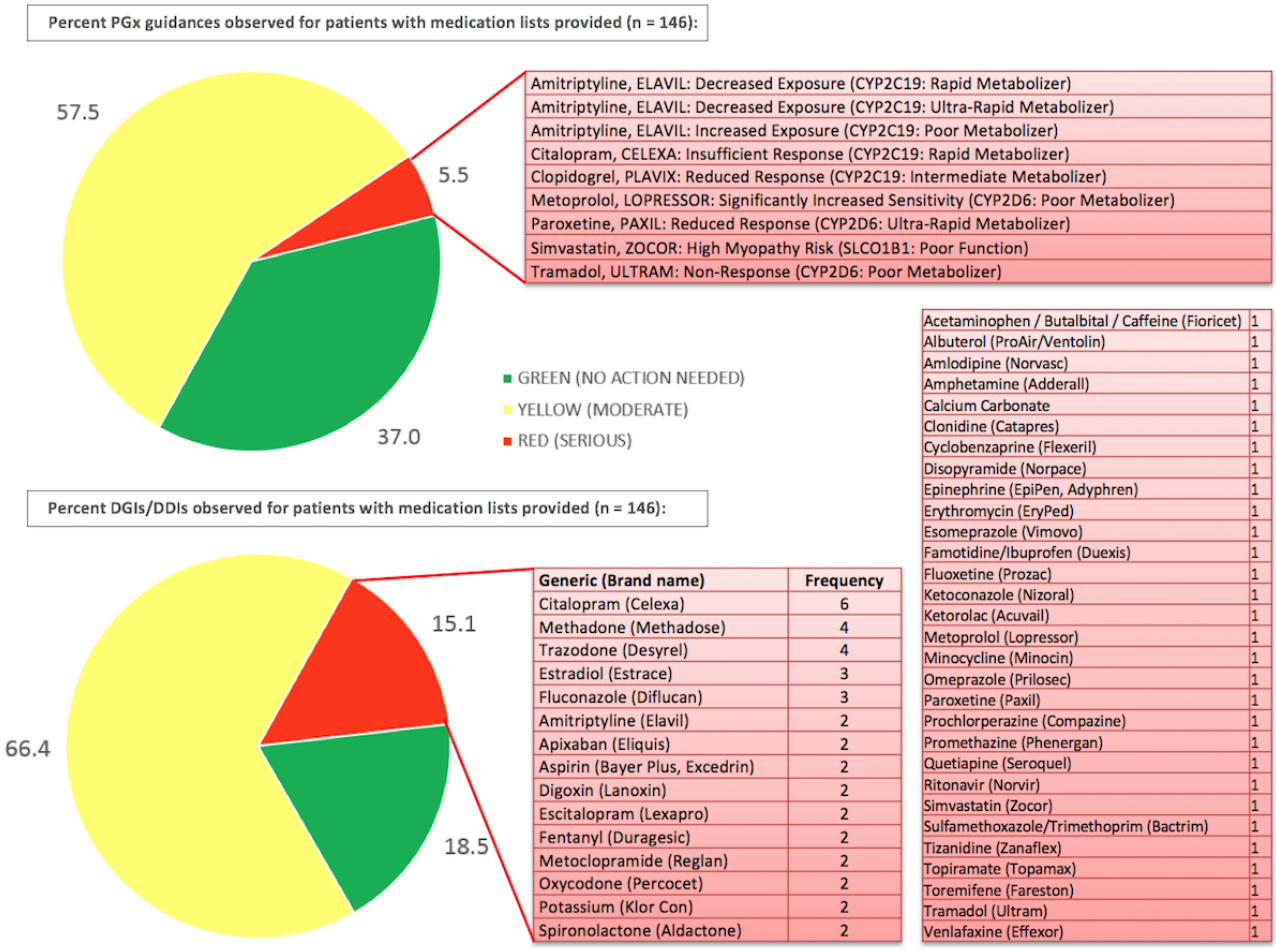
Analytical sensitivity (call rate) was determined at >97.1% by positive agreement of all 141 variants including sex determination through 2 SRY probes and CNVs/indels. Genomic DNA ranging from 0.64 to 26 ng/µL (5-195 ng input gDNA) was sequenced across three validation plate runs with 68 positive control samples showing unambiguous genotypes. Buccal swabs were stored for up to 14 days at 4 °C prior to gDNA preparation; gDNA storage stability at 4 °C was confirmed for up to 6 days and up to 6.5 months for storage at –20 °C with up to 10 freeze/thaw cycles to yield high quality (>99.3%) genotyping results Multimedia Appendix 5.

All alleles covered per gene target or targets and resulting phenotypes were routinely described in the test details section in each PGx report (Table 1) following the results for PGx dosing and DGI or DDI (Figure 2). Of the 171 patients studied, drug adherence data was not available for 69 patients for which PGx report data was summarized. PGx report implementation could only be studied on the remaining 102 patients. A total of 26 PGx reports showed no medication list provided by the clinic, 8 of which medication lists were made available and added onto the PGx report retroactively. Medication lists provided showed that patients were prescribed an average of 5 different medications (ranging from 0 to 25 medications), resulting on average in 1 moderate pharmacogenetic guidance and 3 moderate DDI observations per patient. Among patient PGx reports with medication lists provided (n=146), 57.5% (n=84) showed one or more moderate and 5.5% (n=8) at least one serious PGx (ie, purely gene-based) interaction. A total of 96 (66%) patients showed at least one moderate and 15% (n=22) one or more serious DGIs or DDIs (Figure 3 and Multimedia Appendix 6).

Table 1. Example of pharmacogenetic report test detail summaries and alleles covered.

Gene	Genotype	Phenotype	Alleles tested
CYP2C9	*1/*1	Normal metabolizer	*2, *3, *4, *5, *6, *7, *8, *11, *14, *27
CYP2C19	*2/*17	Intermediate metabolizer	*2, *25, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *12, *14, *15, *17
CYP2D6	*1/*2	Normal metabolizer	*2, *3, *31, *33, *4, *4M, *46, *49, *53, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *29, *35, *38, *41, *44, *5 (gene deletion), XN (gene duplication)
CYP3A5	*3/*3	Poor metabolizer	*1D, *2, *3, *3B, *3C, *4, *6, *7, *8, *9
CYP3A4	*1/*1	Normal metabolizer	*2, *4, *5, *8, *11, *12, *13, *16A, *16B, *17, *18A, *18B, *20, *22
VKORC1	-1639G>A A/A	High warfarin sensitivity	-1639G>A, 1542G>C, 5808T>G, 1173C>T, rs11540137, rs13337470, 698C>T, 2255C>T, 3730G>A
CYP1A2	*1F/*1F	Normal metabolizer—higher inducibility	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W, *7
SLCO1B1	521T>C T/C	Decreased function	388A>G, 521T>C, 467A>G, -11187G>A, 1865+248G>A
COMT	Val158Met A/G	Intermediate *COMT* activity	Val158Met
OPRM1	A118G A/A	Normal *OPRM1* function	A118G
HTR2C	-759C>T C/T	Heterozygous for the C allele (rs3813929)	-759C>T, 2565G>C
SLC6A4	S/La	Decreased serotonin transporter expression	La, S, Lg
ADRA2A	C-1291G C/C	Homozygous for C allele	C-1291G
SLC6A4	463T>G A/A	Homozygous for A allele	La, S, Lg
HTR2A	rs7997012 G/G	Homozygous for G allele (rs7997012)	102C>T, -1483G>A, rs7997012
HTR2C	2565G>C C/C	Homozygous for C allele (rs1414334)	-759C>T, 2565G>C
HTR2A	-1438G>A, T/T	Homozygous for T allele (rs6311)	102C>T, -1483G>A, rs7997012
DRD2	-241A>G, T/C	Heterozygous for rs1799978 C allele	-241A>G, rs2283265, 939T>C, 957C>T
DRD2	rs2283265 C/C	Homozygous for rs2283265 C allele	-241A>G, rs2283265, 939T>C, 957C>T
MTHFR	1298A>C AA 677C>T CC	No increased risk of hyperhomocysteinemia	677C>T, 1298A>C, 1305C>T
MTHFR	677C>T CC	Normal *MTHFR* activity	677C>T, 1298A>C, 1305C>T
Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No increased risk of thrombosis	20210G>A, 1691G>A

Figure 3. Percent PGx dosing guidance, DGIs, and DDIs observed for patients with medication lists provided (n=146) sorted by the expected normal response to a drug based on PGx metabolizer status or no interaction observed for DGIs/DDIs. Green: no action required; yellow (moderate) or red (serious) interactions prompt actionable PGx or DGI/DDI recommendations. Specific drug names and the associated genotype for PGx dosing or frequency for DGIs/DDIs are shown for serious cases. DDI: drug-drug interaction; DGI: drug-gene interaction; PGX: pharmacogenetic.



Phenotypes and associated genotypes are summarized in Table 2 with an overview of population frequencies compared to the SDC. As shown in Figure 3, 5.5% (n=8) of 146 patients showed serious ADRs based on changes in either *CYP2C19* (poor, intermediate to rapid metabolizers) or *CYP2D6* (poor or ultra-rapid metabolizers) and one *SLCO1B1* reduced function genotype. *CYP2C19* genotype frequencies for 3 metabolizer types causing serious ADRs were spread across all 5 super populations ranging from 0.9% to 47.4% frequency (Table 2, *CYP2C19* section). *CYP2D6* genotype frequencies for intermediate to ultra-rapid metabolizers ranged from 1.2% to 57.1% frequency and *SLCO1B1* poor function genotypes from 1.8% to 37% (Table 2, *CYP2D6* and *SLCO1B1* section). While SAS population frequencies for *CYP2C19* ultra-rapid metabolizers and *CYP2D6* poor metabolizers are determined as nonexistent in the 1000 Genome Database data, more recent studies show frequencies of 0.24% [24] and 0.84% [25], indicating possible occurrence within the SAS super population.

Table 2. Observed phenotypes and associated genotypes with an overview of population frequencies compared to this study (N=171).

Gene	Phenotype/functional status	Defining variant	Genotype(s)	Genotype frequencies[a]						
				Super population frequency (1000 Genomes Project; %)						This study (%)
				All	AFR[b]	AMR[c]	EUR[d]	EAS[e]	SAS[f]	SDC[g]
Adrenoceptor alpha 2A										
ADRA2A	Homozygous for G allele	Ancestral: G	G/G	33.3	51.9	13.3	6.4	47.6	35.6	15.9
ADRA2A	Heterozygous for the G allele	rs1800544 (C-1291G)	G/C	42	39	45	39.6	44	44.4	30.7
ADRA2A	Homozygous for C allele	rs1800544 (C-1291G)	C/C	24.6	9.1	41.8	54.1	8.3	20	53.4
Catechol-O-methyltransferase										
COMT	High/normal COMT activity	Ancestral: G	G/G	41.3	52.6	36.9	26.4	52.4	32.9	21.6
COMT	Intermediate COMT activity	rs4680 (1947 G>A, Val158Met)	G/A	43.6	38.6	50.7	47.1	39.3	46	65.1
COMT	Low COMT activity	rs4680 (1947 G>A, Val158Met)	A/A	15.1	8.8	12.4	26.4	8.3	21.1	13.4
Cytochrome P450 family 1 subfamily A member 2										
CYP1A2	Normal metabolizer: possible inducibility	Ancestral: C or G	*1A/*1A (C/C or G/G), *1A/*1V, *1A/*1W	15.2	19.8	7.5	10.9	11.5	22.7	23.7
CYP1A2	Normal metabolizer: higher inducibility	rs762551 (-163)C>A	*1A/*1F (C/A), *1F/*1F (A/A)	84.8	80.2	92.5	89.1	88.5	77.3	74.2
CYP1A2	Poor metabolizer: lower inducibility	rs2069514 (-3860G > A)	*1A/*1C (G/A)	28.9	44.5	38.9	4	40.3	14.7	1.0
CYP1A2	Unknown phenotype	Multiple[h]	*1L/*1L, *1L/*1W	N/A[i]	N/A	N/A	N/A	N/A	N/A	1.0
Cytochrome P450 family 2 subfamily C member 19										
CYP2C19	Normal metabolizer	Ancestral: G or C	*1/*1 (G/G or C/C)	33.7	27.5	57.6	31.8	42.1	18.8	29.5
CYP2C19	Intermediate metabolizer	rs4244285 (19154G>A)	*1/*2 (G/A)	32.8	27.1	19.3	26.6	47.4	41.3	34.4
CYP2C19	Poor metabolizer	rs4244285 (19154G>A)	*2/*2 (A/A)	5.8	3.5	0.9	1.2	7.5	15.1	15.6
CYP2C19	Rapid metabolizer	rs12248560 (-806C>T)	*1/*17 (C/T)	24.7	36.8	20.5	36	3	22.3	20.5
CYP2C19	Ultra-rapid metabolizer	rs12248560 (-806C>T)	*17/*17 (T/T)	3	5.1	1.7	4.4	0	2.5	1.2
Cytochrome P450 family 2 subfamily C member 9										
CYP2C9	Normal metabolizer	Ancestral: G or A	*1/*1	90.5	99.5	92.5	85.7	93.5	78.7	77.0
CYP2C9	Intermediate metabolizer	rs1057910 (A/C)	*1/*3 (A/C)	9.3	0.5	7.5	14.1	6.3	20.7	19.7
CYP2C9	Poor metabolizer	rs1057910 (C/C)	*3/*3 (C/C)	0.2	0	0	0.2	0.2	0.6	3.3
Cytochrome P450 family 2 subfamily D member 6										
CYP2D6	Normal metabolizer	Ancestral: multiple	*1/*1, *1/*2, *1/*4, *1/*5	71.5	82.8	82.3	88.0	41.5	79.6	89.7
CYP2D6	Intermediate metabolizer	*10 - rs1065852 (100C>T)	*5/*10, *10/*15, *4/*17, *4/*29, *4/*41	23.8	11.3	14.8	5	57.1	16.5	4.1
CYP2D6	Poor metabolizer	*4 - rs3892097 (1846G>A)	*4/*4, *4/*5 (A/A)	2.1	1.2	2.9	4.6	0	2.5	3.7

Gene	Phenotype/functional status	Defining variant	Genotype(s)	Genotype frequencies[a]						
				Super population frequency (1000 Genomes Project; %)						This study (%)
				All	AFR[b]	AMR[c]	EUR[d]	EAS[e]	SAS[f]	SDC[g]
CYP2D6	Ultra-rapid metabolizer[j]	XN (Duplication, XN Exon 9)	*1/*2 XN, *1/*4 XN, *1/*35 XN	2.64	4.66	N/A	2.37	1.37	1.37	2.5
Cytochrome P450 family 3 subfamily A member 4										
CYP3A4	Normal metabolizer	Ancestral: G	*1/*1 (G/G)	97	99.8	94.8	90.3	100	98.8	67.6
CYP3A4	Intermediate metabolizer	rs35599367 (intron 6 C>T)	*1/*22 (G/A)	3	0.2	5.2	9.7	0	1.2	28.4
Cytochrome P450 family 3 subfamily A member 5										
CYP3A5	Normal metabolizer	Ancestral: T	*1/*1 (T/T)	22.7	67.6	5.8	0.4	7.9	12.1	5.3
CYP3A5	Intermediate metabolizer	rs776746 (6986A>G)	*1/*3 (T/C)	30.3	28.7	29.1	10.5	41.5	42.3	45.8
CYP3A5	Poor metabolizer	rs776746 (6986A>G)	*3/*3 (C/C)	47	3.6	65.1	89.1	50.6	45.6	54.2
Dopamine receptor D2										
DRD2	Homozygous for rs1799978 C allele	Ancestral: C	C/C	2.2	4.1	0.3	0.6	1	0.8	1.3
DRD2	Heterozygous for rs1799978 C allele	rs1799978 (-241A>G)	T/C	19.5	26.5	14.7	10.7	28	13.7	12.3
DRD2	Homozygous for rs1799978 T allele	rs1799978 (-241A>G)	T/T	78.4	69.4	85	88.7	68.3	85.5	86.4
DRD2	Homozygous for rs2283265 C allele	Ancestral: C	C/C	62	85	55.9	73.6	34.3	51.9	41.6
DRD2	Heterozygous for rs2283265 A allele	rs2283265 (724-353G>T)	C/A	30.6	13.8	35.2	23.3	48.4	39.1	32.4
DRD2	Homozygous for rs2283265 A allele	rs2283265 (724-353G>T)	A/A	7.4	1.2	8.9	3.2	17.3	9	26.1
5-hydroxytryptamine receptor 2A (Serotonin 2A receptor gene)										
HTR2A	Homozygous for G allele (rs7997012)	Ancestral: G	G/G	56.2	97.1	41.8	33.2	56.7	34.2	7.2
HTR2A	Heterozygous for the A allele (rs7997012)	rs7997012 (614-2211T>C)	A/G	33.1	2.9	46.1	47.7	34.9	47.6	30.8
HTR2A	Homozygous for the A allele (rs7997012)	rs7997012 (614-2211T>C)	A/A	10.7	0	12.1	19.1	8.3	18.2	62.0
HTR2A	Homozygous for the C allele (rs6311)	Ancestral: C	C/C	32.4	36	40.1	33	18.3	36	25.2
HTR2A	Heterozygous for the T Allele (rs6311)	rs6311 (-1438G>A)	C/T	46.5	46.1	47.6	46.5	45.8	47	63.8
HTR2A	Homozygous for the T allele (rs6311)	rs6311 (-1438G>A)	T/T	21.1	17.9	12.4	20.5	35.9	17	11.0
5-Hydroxytryptamine receptor 2C (serotonin 2C receptor gene)										
HTR2C	Homozygous for the C allele (rs1414334)	Ancestral: C	C/C	35	15.7	41.2	39	50.2	40.3	52.5
HTR2C	Heterozygous for the C allele (rs1414334)	rs1414334 (2565G>C or 114138144C>G)	G/C	51.9	49.4	53.4	51.3	49.2	54.4	41.9
HTR2C	Homozygous for the G allele (rs1414334)	rs1414334 (2565G>C or 114138144C>G)	G/G	13.1	34.9	5.4	9.7	0.6	5.3	5.5
HTR2C	Homozygous for the C allele (rs3813929)	Ancestral: C	C/C	88.1	98.2	82.1	85.5	85.5	78.1	85.5

Gene	Phenotype/functional status	Defining variant	Genotype(s)	Genotype frequencies[a]						
				Super population frequency (1000 Genomes Project; %)						This study (%)
				All	AFR[b]	AMR[c]	EUR[d]	EAS[e]	SAS[f]	SDC[g]
HTR2C	Heterozygous for the C allele (rs3813929)	rs3813929 (-759C>T)	T/C	10.7	1.8	17.9	13.5	13.5	17.6	12.8
HTR2C	Homozygous for the T allele (rs3813929)	rs3813929 (-759C>T)	T/T	1.2	0	0	1	1	4.3	1.7
Opioid receptor mu 1										
OPRM1	Normal OPRM1 function	Ancestral: A	A/A	62.5	98.2	64.6	70.2	36.7	31.3	53.0
OPRM1	Altered OPRM1 function	rs1799971 (A118G)	A/G	30.4	1.8	30.8	27.2	48	53.8	47.0
OPRM1	Altered OPRM1 function	rs1799971 (A118G)	G/G	7.1	0	4.6	2.6	15.3	14.9	0.0
Solute carrier family 6 member 4										
SLC6A4	Homozygous for C allele	Ancestral: C	C/C	28.7	3.8	30.5	17.9	68.4	31	16.3
SLC6A4	Heterozygous for the C allele	rs1042173 (463T>G C/A)	C/A	39.7	29.5	47.3	51.7	27.6	48.3	64.8
SLC6A4	Homozygous for A allele	rs1042173 (463T>G C/A)	A/A	31.6	66.7	22.2	30.4	4	20.7	18.9
SLC6A4	Normal serotonin transporter expression	5-HTTLPR (L/S) and rs25531 (A/G)	La/La (L'L' group[k])	N/A	27	22	25	8	8	24.7
SLC6A4	Decreased serotonin transporter expression	5-HTTLPR (L/S) and rs25531 (A/G)	La/Lg, La/S (L'S' group[k])	N/A	49	51	50	30	30	43.8
SLC6A4	Low serotonin transporter expression	5-HTTLPR (L/S) and rs25531 (A/G)	Lg/Lg, Lg/S, S/S (S'S' group[k])	N/A	24	27	25	62	62	31.5
Solute carrier organic anion transporter family member 1B1										
SLCO1B1	Normal function	Ancestral: T	T/T	43.5	72.9	27.4	15.1	57.1	30.3	81.6
SLCO1B1	Decreased function	rs4149057 (521T>C)	T/C	39.5	25.3	44.4	48.3	37.1	48.9	16.8
SLCO1B1	Poor function	rs4149057 (521T>C)	C/C	17	1.8	28.2	36.6	5.8	20.8	1.6
Vitamin K epoxide reductase complex subunit 1										
VKORC1	Low warfarin sensitivity	Ancestral: G	G/G	50.9	89.5	35.2	38.2	1.8	73.4	49.8
VKORC1	Intermediate warfarin sensitivity	rs9923231 (-1639G>A)	G/A	27.1	10	47.6	46.1	19.4	24.1	39.7
VKORC1	High warfarin sensitivity	rs9923231 (-1639G>A)	A/A	22	5	17.2	15.7	78.8	2.5	10.5

[a]The frequencies for this table were referenced from the 1000 Genomes Database Ensembl [26]. Further information is available at the Human CYP Allele Nomenclature Database [27]. Populations have been divided into 5 super populations (AFR, SAS, AMR, EAS, and EUR) and this study (SDC).

[b]AFR: African.

[c]AMR: Ad Mixed American.

[d]EUR: European.

[e]EAS: East Asian.

[f]SAS: South Asian.

[g]SDC: San Diego cohort.

[h]See Soyama et al [28].

[i]N/A: not applicable.

[j]Based on Beoris et al [29].

[k]Group definition as per Pascale et al [20]. Population frequencies for *SLC6A4* 5-*HTTLPR* (L/S), rs25331 (A/G) derived from Haberstick et al [30].

Medications affecting patients most severely based on their individual genotype in this cohort were amitriptyline for decreased exposure among 2 *CYP2C19* rapid metabolizers and increased exposure for 1 *CYP2C19* poor metabolizer, citalopram (insufficient response, *CYP2C19* rapid metabolizer), clopidogrel (reduced response, *CYP2C19* intermediate metabolizer),

metoprolol with significantly increased sensitivity for a *CYP2D6* poor metabolizer, paroxetine (reduced response in *CYP2D6* ultra-rapid metabolizer), simvastatin (poor function of *SLCO1B1* inducing high myopathy risk), and tramadol (*CYP2D6* poor metabolizer with risk for no response). The top 15 medications affecting patients based on a DGI or DDI were identified (Figure 3). The most frequently occurring moderate DDI involved opioids observed in combination with central nervous system depressants such as muscle relaxants, benzodiazepines, sleep drugs, or the nerve pain medications gabapentin and pregabalin (Multimedia Appendix 6).

Prescription regimens were determined for 102 patients based on drug adherence report data before and after the PGx report was made available. Remaining patients either showed no drug adherence data or limited drug adherence data before the PGx report but no further information afterward. An active change in prescriptions based on the PGx report was observed for 85 (83%) patients for which a specific drug was either discontinued or switched within the defined drug classes of the report, or a new drug added. A total of 17 (17%) patient reports showed no predictive evidence of ADRs even when prescribed up to 11 medications (on average 2.5 medications per patient). Appropriately, no action was taken by the provider in these cases to deviate from the original prescription regimen. All adjustments made to patient prescriptions were studied for potential contraindications or possible new ADRs based on the PGx report.

Of the 85 patients whose medication lists were adjusted, only 3 showed that recommendations in the PGx report were not being followed for unknown reasons. “Patient A” was shown to be administered 5 medications (Keflex, Pennsaid, Skelaxin, MS Contin, and Lidocaine CV). PGx reporting indicated a normal PGx response and one moderate DDI to MS Contin (morphine) and Skelaxin (metaxalone), and a moderate PGx interaction for Pennsaid (diclofenac). Cessation of Skelaxin and Pennsaid removed all moderate ADRs; however, the addition of Percocet (oxycodone and acetaminophen) was not recommended:

> *Oxycodone - CYP2D6 Poor Metabolizer. Test results indicate a possible increased risk of therapeutic failure. Monitor for decreased response or may select alternative medication.*

The decreased response was alleviated with morphine prescriptions, for which there were no contraindications. Progress notes showed patient A:

> *has tried to use topical patches but experienced a localized reaction to the adhesive on the patch. Oral pain medication of MS Contin and Percocet is helpful. Patient A notes that some days Patient A does not require the max dose of the Percocet.*

Coreg (carvedilol) was added to the prescription regimen causing a moderate PGx warning:

> *CYP2D6 Poor Metabolizer: Test results indicate an increased risk of dizziness during up-titration. Consider standard prescribing and monitoring practices with careful dose titration.*

The addition of Silenor (doxepin) was also contraindicated by the PGx report:

> *CYP2D6 Poor Metabolizer: Test results indicate an increased risk of adverse effects. Consider an alternative medication or a 50% dose reduction with therapeutic drug monitoring.*

In this case the prescribed doxepin dosage was minimal (10 mg/day) according to progress notes. For the treatment of major depression or anxiety, adult oral dosages are initially 75 mg per day. The addition of Wellbutrin (bupropion), Soma (carisoprodol), Topamax (topiramate), and Prilosec (omeprazole) showed no contraindication except a moderate DDI between carisoprodol and morphine. The dose reduction for doxepin and the remaining moderate interaction for carvedilol were acceptable, as carvedilol was discontinued and the appropriate monitoring practices were carried out for patient A.

Similarly, for “Patient B,” 7 medications were listed, which showed a switch from codeine to morphine although no warnings against codeine were indicated (patient *CYP2D6* normal metabolizer status). Instead, a switch to morphine warned:

> *The patient does not carry the COMT Val158Met variant. The patient may require higher doses of morphine for adequate pain control*

Additionally, quetiapine and citalopram could cause a serious DDI (“concurrent use with agents known to prolong the QT interval should be avoided”), and the combinations of opioids with gabapentin prompted to “monitor patients for gabapentinoid-related side effects.” Further investigation into progress notes for patient B showed a suspected allergy or ADR to hydrocodone and oxycodone resulting in “nausea,” possibly explaining the emphasis on morphine and the patient avoiding exposure to other opioids such as codeine, hydrocodone, or oxycodone. An increase in morphine 15 mg immediate release formulation tablets (MSir) was initiated from 3 to 4 times daily, eventually 15 mg MSir 3 times per day with an additional 15 mg MS Contin (extended release) 2 times per day. Patient B:

> *has tried and failed following medications: anti-inflammatory meds, hydrocodone and oxycodone/oxycontin in the past. Patient reports the medication initiated last office visit has provided better relief in pain, notes oral pain medications in form of MSIR and MS Contin are effective and decreases low back pain by no less than a 60% relief in pain, pain level today is 6/10. Upon questioning patient denies adverse reactions such as euphoria/dysphoria*

Monthly reviews of the patient’s condition show:

> *Denies trouble breathing, shortness of breath, asthma, sleep apnea, seizures, blackouts, trouble with memory, headache, fainting spells, numbness, weakness and tremors.*

Patient C was maintained on 10 of 11 initial medications with the appropriate removal of Plavix (clopidogrel) after 2 serious PGx warnings:

> *Reduced Response to Clopidogrel (CYP2C19: Intermediate Metabolizer) Consider alternative therapy*
>
> *High Myopathy Risk (SLCO1B1: Poor Function). Simvastatin plasma concentrations are expected to be elevated. Consider avoiding simvastatin and prescribe an alternative statin, or consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine creatine kinase (CK) monitoring is also advised. The FDA recommends against the 80 mg daily dose.*

An additional serious DDI for Zocor (simvastatin) and Norvasc (amlodipine) warned:

> *do not exceed a dosage of 20 mg daily of simvastatin in patients receiving concurrent therapy with amlodipine. If concurrent therapy is deemed medically necessary, monitor patients for signs and symptoms of myopathy/rhabdomyolysis, including muscle pain/tenderness/weakness, fever, unusual tiredness, changes in the amount of urine and/or discolored urine.*

After PGx reporting, clopidogrel was no longer observed in medication lists for drug adherence reports, but simvastatin was continued with amlodipine, and 9 moderate DDIs remained, cautioning to "limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect." The only alternative statin without adverse interactions recommended was fluvastatin. Progress notes for patient C showed simvastatin was prescribed less than 80 mg per day as recommended by the FDA in the PGx report at 40 mg per day. Patient C "denies muscle cramp, muscle twitches, muscle wasting, muscle weakness, neck pain, joint swelling. Denies fever, fatigue"; however, patient C eventually reported "muscle pain or tenderness" in the latter part of the 2-year treatment window. Monthly urinalysis screens and blood testing showed no discoloration in urine or abnormal glomerular filtration rates, but the reported muscle pain/tenderness and the combination of reduced *SLCO1B1* gene function with concurrent daily 40 mg simvastatin and 5 mg amlodipine possibly indicated a statin-induced myopathy [31].

Discussion

Serious ADRs can occur based on incidences of poor, intermediate, rapid, and ultra-rapid metabolizer types in all 5 super populations for prescriptions such as amitriptyline, citalopram or clopidogrel, metoprolol, paroxetine, simvastatin, and tramadol. While PGx cannot predict all ADRs (eg, allergies cannot be detected), dosing guidance and the additional DGI and DDI algorithm provided valuable insight to optimize prescription regimens. Limitations within this retrospective study include the lack of detailed patient demographics associated with UDT and PGx reports, and limited access to progress notes and long-term treatment outcomes. Rather than resorting to 1000 Genome Database population frequencies to characterize the SDC, specific demographics and additional case studies as the three previously presented would allow more comprehensive insights as to the combinatorial effect of prescription drugs among polypharmacy pain management patients.

In summary, the effect of PGx reports newly made available to medical staff in this context seems quite significant as observed by the individual PGx dosing/metabolizer status and DGI and DDI recommendations showing a corresponding modification of the medication regimen for each patient. Preventative action was observed for all serious interactions, and only moderate interactions were tolerated where there may not have been other alternatives. This study demonstrates the predictive value of PGx testing combined with a customized informational report to help improve clinical outcomes, which resulted in a successful application for patients in a pain management setting.

Authors' Contributions

CT and DJS conceptualized the study. CT designed the methodology. CT and MJCM conducted the validation and formal analysis. DJS designed the resources. CT wrote the original draft. CT and MJCM reviewed and edited the manuscript. DJS provided supervision. CT was the project administrator.

Conflicts of Interest

CT and MJCM are current employees of Alcala Testing and Analysis Services (ATAS). DJS is a stakeholder and the Medical Director of ATAS.

Multimedia Appendix 1
Overall positive correlation (*) between 1000 Genome Database super population groups and the San Diego cohort (N=171).
[XLSX File (Microsoft Excel File), 10 KB - xmed_v3i2e32902_app1.xlsx]

Multimedia Appendix 2
79 Target regions - start and stop coordinates.
[XLSX File (Microsoft Excel File), 23 KB - xmed_v3i2e32902_app2.xlsx]

Multimedia Appendix 3
Primer sequences.

[XLSX File (Microsoft Excel File), 9 KB - xmed_v3i2e32902_app3.xlsx]

Multimedia Appendix 4
Summary of PGX DOSING versus drug-gene or drug-drug (DGI/DDI) interactions covered by the ATAS PGx panel.
[XLSX File (Microsoft Excel File), 93 KB - xmed_v3i2e32902_app4.xlsx]

Multimedia Appendix 5
Stability data.
[XLSX File (Microsoft Excel File), 16 KB - xmed_v3i2e32902_app5.xlsx]

Multimedia Appendix 6
Summary of PGx (Pharmacogenetic), DGI (Drug-Gene-Interactions) and DDI (Drug-Drug-Interactions) data and implementation.
[XLSX File (Microsoft Excel File), 182 KB - xmed_v3i2e32902_app6.xlsx]

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Abbreviations

5-HTTLPR: 5-HTT gene-linked polymorphic region
ADR: adverse drug reaction
AFR: African
AMR: Ad Mixed American
ATAS: Alcala Testing and Analysis Services
bp: base pairs
CNV: copy number variation
CPIC: Clinical Pharmacogenetics Implementation Consortium
DDI: drug-drug interaction
DGI: drug-gene interaction
DLSO: downstream locus-specific oligo
EAS: East Asian
EUR: European
FDB: First Databank
FDA: Food and Drug Administration
GATK: Genome Analysis Toolkit
gDNA: genomic DNA
L: long
NGS: next-generation sequencing
PCR: polymerase chain reaction
PGx: pharmacogenomic
rsID: reference single-nucleotide polymorphism cluster ID
RTA: Real Time Analysis
S: short

SAS: South Asian
SDC: San Diego cohort
SNP: single-nucleotide polymorphism
TSCA-LI: TruSeq Custom Amplicon Low Input
TSI: Translational Software Inc
UDT: urine drug toxicology
ULSO: upstream locus-specific oligo

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Original Paper

Patient Recommendations for the Content and Design of Electronic Returns of Genetic Test Results: Interview Study Among Patients Who Accessed Their Genetic Test Results via the Internet

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Abstract

Background: Genetic test results will be increasingly made available electronically as more patient-facing tools are developed; however, little research has been done that collects data on patient preferences for content and design before creating results templates.

Objective: This study identifies patient preferences for the electronic return of genetic test results, including what considerations should be prioritized for content and design.

Methods: Following user-centered design methods, 59 interviews were conducted by using semistructured protocols. The interviews explored the content and design issues of patient portals that facilitated the return of test results to patients. We interviewed patients who received electronic results for specific types of genetics tests (pharmacogenetic tests, hereditary blood disorder tests, and tests for the risk of heritable cancers) or electronically received any type of genetic or nongenetic test results.

Results: In general, many of participants felt that there always needed to be some clinician involvement in electronic result returns and that electronic coversheets with simple summaries would be helpful for facilitating this. Coversheet summaries could accompany, but not replace, the more detailed report. Participants had specific suggestions for such results summaries, such as only reporting the information that was the most important for patients to understand, including next steps, and doing so by using clear language that is free of medical jargon. Electronic result returns should also include explicit encouragement for patients to contact health care providers about questions. Finally, many participants preferred to manage their care by using their smartphones, particularly in instances when they needed to access health information on the go.

Conclusions: Participants recommended that a patient-friendly front section should accompany the more detailed report and made suggestions for organization, content, and wording. Many used their smartphones regularly to access test results; therefore, health systems and patient portal software vendors should accommodate smartphone app design and web portal design concomitantly when developing platforms for returning results.

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KEYWORDS

user-centered design; genomic medicine; patient portals; electronic health records; return of results; bioethics; genetics; genetic testing; patient preferences; design; human factors; mobile phone

Introduction

Health care systems must provide timely electronic access to genetic test results within the terms of Health Insurance Portability and Accountability Act regulations and meet meaningful use requirements [1]. Genetic test results that are provided in person by a genetics professional allow for appropriate counseling and prompt clinical management decisions, but increasingly more health systems are delivering test results via patient portals that are linked to electronic health records (EHRs). This approach supports the 21st Century Cures Act in facilitating patients' access to information in their EHRs [2]. Nearly 80% of health care providers use certified EHRs [3], and with that use comes the potential to communicate with patients through EHR-linked patient portals [4]. The expansion of the applications of genetic testing and the increased role of patient-facing health information technology together present an opportunity to design genetic test report content and web-based report templates to respect the information needs and preferences of diverse patients. To ensure a patient- and user-centered approach, patient input is needed to guide the design and content of electronic reporting templates at the outset.

Although there have been robust discussions on the return of genetic results [5-7], including the results of carrier screening [8,9], results for research participants [10-12], and incidental findings [13], and a growing amount of literature studying patient portal usage [14-16], there have been few studies concerning the design aspects for the electronic return of genetic test results via patient portals [17-19]. These issues may be particularly fraught in the context of results that can be sensitive or difficult to understand [20]. Often, results need to be interpreted carefully in terms of patients' medical and family histories; a negative result, for example, may have a different significance depending on how strongly a patient's family history suggests the presence of an inherited disorder [21].

Ensuring that portals are tailored to meet patient needs has the potential to not only ensure the appropriate delivery of results but also enable the use of patient portals to encourage appropriate follow-ups [22]. For example, some studies have demonstrated that patients respond to electronic reminders, which are sent through patient portals, to schedule screenings and other preventive services [23]. Although more research is needed, some patient populations may require additional support to use portals [24,25] and understand genetic test results in particular [26]. Patients from underserved populations [27] and those with limited health literacy may need engagement methods that assist them in effective portal and information use [26,28-30]. Some research has suggested that patient preferences for the return of negative genetic test results or normal nongenetic results [31] generally exhibit more openness for impersonal returns (such as electronic returns) than that for returns of results that are positive or abnormal; however, patient preferences vary greatly, and as noted previously, negative genetic results may have nuanced implications [32,33]. Additionally, in general, patients can misinterpret risk [34]. However, patient recipients are interested in participant-driven approaches, such as user-centered design, that consider how results are delivered [35]. As more and more genetic results are returned to patients via electronic portals, more understanding of these design elements is necessary to ensure that patients are able to not only access their medical information but also understand the implications of these results for their families' and their own health. We sought to identify patient perspectives on design-related issues, such as those regarding the content, formatting, and structure of reports, with the electronic return of clinical genetic test results and other test results to patients.

Methods

Participant Recruitment

We identified patients from within the University of Washington (UW) Medicine EHR system who had undergone a genetic test within the 12 months prior to the start of recruitment and had also been active on the UW Medicine patient portal. Participants were invited if they had undergone genetic tests corresponding to 1 of the following 3 levels of concern, as identified by the study team and project advisory board: (1) fraught (ie, positive results for hereditary cancer risk), (2) moderately fraught (ie, blood coagulation genetic risk or α-thalassemia risk), and (3) not fraught (ie, pharmacogenetic or negative results indicating that the patient did not have a pathogenic variant). Pharmacogenetic results were considered to be not fraught, as they only have implications for how a health care provider treats a known condition (eg, selecting the safest and most effective drug or dosage for the patient's metabolism) rather than for predicting disease risk or indicating the presence of a condition.

Patient information was queried through the Institute for Translational Health Sciences bioinformatics research service, which maximized patient privacy prior to enrollment, as researchers only had access to eligible patient names, contact information, basic demographics, and the types of genetic tests that patients underwent; they did not have access to additional details about patients' health or reasons for testing. Potential participants were invited by email or phone up to 3 times per person until we reached the stratified sampling goals for test types and data saturation. We prioritized invitations to ensure a broad representation of available demographics (age, gender, race, and ethnicity). Participant demographics (N=59) are summarized in Table 1.

Table 1. Participant demographics (N=59).

Characteristics	Value
Age (years), mean (SD)	48.5 (15.3)
Age (years), n (%)	
<30	7 (12)
30-39	15 (25)
40-49	8 (14)
50-59	11 (19)
60-69	12 (20)
≥70	6 (10)
Self-reported gender, n (%)	
Female	39 (66)
Male	20 (34)
Race and ethnicity, n (%)	
African American or Black	4 (7)
Asian	5 (9)
American Indian or Alaska Native	0 (0)
Hispanic or Latinx	5 (9)
White	43 (73)
Unreported	2 (3)
Type of result[a], n (%)	
Fraught	18 (31)
Moderately fraught	32 (54)
Not fraught	9 (15)

[a]Fraught results included positive results for cancer risk variants, moderately fraught results included blood coagulation types and α-thalassemia test results, and not fraught results included pharmacogenetic and negative cancer risk variants.

Ethics Approval

This study was approved by the UW Institutional Review Board (STUDY00005045).

Data Collection

A semistructured interview guide (Textbox 1) was developed by the study team with guidance from the project advisory board, and it was piloted to ensure its appropriateness for a patient audience. To minimize participant burden, about half of the participants (30/59, 51%) discussed design-related issues based on their experiences with receiving a specific genetic test result through the patient portal, and about half (29/59, 49%) were asked to compare their experiences with receiving a specific genetic test result through the patient portal to their experiences with receiving a nongenetic test result that they identified through the patient portal (eg, cholesterol levels, blood counts, and radiology reports).

In-depth telephone interviews were conducted from May to August 2019, were audio-recorded, and lasted for an average of 35 minutes. Participants were offered a modest gift card for their participation. All interviews were professionally transcribed, and transcripts were deidentified and reviewed for accuracy.

Textbox 1. Selected questions from semistructured interview guide.

Questions for genetic and specific nongenetic results

- "What was it like for you to receive your test result on eCare?"
- "What was good about the experience? What would have improved the experience?"
- "How were you able to interpret (or make sense of) the results?"
- "What, if anything, did you do with the test result that you received? What role, if any, did electronic return play in the usefulness of the test result?"

Questions for genetic results only

- "How would you describe your understanding of the results reported in eCare?"
- "What information was included with your *[insert specific genetic test]* result in eCare?"
- "What did you think about the text and visual materials?"
- "Can you give an example of what was communicated clearly?"
- "What could have been communicated more clearly?"
- "Would you have preferred to have more or less information available through eCare?"
- "What information, if any, was provided about next steps?"

Data Analysis

A short, design-focused coding scheme was developed by 2 qualitative analysts. The first analyst (KMW) coded all transcripts for design-related elements by using Atlas.ti 8 software (Scientific Software Development GmbH). The second analyst (DMK) then performed a directed content analysis to identify specific design element themes within a set of categories derived deductively from the interview guide (eg, suggestions for layout, content, organization, wording, etc). Themes were identified deductively and were based on topics that participants raised during the interviews. For example, a summary coversheet was not mentioned in the interview guide, but as more participants suggested the functions of a summary, this topic was explored by interviewers more explicitly and comprised an inductively derived theme within the *content* category.

Results

Summary of Results

We interviewed 59 UW Medicine patient users of the electronic patient portal in Washington State. The sample was predominantly White (43/59, 73%) and female (39/59, 66%) and represented a wide range of ages (mean 48.5; range 26-78 years; Table 1). The key domains discussed covered how the electronic result returns would appear to the users (design) and considerations for what is contained in the result returns (content).

Domain 1: Design of Electronic Result Returns

Design Recommendation 1: Include a Simple Summary Coversheet in the Electronic Report That Summarizes the More Detailed Report

Participants generally felt that a summary would be helpful and that less information would be preferred. They offered some analogies for how this summary might appear:

> *...Say this was something like cancer risk. And [the coversheet summary] would comment on this is likely an inherited risk, therefore [it] could impact your family. And I wouldn't go anything beyond that. And then [beyond] that could be up for the discuss[ion] with your provider.* [Participant #25]

One participant compared the electronic summary to the abstract of a manuscript:

> *You'd lay it out basically like an abstract for a research paper. You tested positive or negative against this whatever, then you go to the next part, because of this result, this will affect your treatment in this way. After that, next probable steps to take will be a couple of these things based on what your doctors have said.* [Participant #34]

Another participant referred to the coversheet that one receives during car maintenance as a valuable framework:

> *I kind of want it to be like when I go to my car dealership and I get my car serviced and they give you like, this is where your car stats are at, your battery's great, your tire was a little low. We adjusted this.... I want a summary page…I also want an opening cover that says here's your test results. This is what the results mean. This is what the markers mean. This is how it applies to you, what it means for you. This is my area [of] concern or not concern. This is the next step I think you should take.* [Participant #43]

Design Recommendation 2: Include the Electronic Summary Coversheet to Supplement, but Not Replace, the Detailed Clinical Report

Although many participants wanted a brief, patient-friendly summary, some participants also valued the clinical report because it serves as a matter of record—one that is available on the internet—of the test details that might be difficult to

remember from a conversation. They may wish to use these details to further explore their specific variants after a clinic visit. One participant said:

> *In genetic testing there are so many variations,...but you didn't bring paper to write that down...exactly what that was or what that means. So then to have it in writing so I can see "oh it's this gene mutation" with all the numbers and the letters that go along with it.... So I can have that documented and then if I want to do more research online I can do that...copy that I can look at.... Details, once again, confirmation in my head that I heard correctly.* [Participant #29]

Other participants appreciated the value that a detailed electronic report could have for other clinicians, viewing it as a part of their medical history that would be relevant to future care:

> *I think it's good to have them [the detailed results] through [the patient portal], because I know having the records on there, other doctors can access [them]...it would be important to have all of that information for someone as a health professional that could go back in and see your history. They're going to need more than just a brief description like the patient would want...you could offer both.... You know, this section is mostly for the patient to understand what they're looking at, and then this is the test results and the exact information that we based this information off of.* [Participant #47]

Design Recommendation 3: Ensure That Both Web and Smartphone Functionalities Are Accounted for in the Design

Many participants preferred to use their smartphones to manage their health and health care; however, several felt that patient portals are still designed for optimal use on a computer using a web-based layout rather than the more modular smartphone layout. As several participants pointed out, their phones were always with them, and they could use smartphones to share data in real time during clinical appointments, particularly when seeking care at a new or out-of-network clinic. As one participant described:

> *I had to go to the ER.... My home base is [institution name], but I went to [another place] this particular day because it was closer. Even though they are connected, they could not see my history. So rather than wait for my doctor, I just pulled up my history on my phone so the ER doctor could help diagnose me better. So even though he didn't get to speak to my doctor, he still had the reference and the notes to get the answers he needed. So even though the context didn't make sense to me, it made sense to him.* [Participant #36]

Several participants however expressed a concern that smartphone patient portal apps did not have the same range of functionality as that supported by computer-based applications, raising some points about the strengths and weaknesses of smartphone delivery versus computer delivery. Several commented on the size of smartphones being an inherent weakness when a lot of information or text needs to be displayed. These weaknesses have implications for designing usable results sections that meet the needs of patients and their health care providers. For instance, one participant said:

> *There's a lot in information on the page. It's a lot easier to see it all spread out on the computer...I think that was the problem on the smartphone. It was just hard to read.* [Participant #8]

Domain 2: Content of the Patient-Friendly Results Summary Coversheet

Content Recommendation 1: Include a Personalized Note From the Clinician With the Electronic Test Results

For results that were returned via the internet, many participants felt that those results should include a personal message from a clinician. For some participants, the inclusion of such a personal note was the one thing that distinguished the web-based return of genetic results from the web-based return of routine test results (eg, blood panels):

> *...with the genetic testing [my clinician] did include the note right then. They normally don't do the note. So that was the difference, really, between the two, versus regular blood work results and genetic testing...she had a little note in there saying it was all clear...it made it a more personal experience, which I like a little better...as personal as you can get through an email or [a patient] portal site.* [Participant #23]

These personal notes helped to humanize the interactions for some participants, making them feel heard and improving their satisfaction with their care. One participant said:

> *Having that small note says that somebody is identifying that this is a real person...conversation, even if it is through email, or through [the patient portal]. It's still something, rather than pushing you through and here's your numbers, and if you have any questions, yeah, yeah, we'll call you. Or you can call us, but we're not going to call you.... Start with the note, and then, you can go to the test results…I feel way more informed, and more like everything is being taken care of. That I'm not being ignored.* [Participant #51]

Content Recommendation 2: Report Only Key information in the Results Summary Coversheet

Several participants mentioned that there was too much information in the report that they did not understand. As one participant succinctly put it:

> *You're overwhelmed by all of this jargon and underwhelmed at the same time by how little is actually said without directly telling you yes or no.* [Participant #34]

Another participant suggested that starting the report with an easily identifiable and comprehensible "bottom line" would be helpful:

> *We have this thing in the Navy, I don't really know how it would be operationalized in healthcare, but we have this thing called BLUF.... When you're writing somebody an email...at the top of the email in capital letters you put B-L-U-F: stands for bottom line up front.... Okay, bottom line up front: "Of the 60 types of cancers we screened for, you are not genetically predisposed to any." Then, "[Participant name], we did this test and…this is what it tested for, and while this is only looking at your genetic makeup and not looking at environmental factors…we estimate that you have this percentage chance...." The same thing is true whether it's the genetic testing or testing my lipids...particularly when you're talking about healthcare and something as complicated or convoluted as genetic testing, it would really seem to me that the person who is delivering the news either in writing, or over the telephone, or in person, needs the BLUF.* [Participant #45]

The extensive details in reports seemed unnecessary to participants who were largely focused on what the results would mean for them personally. For example, a participant said:

> *As a whole, the detail that they gave, I didn't understand. The end result, I understood. It was as clear as day because it [was] negative. When I look at the test results, they give me the gene sequence and value notes. They give me all this gene coding stuff…I don't know those from Adam.... But then it gives me the result, and it says negative for mutations, the interpretation. And...the disclosure statement saying, "Hey, even though this is what's found, we're not guaranteeing you anything...." The important parts are in bold, and I understood them just fine. The gene sequence: probably not all that important. Because for me, it doesn't do anything.* [Participant #37]

Content Recommendation 3: Use Clear, Accessible, Jargon-Free Language in the Results Summary Coversheet

Participants pointed out the disconnect between medical terms and how everyday people use language. Several participants suggested that the terms *positive* and *negative* were confusing in the context of how these words are used in the vernacular:

> *I feel like the positive and negative, it really trips me up. Like getting a..."Your HIV test came back negative." And you're like, "Wait a minute. It's negative. Negative is good." So, I think the negative and the positive, they're obviously not opposite meaning. It's very clear, like, "This came back with nothing." Or "This came back with...." But it can be an immediate gut-wrenching reaction, of like, "Uh-oh." I'm used to associating that word with a bad thing.* [Participant #8]

Using these words was particularly confusing when they were unaccompanied by an explanation or sufficient context. One participant stated:

> *...without getting into...too much detail. We were looking for [a] particular marker, right?...And in this case it was negative...And it tells me it's negative. But I don't have any of the qualitative information. Is negative good or bad?...And what's it mean? ...it's not like something that you could just say, "In range or out of range." Right? Is that thumbs up or thumbs down?* [Participant #1]

Some participants offered specific suggestions for sections in the coversheet where wording could be made friendlier for nonexperts and enhanced to provide reassurance:

> *...if it just says heterozygous they really don't know what that means...just put a sentence in there added to it saying, "There's two copies. If you only have one copy, it's much less serious than if you have two copies." You know, "If you do have two copies, we still have treatments that work," just like Dr. [provider name] explained to me. That little, short two-sentence explanation, would ease people's minds.* [Participant #40]

Content Recommendation 4: Include Next Steps in the Results Summary Coversheet

Participants wanted to have major next steps included in the patient-friendly summary:

> *Definitely having some sort of "so here are the recommended things that you should do" so you can make educated choices about what you want to do now that you have those [risk] results…you might think, "Oh I have no chance of getting it." That's not really true…[Negative result] might be a false sense of security.* [Participant #58]

In cases where next steps could not be included (eg, because they were complex or very individualized), participants wanted to know that next steps were coming in a more detailed follow-up, such as a conversation:

> *[There should be] a notice that the next steps were coming.... "Based on our testing, you are predisposed to 14 different kinds of cancer. Action items: we need to meet to discuss this...." ...follow up or action items, that is again, simple, declarative...and stands out visually.* [Participant #45]

> *[The genetic test results] didn't have any like, these are the health implications you could deal with for the rest of your life, or something like that. Or this is what you could possibly be dealing with. That was nonexistent...I would find it helpful to say like, maybe we schedule a follow-up visit if it warrants it, or maybe just a more detailed response on their part.* [Participant #47]

Content Recommendation 5: Include Encouragement and Easy-to-Find Information for Contacting the Health Care Provider if There Are Follow-up Questions

Several participants understood that complex results would likely be returned electronically in the future. As such, they believed that follow-up contact with a clinician was an extremely

important service that should be accommodated. In the electronic report, participants wanted to receive both encouragement to follow up (ie, as a way to reinforce the fact that their potential concerns would be taken seriously) and the contact information of an appropriate health care provider:

> *I think maybe always giving the option of a follow-up and a personal note. Always include, "If you would like to discuss more, feel free to call us" at this [number].*" [Participant #23]

Even when receiving written encouragement in the patient portal, some participants shared concerns that they would not feel comfortable with reaching out to busy health care providers with their questions. In this case, they preferred having a health care provider or a health care provider's office contact them via a brief telephone call, rather than a note, to encourage them to ask any questions. One participant said:

> *I...think it's important to break the ice...even if eventually you get most of your results electronically, I still think it's important to have somebody, even if it's some sort of medical assistant in the office, call and say "We're here for you and if you have any questions, please call us...." Because I often hesitate because I think if they didn't say anything, and maybe I'm just stupid.* [Participant #48]

Discussion

Principal Results

Our study offers an exploration of both the design and content of electronic returns of genetic test results, sharing perspectives from adult patients who vary widely in terms of age; come from a large, urban, academic medical center; have undergone genetic testing; and are fluent in English. Results that are returned electronically should start with a summary coversheet containing the most pertinent information. For example, participants recommended that genetic test results should include simple summaries that provide an overview of their test results in an accessible language. This content would be placed at the beginning of the test results (eg, on the test result landing page for a specific result) and would function as a coversheet that precedes the more detailed clinical report. Many participants wanted a personal note from a clinician, and some participants suggested that this note should be placed at the very beginning of the electronic report. Participants offered specific feedback on content for the summary, which at a minimum should include the "bottom line" (eg, whether a medically important genetic variant was found), patients' next steps, and explicit encouragement to contact health care providers with any questions or concerns. Summaries must be written in a clear language and avoid technical jargon, which might include avoiding the words *positive* and *negative* in this section. Importantly, participants wanted this summary coversheet in addition to—not in place of—the more detailed clinical report.

Many participants used both their computers and their smartphones to access their patient portals but found that while using a smartphone was very helpful, the interface was not optimal. As more patients across many demographics use smartphones to manage their health, it is important to prioritize designing genetic test results information for delivery on smartphones instead of test results that are more akin to genetic counseling results letters.

Comparison With Prior Work

Attention to the Design of Electronic Delivery is Needed, as Genetic Tests Outpace Clinician Hours

Although there has been effort for designing letters to return genetic test results to patients [36], the specific challenges of leveraging web-based electronic capabilities for result returns have not yet been well explored [4]. Some of this delay might be due to service delivery models that mandate or strongly recommend in-person returns for test results that are deemed sensitive (eg, genetic [37,38] or radiology results [39,40]). Although the number of clinical genetic tests is on the rise, the supply of genetic counselors and other health care providers who are qualified to fully return results is not keeping apace [41-43]. Electronic portals may offer a patient-friendly and acceptable alternative for returning results that allows for the prioritization of genetic counselors' time to address the most complex or sensitive genetic results [22]. Electronic portals have substantially more functionality than a simple paper letter; therefore, there is great potential for leveraging informational hierarchies, external links to additional information, and the patient-directed use of the result page for both patients' own use and their physicians' use. However, our data demonstrate that current approaches to electronic result conveyance do not meet patient needs, supporting the necessity for bringing attention to these design elements to make effective and acceptable use of this model, such as creating a summary coversheet template that has been user-tested with patients from a range of heath literacy and educational backgrounds.

Getting the Content Right Will Continue to Be a Critical Concern for the Electronic Return of Genetic Results

Genetic information has been described as "informationally complex" and "hard to interpret" even among medically trained professionals [44-47]. Similarly, our data show that some patients struggle to understand genetic results reports as they are currently written due to the volume of information to sift through; the use of medical terms; and the lack of straight-forward, lay-friendly interpretations of the results. Indeed, many genetic results letters still do not meet Centers for Disease Control and Prevention–recommended literacy levels for health-related communication [48,49], and as our English-fluent participants noted, results letters can be confusing when they convey informationally complex results or even fairly simple results, such as "positive" or "negative." Specifically, the differences in the significance of various types of genetic results and these differences' impact on returning genetic results to individuals have been discussed in several contexts [37]. Patient preferences for the return of negative test results generally exhibit more openness for impersonal returns (eg, via secure messaging) than that for returns of results that are not normal; however, patient preferences vary greatly, and as noted previously, negative genetic results may have nuanced implications [32,33]. Our data further support previous calls for the improved communication of genetic information to

patients and the tailoring of these calls to the electronic return process.

User-Centered Approaches Are Needed When Developing Electronic Test Results Templates

Research with patients supports a user-centered design approach for the return of test results [35], including the return of genetic results [50]. Ensuring that portals are tailored to meet patient needs has the potential to not only ensure the appropriate delivery of results but also enable the use of patient portals to encourage appropriate follow-ups [22,51].

Many patient portals are add-ons to commercial EHR software packages; often, they are designed without patient or clinician input [4,52,53]. Ensuring that patient portals are able to deliver results on a range of electronic devices in ways that are user-centered, in terms of both design and content, is crucial [54].

We acknowledge that a patient-centered approach may elicit suggestions for content and design that might not be easily accommodated by available patient portal software (such as those available through EHR software), the clinical workflow of health care systems, or the preferences of individual health care providers. These issues are beyond the scope of our study but must be considered in the final decisions regarding the portal-based return of genetic results.

Limitations

Focusing our study sample on the patient population of a single, although large, urban academic health system in the Pacific Northwest may have limited the scope of the views shared in this paper. Our participant cohort was largely female and White, and all participants were fluent English speakers who have used the patient portal. It is possible that underrepresented groups may tend to be nonusers of the patient portal [29,55] or tend to not undergo genetic testing [56]. Further, enrolled participants responded to email or phone invitations to participate in the study, which may have also biased our sample toward people who are more comfortable in engaging with research or medical concepts and thus may have a higher comfort level with receiving medical information via the internet than those who did not accept the invitations. All interviews were conducted by phone and in English; thus, our findings do not take into account views of people with limited English proficiency or those who are unable to use phones or other technology. Understanding the content needs of those with limited English proficiency is a crucial step toward ensuring that the development of patient portal services for result returns is appropriate for a wide range of users. Finally, as this was an exploratory qualitative study, we cannot estimate how widely shared our participants' views are or whether they would be shared by patients in other geographic regions or health care systems. We also discovered through our qualitative interviews with patients that using patient portals to return certain results (eg, those that are considered particularly complex or fraught) should only be supplemental, as a conversation is usually preferred in such instances. Our paper on the types of tests should or could be returned electronically is forthcoming. This has limited what we have chosen to report with regard to patient recommendations for the content and design of returns of less fraught, but potentially confusing, genetic test results.

Conclusions

Although research has been conducted to explore the needs of patients when genetic test results or other test results are returned and to determine some patient portal design needs, the design of electronic results reports lags behind patient consumers' expectations for using and accessing their test results. Our study results indicate that patients value the details that are included in formal laboratory reports, but as many of them access their tests electronically through patient portals, including via their smartphones, report templates must take into consideration where, when, why, and how patients use their electronically available health information. Our participants recommended the creation of a coversheet that includes a brief "bottom line," is easily accessible and visually distinct, and uses broadly understandable content that prioritizes next steps and encourages patients to follow up with their health care providers to obtain more information. It is important for this coversheet to be available in a usable form on smartphones, since many participants accessed their results and shared content (eg, with their clinicians during medical appointments) via their smartphones. There is a real opportunity for development approaches that use interaction design principles and user-centeredness in new ways beyond merely translating a detailed clinical report for electronic delivery.

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Conflicts of Interest

None declared.

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Abbreviations

EHR: electronic health record
UW: University of Washington

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Original Paper

Toward Human Digital Twins for Cybersecurity Simulations on the Metaverse: Ontological and Network Science Approach

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Abstract

Background: Cyber defense is reactive and slow. On average, the time-to-remedy is hundreds of times larger than the time-to-compromise. In response, Human Digital Twins (HDTs) offer the capability of running massive simulations across multiple domains on the Metaverse. Simulated results may predict adversaries' behaviors and tactics, leading to more proactive cyber defense strategies. However, current HDTs' cognitive architectures are underdeveloped for such use.

Objective: This paper aims to make a case for extending the current digital cognitive architectures as the first step toward more robust HDTs that are suitable for realistic Metaverse cybersecurity simulations.

Methods: This study formally documented 108 psychology constructs and thousands of related paths based on 20 time-tested psychology theories, all of which were packaged as Cybonto—a novel ontology. Then, this study applied 20 network science centrality algorithms in ranking the Cybonto psychology constructs by their influences.

Results: Out of 108 psychology constructs, the top 10 are Behavior, Arousal, Goals, Perception, Self-efficacy, Circumstances, Evaluating, Behavior-Controllability, Knowledge, and Intentional Modality. In this list, only Behaviors, Goals, Perception, Evaluating, and Knowledge are parts of existing digital cognitive architectures. Notably, some of the constructs are not explicitly implemented. Early usability tests demonstrate that Cybonto can also be useful for immediate uses such as manual analysis of hackers' behaviors and automatic analysis of behavioral cybersecurity knowledge texts.

Conclusions: The results call for specific extensions of current digital cognitive architectures such as explicitly implementing more refined structures of Long-term Memory and Perception, placing a stronger focus on noncognitive yet influential constructs such as Arousal, and creating new capabilities for simulating, reasoning about, and selecting circumstances.

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KEYWORDS

human behavior modeling; cognitive twins; human digital twins; cybersecurity; cognitive systems; digital twins; Metaverse; artificial intelligence

Introduction

The General Landscape

Humans are well recognized as the weakest link in the cybersecurity defense chain [1,2]. Insider threat incidents cost both small and large companies billions of dollars annually [3]. Nonetheless, cyber defenders are still reactive and slow. On average, hackers need 15 hours to compromise a system, while defenders need 200 to 300 days to discover a breach [2]. Meanwhile, the cybersecurity threat landscape keeps expanding. Cyber defenders respond by enlisting interdisciplinary knowledge from numerous fields such as mathematics, psychology, and criminology [2,4-6]. In such a climate, Digital Twins (DTs) and Human Digital Twins (HDTs) offer the capability of running simulations across multiple knowledge domains on the Metaverse to improve proactive cyber defense strategies.

DTs are computational models of physical systems, including humans. The DT market is rapidly growing at a compound annual rate of 45.4% [7]. Notably, massive DT projects such as the British National Digital Twin [8] are being built. Within the intertwined DT networks, individual smart DTs such as HDTs should be capable of not only executing mimetic behaviors but also having local and global awareness, self-learning, and self-optimizing [7].

HDTs should coexist with other DTs within the paradigm of agent-based modeling and simulation for cybersecurity. Nonhuman DTs can be components of an Information Systems (routers, servers, and Internet of Things systems), while HDTs are the system users, system admins, and malicious actors. Agent-based modeling offers cost-effective, rigorous, and risk-free scenario testing that should inspire more proactive cybersecurity defense strategies. The *Prior Work* section discusses some use cases of HDTs and agent-based modeling in cybersecurity.

Zooming out to a broader perspective, the "Metaverse" is a gigantic, persistent, and unified realm of various virtual environments such as DT networks, social networks, digital publishing networks, virtual 3D networks, cyber-physical infrastructures, cloud infrastructures, and blockchains. Lee et al [9] proposed a "digital twin-native continuum" reflecting three Metaverse development stages. The first stage mainly involves digital twins and the effort of digitalizing the real world. In the next stage, digital twins and other virtual entities form isolated cyber-physical environments that are called "many virtual worlds." Finally, the many virtual worlds will be connected to form the Metaverse. The paper focuses on this vision for the Metaverse in which large-scale simulations can be collaboratively done by massive networks of interconnected DTs.

Backgrounds on HDTs

The concept of HDTs previously appeared in human-computer interaction studies. In comparison with traditional models, HDTs for the Metaverse have broader scopes with emphasis on both behavioral and cognitive activities. The work of Somers et al [10] is an excellent example in which HDT acts as a sensible personal assistant in organizing social events. Notably, the HDT did not explicitly ask potential event participants for their preferences. Instead, it observed the people's social dimensions and then modeled the cognitive processes underlying an expert event planner's decision.

Such a continuous process of dynamic knowledge acquisition and utilization was described by Zhang et al [11] as HDTs' self-awareness involving numerous feedback loops. Well-designed ontologies are essential for those information exchange loops [12,13]. Among ontologies, reference ontologies are supposed to be much more canonical and reusable than application ontologies [14].

Backgrounds on Cognitive Frameworks

Cognitive frameworks are essential for building HDTs' cognitive features. ACT-R [15] is representative of the psychological modeling group with Clarion and Epic as other members. SOAR [16] is representative of the agent functionality–focused group, which also includes Sigma, Lida, Icarus, and Companions. ACT-R and SOAR differ on architectural constraints, memory retrieval, conflict resolution strategies, and exhaustive processing [17]. ACT-R sequential architecture forces developers to watch out for bottlenecks, while SOAR's parallel architecture is more relaxed [17]. ACT-R provides two options for resolving conflicts, while SOAR offers none.

Both SOAR and ACT-R share the same general cognitive cycle and common architectural modules such as perception, short-term memory, declarative learning, declarative long-term memory, procedural long-term memory, procedural learning, action selection, and action. While ACT-R, SOAR, and other cognitive systems rely on the symbolic input or output and rule database, their symbols may contain statistical metadata, and their architectures allow for the integration of deep learning systems.

Backgrounds on Cybersecurity Ontologies

Ontologies are essential for HDTs' feedback loop communications, symbolic operations, the building of a knowledge base, and explainability. Ontologies can be manually built from scratch [18,19] or be automatically extracted [20,21]. DOLCE [22] vs Basic Formal Ontology (BFO) [14] highlights the importance of ontological commitments by choosing a top-level ontology. DOLCE top-level ontology is grounded in natural language, while BFO top-level ontology is grounded in the real world [23]. Because objects can be conceptual or actual in a language-based ontology, there is always a risk of one actual object being recognized as two or more different conceptual objects.

Oltramari et al [24] introduced Cratelo, which is based on DOLCE. The ontology's human behavioral structures are confined within the cyber operation scope. Costa et al [25] used the natural language processing approach in building their Insider Threat Indicator Ontology. The ontology inherited considerable amounts of language ambiguity and did not support the identification of deeper behavioral structures. In 2019, Greitzer et al [26] built upon their 2016's work and introduced the Sociotechnical and Organizational Factors for Insider Threat (SOFIT). Owing to the absence of a top-level ontology and the behavioral language that leans heavily toward organizational insider threat activities, SOFIT is an application ontology rather than a reference ontology. Greitzer et al [26] also admitted that ontology validation exercises only covered 10% of the ontology.

Meanwhile, Donalds and Osei-Bryson [27] reported that cybersecurity ontologies have been insufficient owing to fragmentation, incompatibility, and inconsistent use of terminologies. The team proposed a cybercrime classification ontology structured around attack events [27]. While the ontology provides a holistic, multi-perspective view regarding cybercrime attacks, its behavioral components are limited and lack theoretical grounding.

Open Problems

While massive DT projects are underway, digital cognitive twin development is pale in comparison, and HDT for cybersecurity is underdeveloped. This paper examined both ACT-R– and SOAR-published research repositories and found no cybersecurity-dedicated track with topics such as cybersecurity, web-based ethical decisions, cyber criminology, or cyberattack or defense simulations. Recommended explorative questions are as follows: (1) What types of HDT (malicious hackers, groups as single HDT, and defenders) should be built? (2) What will HDT for cybersecurity feedback loops look like? (3) How will existing cognitive architectures be extended to best facilitate those feedback loops? (4) What shall we learn from our continuous observation of those HDTs on the Metaverse?

Current cybersecurity-related autonomous agents focus on narrow tasks and are far from the HDTs that can automatically interact with other DTs while building up their own awareness. For one reason, existing cognitive architectures do not provide enough granularity. This leads to further problems with multimodal understanding and meta-cognition. For example, current long-term memory architecture can be further divided into experiences and beliefs. It is possible for two persons sharing a strong belief to have different interpretations of the same data (difference experiences). Additionally, processing big chunks of data owing to a lack of granularity may lead to cognitive bottlenecks at system levels. Deciding which chunks of data to be loaded, excluded, or be permanently erased from memory remains a challenge.

Finally, we do not have a reference ontology for documenting and sharing behavioral cybersecurity knowledge among humans and DTs. Existing cybersecurity ontologies that have behavioral components are mostly application ontologies with none or weak ontological commitments. Such ontologies will not fit for use in massive networks of DTs on the Metaverse.

Therefore, this paper aims to make a case for extending the current digital cognitive architectures as the first step toward more robust HDTs that are suitable for realistic Metaverse cybersecurity simulations. This paper proposes the Cybonto Conceptual Framework—a grounded and scoped vision on how interconnected DTs and HDTs on a Metaverse may predict real-world behaviors and tactics of hackers. Specifically, the paper unified 20 most cybersecurity-relevant finalists from a knowledge body of over seventy behavioral psychology theories. The theory-informed knowledge and other cybersecurity constructs were then encoded as the novel Cybonto ontology, which sits at the framework's core and is the paper's key contribution.

Methods

Identifying Relevant Theories

In total, 50 candidate theories were selected from the behavioral or cognitive psychology body of knowledge with more than 70 theories. Each theory was ranked in accordance with its ability to generate research, relevancy to cybersecurity or criminology, and consistency. Table 1 presents the top 25 theories.

For each theory's original peer-reviewed paper, the total number of citations and the publication year were extracted and used to calculate the citations per year value. The "Google Scholar Results" value (value A) is the total number of Google Scholar search results of the search query (query A) containing the quoted theory's name and its founder's last name. The keyword "cybersecurity" was added to the previous search query to form a new query (query B) and get a new search result value (value B). Value B was divided by value A to form the "CySec Density" metric. "CySec impressions" is the total number of cybersecurity relevant papers within the top 10 papers automatically ranked and displayed by Google Scholar after performing query B. Similarly, "Criminology Impressions" is the result of repeating the same steps for calculating "CySec Impressions" but with the "criminology" keyword instead. All values were normalized into a range from 0 to 10. The final ranking score is the average of "Fitted citations per year," "CySec Impressions," "Criminology Impressions," and "CySec Density Fitted."

Table 1. Top 25 cybersecurity applicable behavioral theories.

Theory name	Google Scholar results, n	CySec Impressions	CySec Density Fitted	Criminology impressions	Fitted citations per year	Final score
Protection Motivation Theory [28]	10,500	10	9	7	0	6.5
Prospect Theory [29]	66,200	8	1	6	10	6.3
General Theory of Crime [30]	13,500	9	1	10	1	5.3
Self-Efficacy Theory [31]	212,000	9	0	6	5	5
Social Norms Theory [32]	47,400	7	9	2	0	4.5
Affective Events Theory [33]	6880	10	1	6	0	4.3
Differential Association Theory [34]	10,700	9	1	7	0	4.3
Extended Parallel Processing Model [35]	412	7	4	6	0	4.3
Focus Theory of Normative Conduct [36]	6220	6	10	1	0	4.3
Containment Theory [37]	2240	9	1	6	0	4
Theory of Planned Behavior [38]	85,800	9	1	3	3	4
Social Identity Theory [39]	66,200	7	0	7	1	3.8
Goal Setting Theory [40]	51,700	6	1	7	1	3.8
Transtheoretical Model of Behaviour Change [41]	35,900	6	0	7	0	3.3
Self-Determination Theory [42]	165,000	8	0	4	0	3
Operant Learning Theory [43]	40,500	7	1	4	0	3
Social Cognitive Theory [44]	162,000	8	0	3	1	3
Change Theory [45]	54,700	8	0	2	0	2.5
Precaution Adoption Process Approach [46]	2590	6	1	3	0	2.5
Diffusion of Innovations [47]	96,700	4	1	3	2	2.5
Control Theory [48]	11,500	6	1	1	0	2
Risk as Feelings Theory [49]	550	5	2	1	0	2
Social Learning Theory [50]	145,000	2	0	6	0	2
Norm Activation Theory [51]	4610	5	1	1	1	2
Technology Acceptance Model [52]	48,100	2	3	1	2	2

A full table with links to Google Scholar queries, descriptions of Cybonto in RDF store, the Neo4J relational database, theory ranking details, and other documentation is available at Cybonto-1.0 GitHub repository [53].

Ontology Designing

Cybonto elected the BFO as its top-level ontology from more than 30 candidates. BFO [14] is the only top-level ontology that adopts materialism, commits to actual-world possibilia, and has an intensional criterion of identity. The Cybonto Core is grounded further by employing Mental Functioning (MF) as its mid-level ontology. MF follows best practices outlined by the OBO Foundry and aligns with other projects in the Cognitive Atlas—a state-of-the-art collaborative knowledge-base in Cognitive Science [54].

Materialism is the key ontological commitment. It views the world as a collection of materialized objects existing in space and time [23]. Committing to materialism through BFO offers a fundamental distinction in the way Cybonto represents psychological constructs. For centuries, psychological activities were considered abstract particulars that could only be described through languages. This tradition is the reason why most behavioral components in cybersecurity ontologies are language based. Recent breakthroughs in the brain-machine interface such as those of Neuralink [55] enable measurements of brain activities that correspond to certain cognitive constructs. Therefore, it is now possible to ground behavioral or cognitive ontologies in materialism. Cybonto rejects conceptual objects, different linguistic descriptions of the same actual objects, process-based objects, and object labels that cannot be measured in real life.

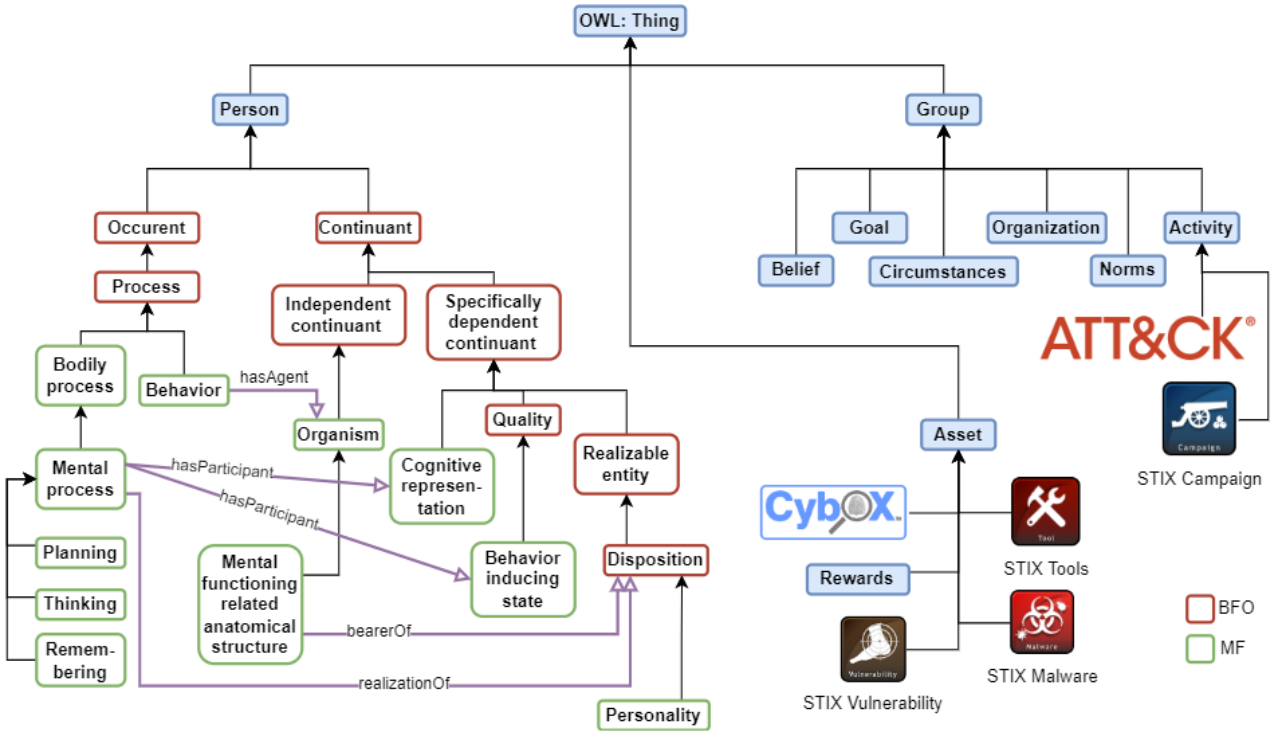
Figure 1 shows the main hierarchies of Cybonto. The current Cybonto core is based on the top 20 psychology theories. Each chosen one was codified into tuples of (construct, “influence” relationship, and construct). A total of 108 constructs and the relationships among them were put under MF (green), which is covered by BFO (red) under Person. All these constructs form the “Cybonto core.”

Cybonto chooses MITRE's ATT&CK framework [56] as the main taxonomy for malicious behaviors under both Person and Group classes. The ATT&CK framework has always been in active development and has been widely endorsed by the cybersecurity community members. The main ATT&CK behavioral categories of malicious behaviors are recon, develop resources, acquire initial access, execute, persist, escalate privilege, evade defense systems, acquire credential access, discover, move laterally, collect, command and control, exfiltrate, and cause impacts [56].

Cybonto choose MITRE's Structured Threat Information eXpression (STIX) to describe Asset subclasses and malicious campaigns under Group Activity. STIX subclasses are STIX Tools, STIX Malware, STIX Vulnerability, Cybox, and STIX Campaign [57]. STIX Tools describe legitimate software tools that can be leveraged by malicious actors to perform attacks. STIX Malware describes malicious programs that can compromise the confidentiality, integrity, or availability of the victims' data. STIX Vulnerability describes vulnerabilities in legitimate software programs that can be exploited by malicious actors. Cybox—Cyber Observable eXpression—is a standardized language for describing cyber observables such as accounts, files, disks, devices, sessions, etc. STIX Campaign falls under the Group Activity subclass and describes specific sets of malicious behaviors that involve specific sets of targets, periods, and goals.

The use of "Group," "Asset," and their subclasses depends on each use case. For example, postarrest investigators may be only interested in Person and Asset classes to answer questions such as "Why did a hacker choose to attack a certain system and not others?" whereas threat intelligence teams may be interested in Person, Asset, Group, and other classes. In other words, usages of classes other than Person are nonconclusive and are subjected to inclusions or exclusions per each use case.

Figure 1. Cybonto's main hierarchies. BFO: Basic Formal Ontology; MF: Mental Functioning.



Ranking Cybonto Core Constructs by Network Centrality Algorithms

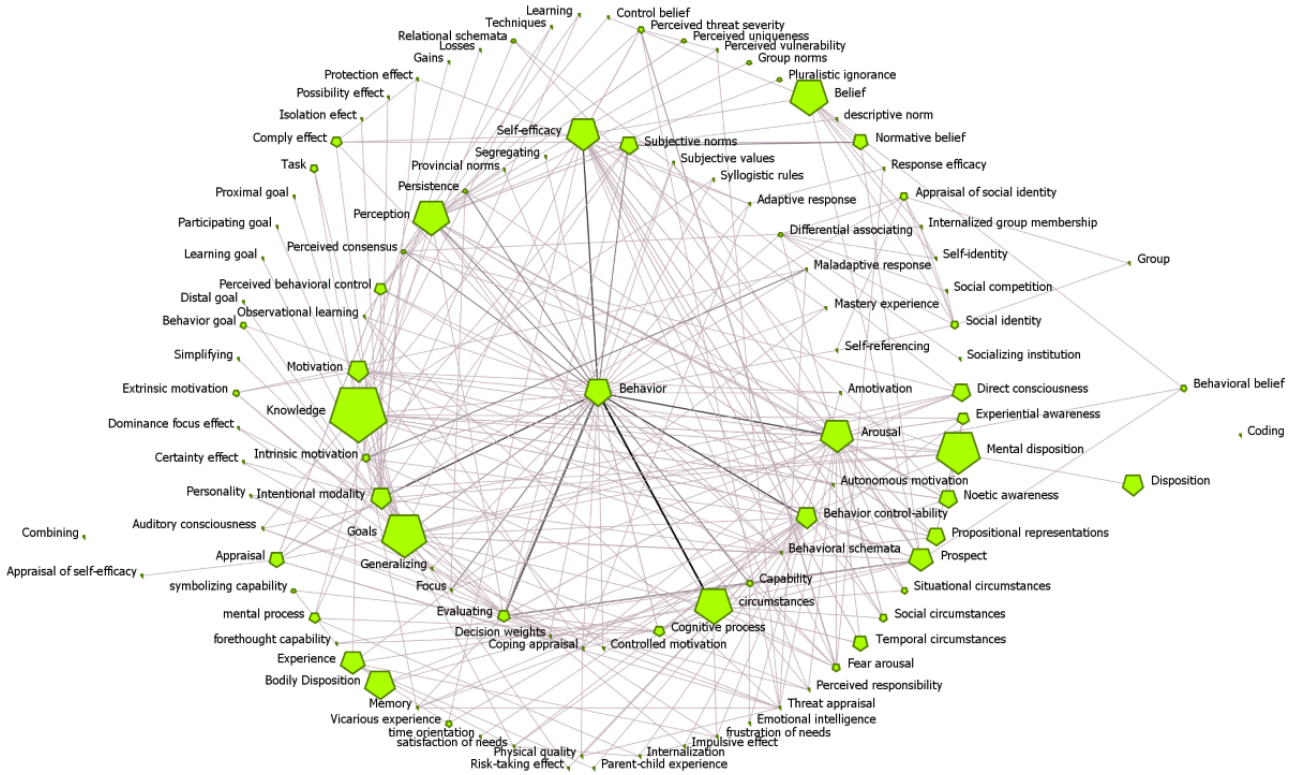
Figure 2 shows the network of Cybonto core's horizontal relationships. Constructs are nodes and the "influence" relationships are the edges. Each node's size equals the log scale of the node's page rank. A darker link color indicates a higher link value. Nodes were automatically arranged in a multi-circle layout with higher betweenness centrality (BC) nodes closer to the center. Key centrality metrics will be briefly described as follows.

Top authority centrality (AC) constructs receive influence from constructs that have the most influence on others. Top BC constructs are the ones that sit in the shortest paths among other constructs. BC constructs can serve either as bridges or gatekeepers of other constructs and processes. Top Eigenvector centrality (EC) constructs are the leaders of their cliques. A clique is a group of constructs in which each member has relationships with the others. In the context of the cognitive digital twin, a clique may represent a strong cognitive or behavioral pattern. Not only the top EC constructs are well-connected with their clique members, but also they also have relationships with other cliques.

Contribution centrality is EC on inverse-Jaccard weighted values of the input networks. A link between two constructs has the most contribution weight when the neighbors of one end are most different from the neighbors at the other end. Degree centrality (DC) has two submeasures—out-degree and in-degree. Top out-degree centrality constructs have the most out-links (influencing) to others while top incoming centrality constructs are influenced by the most important incoming neighbors. The

top PageRank constructs have relationships with the most influential neighbors whether it is incoming or outgoing.

Figure 2. Cybonto "influence" relationships visualized.



Results

The top 10 constructs across 20 network centrality measures are Behavior, Arousal, Goals, Perception, Self-efficacy, Circumstances, Evaluating, Behavior-Controllability, Knowledge, and Intentional Modality. Figure 3 shows the most influential constructs based on 6 different network centrality scores.

Table 2 presents top constructs' specific fitted scores for 4 centrality categories. Depending on which centrality scores were chosen, there are differences in the ranking of constructs as is observable by comparing results in Figure 3 and Table 2. However, the differences are light. For example, most of the top constructs listed in Figure 3 remain within the top 20 with different reasonable choices of centralities.

A comprehensive report with scores, unscaled scores, and statistics across twenty network centrality scores are available at Cybonto-1.0 GitHub repository [53].

Among the top 9 most influential constructs shown in Figure 3, only Behaviors, Goals, Perception, Evaluating, and Knowledge are parts of existing digital cognitive architectures, and in most cases, are not explicitly implemented. It is possible that before this study, influential cognitive structures have been studied per independent use-cases and thus could not collectively attract attention from conservative cognitive system designers. Now with a birds-eye view across 20 behavioral theories, these top 10 constructs deserve better attention.

Within cognitive architectures, we may consider implementing Goals, Knowledge, Perception, and Evaluating explicitly and with finer granularity. For example, Perception is more than short-lived sensory perception. Alice perceives Bob as a nice guy, and such perception may persist even when Bob is no longer there with Alice. Finer structures mean more symbolic labels or more nodes in the knowledge graph and may lead to improvements such as more diverse rule firing mechanisms and more explainable information decay.

Additionally, we should consider adding Arousal and Intentional Modality. Although Arousal is a noncognitive construct, it is ranked in second place and influences several cognitive constructs within the top 10, such as Evaluating and Intentional Modality. Unfortunately, the current state of research regarding Arousal as a part of a digital cognitive process is almost nonexistent. SOAR-related research results show a few papers studying the effects of general emotions. ACT-R research repository shows just 4 papers studying the effects of Arousal on memory management.

Circumstance is another noncognitive construct with a significant influence on behavioral outcomes. The paper recommends expanding the existing Mental Image module in existing cognitive architectures to include nonphysical environment variables such as urgency, group dynamics, and social sentiments. Finally, the paper recommends a new component—Imagining—to enable the HDT to run its own situational simulations and reason about possible circumstances.

Figure 3. Most influential constructs.

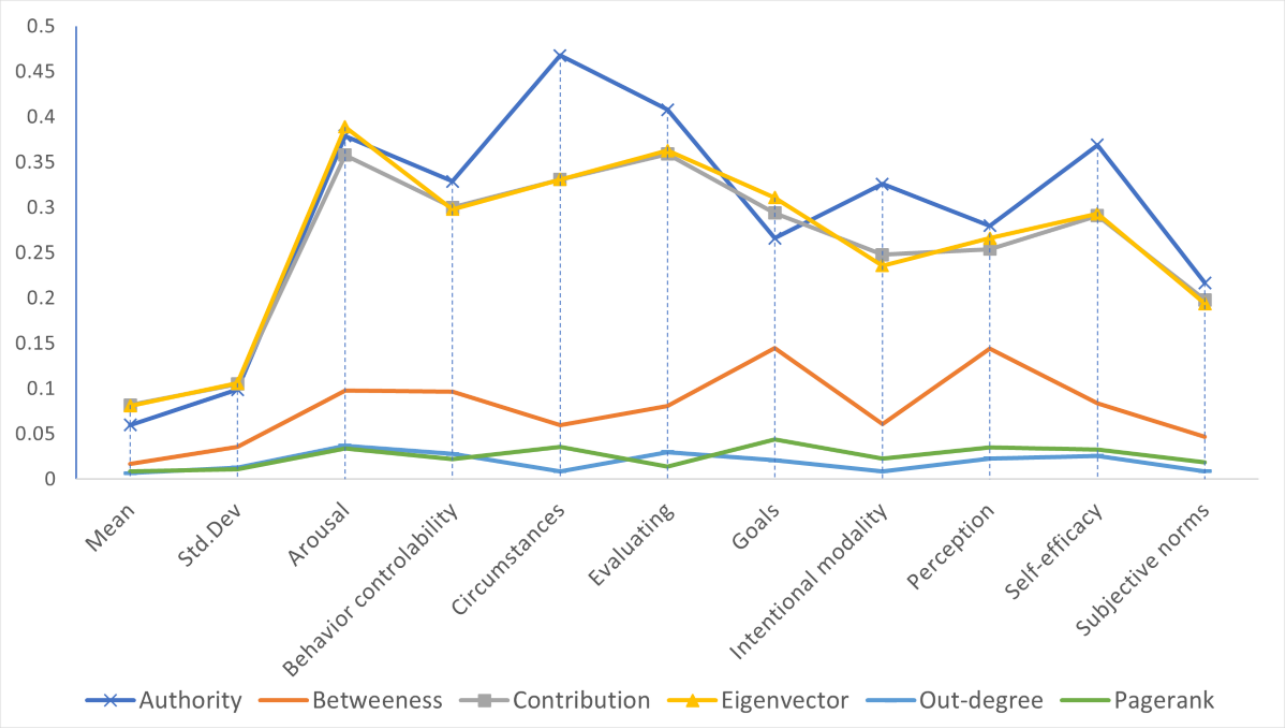


Table 2. Top constructs and their fitted key scores.

Constructs	Fit PR[a]	Fit EC[b]	Fit BC[c]	Fit DC[d]	Total
Behavior	10	10	10	5.333333	35.33333
Self-efficacy	2.978651	4.09735	5.791371	10	22.86737
Arousal	2.45894	6.494922	3.033944	8	19.98781
Goals	2.095989	4.048915	3.31916	6.666667	16.13073
Prospect	1.609572	2.008954	3.335824	8.666667	15.62102
Evaluating	3.373531	5.205153	2.811666	4	15.39035
Circumstances	2.225146	2.591971	2.975886	6.666667	14.45967
Behavior controllability	1.079106	1.051652	2.320296	6.666667	11.11772
Differential associating	1.938038	1.952155	4.191495	2.666667	10.74835
Knowledge	0.971335	3.448437	0.799434	5.333333	10.55254
Perception	1.933234	2.995944	1.233271	4	10.16245
Protection effect	3.419006	0.956777	1.811712	2	8.187495
Noetic awareness	0.800599	2.70121	0.248913	3.333333	7.084055
Intentional modality	0.948893	1.585625	0.357986	4	6.892503
Behavioral schemata	1.354209	4.679314	0.091006	0.666667	6.791195
Propositional representations	0.70164	2.70121	0.04671	3.333333	6.782894
Satisfaction of needs	0.381798	1.190226	1.13073	4	6.702753
Cognitive process	1.554735	2.509832	0.514903	1.333333	5.912803
Persistence	0.647449	2.104271	0.172818	2.666667	5.591204

[a]Fitted page rank.

[b]Fitted Eigenvector centrality.

[c]Fitted betweenness centrality.

[d]Fitted degree centrality.

Discussion

Principal Findings

Out of 108 psychology constructs, the top 10 are Behavior, Arousal, Goals, Perception, Self-efficacy, Circumstances, Evaluating, Behavior-Controllability, Knowledge, and Intentional Modality. In this list, only Behaviors, Goals, Perception, Evaluating, and Knowledge are parts of existing digital cognitive architectures. Notably, some of the constructs are not explicitly implemented. Early usability tests also demonstrate that Cybonto can be useful in other immediate uses such as manual analysis of hackers' behaviors and automatic analysis of behavioral-cybersecurity knowledge texts.

Usability Testing

Manual Analysis of Hackers' Behaviors

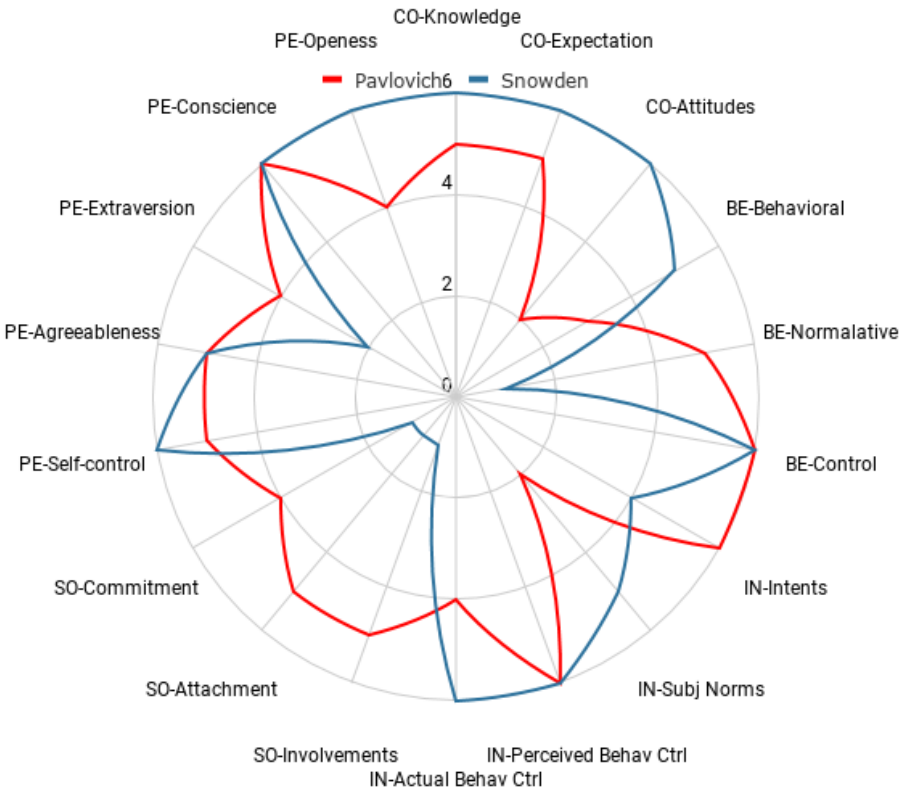
The main goal of Cybonto is to provide one more reason for pushing current cognitive system designs, which may appear distant to some audience. Hence, this paper aims to demonstrate that Cybonto can be immediately employed in current cybersecurity-related tasks. Manual analysis of malicious actors' behaviors is one essential task for cybersecurity intelligence gathering. It is also the first step in designing a virtual human digital twin of a real hacker. The demonstration is as follows.

A small group of cybersecurity professionals working in one of the US Federal Reserve Bank's branches participated in a Cybonto workshop. Group members had to choose either Snowden's biography or Pavlovich's biography as their reading assignment before the workshop. Both Snowden and Pavlovich are notorious cyber actors. In the workshop, participants were taught a simplified version of Cybonto. Notably, most of the members do not have a background in behavioral psychology. A table with columns of Knowledge, Expectation, Attitudes, Behavioral Belief, Normative Belief, Control belief, Intents, Subjective Norms, Perceived Behavioral Control, Actual Behavioral Control, Social Involvements, Social Attachment, and Social Commitment was provided. The goal was to have members establish a basic behavioral profile for each actor by filling values ranging from 0 to 6 in each of the table's columns.

Members of the group who read Snowden's biography book (the Snowden group) presented evidence for each column. The strength of evidence would determine the relevant column's score. Members in the other group (the Pavlovich group) may debate about the Snowden group's analysis and scoring. In the case of a stalemate, the author would assist with negotiating the scores. The same process was used for establishing Pavlovich's behavioral profile. The workshop lasted 2 hours and produced results shown in Figure 4.

Overall, this usability test has shown that (1) Cybonto can be friendly to the professionals who do not have a behavioral psychology background; (2) Cybonto is descriptive and can help with pointing out the behavioral differences between two distinct cyber actors; (3) Cybonto is consistent so that consensus in a manual analysis of cyber actors can be reached within a reasonable amount of time.

Figure 4. Behavioral differences between Snowden and Pavlovich. BE: belief; CO: cognitive; Ctrl: control; IN: intentions; SO: social bonds; PE: personality.



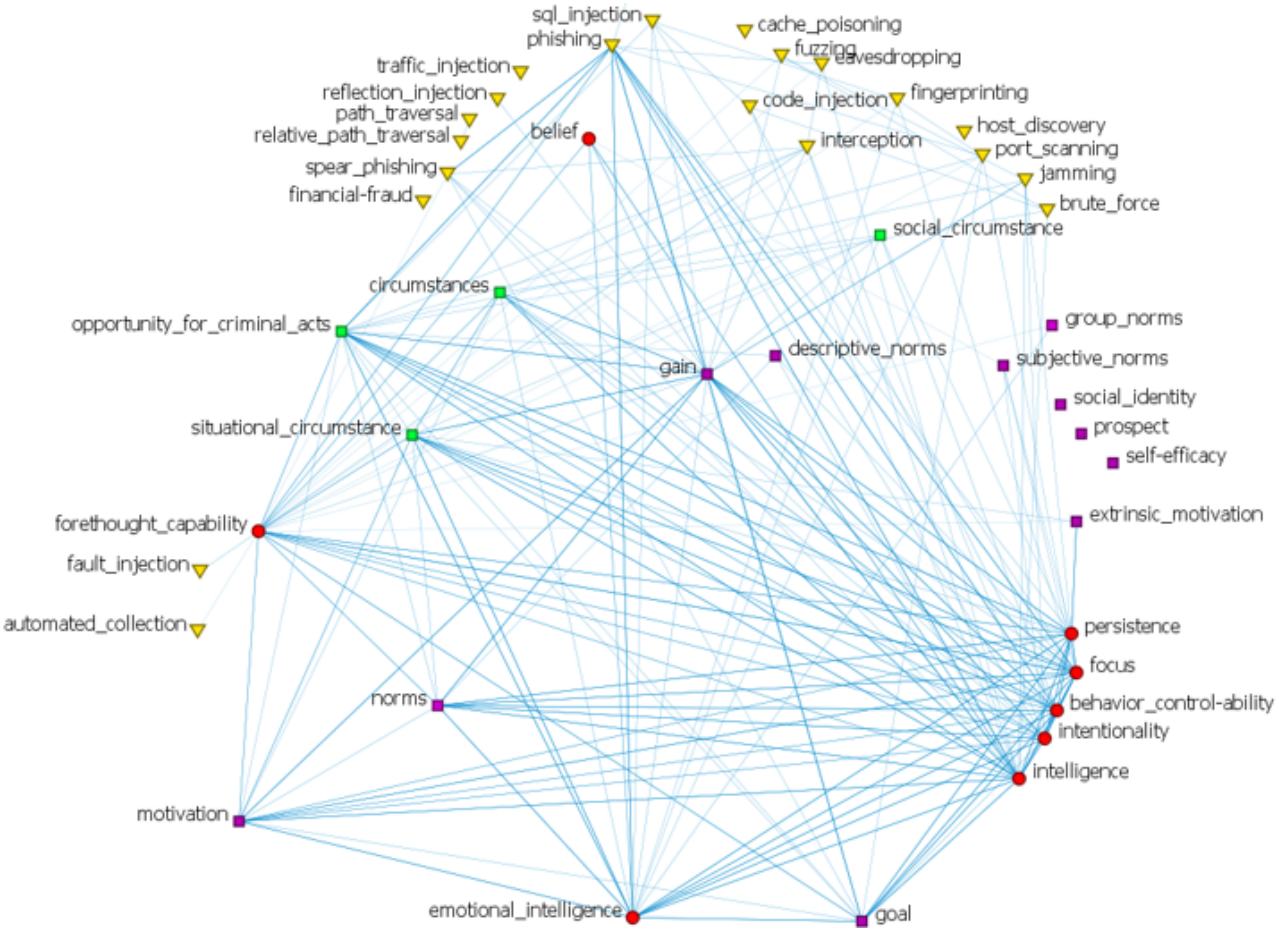
Analysis of Behavioral Cybersecurity Research Papers

Cybonto can also be used in machine learning–assisted domain knowledge analysis. For a demonstration, more than 3000 full texts of behavioral cybersecurity research within the past 5 years were downloaded from Google Scholar. A total of 2380 PDF files were selected and converted to plain text files. Natural language processing techniques were deployed on the text files and produced a concept list. The automatically generated list was then manually inspected and mapped into corresponding Cybonto constructs. A meta-network of related Cybonto's constructs in each document was generated. Then, analysis was carried out on a unionized meta-network of all document-level meta-networks.

Figure 5 provides a snapshot of the result with the following observations. Gain appears to be the most discussed construct with healthy connections to construct groups of attacks (yellow triangles), circumstances (green squares), and personality (red dots). Most studies focused on the direct relationships between the attacks and hackers' personalities. A much lower number of studies focused on how circumstances may directly influence malicious behaviors.

Overall, this simple experiment shows that Cybonto can be used to automatically analyze texts within the intersection of behavioral psychology and cybersecurity. Analyzed results may provide insights such as knowledge gaps and imbalance. Such interdisciplinary capabilities can be beneficial to teams with limited expertise. Future general artificial intelligence agents may also leverage Cybonto for their automatic knowledge analysis and acquisition.

Figure 5. Analysis snapshot of behavioral cybersecurity research papers within the past 5 years.

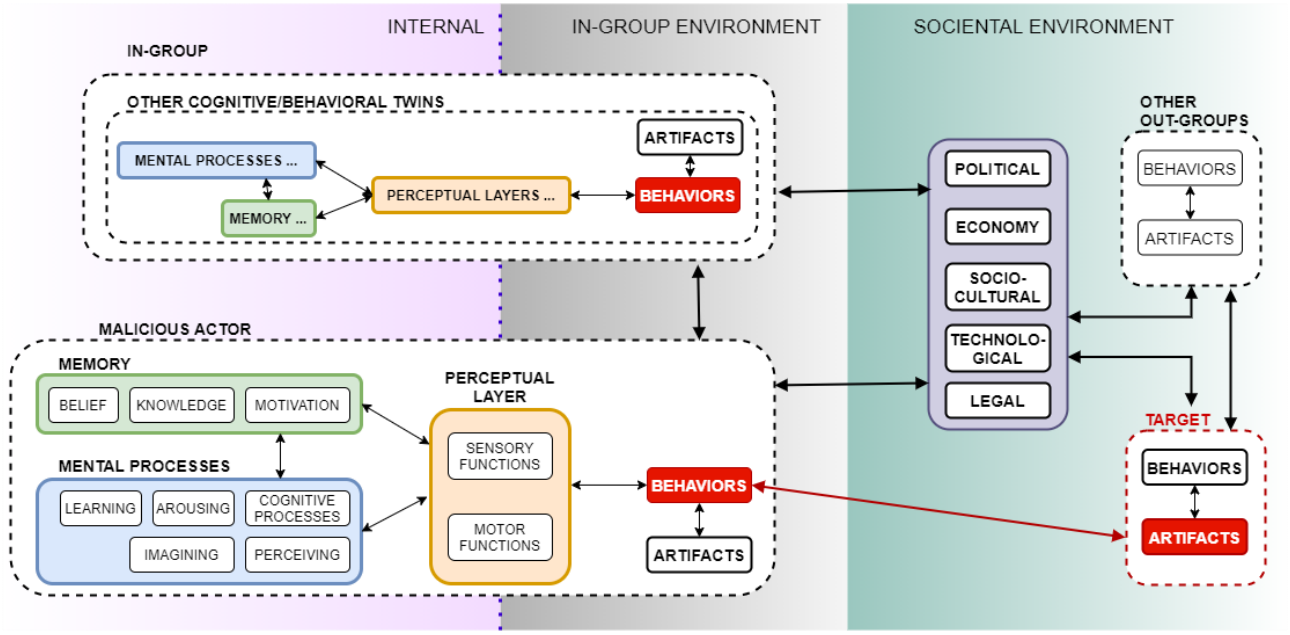


Expanding the Vision With The Cybonto Conceptual Framework

The novel Cybonto conceptual framework aims to provide general directions on answering the previously mentioned questions regarding the vision of DTs and HDTs for cybersecurity. The framework targets the cognitive process of a malicious actor as an HDT within a DT system. Cognitive space is defined by the behavioral or cognitive component of the Cybonto ontology. The action space is limited by the HDT's set of encoded actions, its ability to improvise new moves, and the other DTs' interaction interfaces.

The Cybonto conceptual framework was formed upon analysis of the Cybonto ontology. Figure 6 presents the Cybonto conceptual framework with 3 environment types and four groups of digital twins.

Figure 6. The Cybonto conceptual framework.



The internal environment (INE) is private to each DT. It contains both cognitive components and noncognitive components. Opposite to the internal environment is the societal environment (SOE) where everything is public. In between, the in-group environment (IGE) connects INE with SOE. All environments follow the Bronfenbrenner Ecological System Theory [58], which describes influences as progressive, varying, and reciprocal forces among individuals and environments. For example, a seemingly distant public event may still be able to affect certain private mental processes.

The IGE and the SOE are relative to the malicious HDT. The IGE is equivalent to the Bronfenbrenner Micro and Meso systems. The microsystem is the most influential external environment with members such as family, close friends, school, lovers, and mentors. SOE is equivalent to the Bronfenbrenner Exo, Macro, and Chrono systems. The Cybonto conceptual framework requires four representatives from 4 DT groups. We need one attacker HDT and one defender HDT. Unlike traditional models to which data and feature specifications were explicitly fed, an attacker HDT must collect the data by itself. Group-related data cannot be inferred if the fundamental group structure is not met. Hence, we then need at least two more DTs to present IGE and SOE identities.

An HDT can perform two main types of behaviors: the artifact-creating or -altering behavior and the nonartifact behavior. An artifact can range from a piece of code to a complex noncognitive digital twin. Viewing a malware's codes is a nonartifact behavior, while running the codes can be an artifact-altering behavior if the codes make changes to other artifacts. The perceptual layer sits on the border between the internal and external environments (IGE and SOE). Different perceptual layers in combination with different cognitive systems will have different perceptions of the same data streams. Refined perceptions constitute only a small part of a digital cognitive system. The Cybonto ontology details thousands of cognitive paths for processing initial perceptions. The result of a cognitive processing chain will be either a nonartifact behavior or an artifact-creating or -altering behavior. The behaviors (data streams) will be observed by other HDTs, and a new round of feedback loops begins. It is essential to note that a behavior can be kept secret within the in-group environment.

In this framework, (1) HDTs have the complete freedom to interact with other DTs per published protocols, and automatically seek whatever data are made available to them. (2) By releasing their behaviors, HDTs generate new data, which may then be consumed by other HDTs. (3) The cognitive architecture within each HDT determines its cognitive capabilities, which should include awareness and adaptation. (4) Cybonto DT simulation's objectives should be more about discovering new knowledge (the *why* and *how*) rather than mining specific data (the *what*).

Limitations

The biggest internal threat to validity is the maturation of the Cybonto ontology. The current Cybonto version should be treated as the "alpha release," and numerous development steps will be needed. First, the mapping of each theory to triplets of (construct, influence, and construct) must be cross-checked by more psychologists. Second, missing and duplicated constructs must be identified by careful vetting and deliberations. Finally, ontology testing steps must be carried out. The risk of bias theory selection should be minimal as more theories will be incorporated over time.

The biggest external threat to validity is the various implementations of Cybonto. Understandably, solution developers should only implement the Cybonto constructs that are needed for solving their practical problems. In other cases, solution developers must add new constructs that were not packaged with Cybonto. Uncareful addition and removal of constructs may weaken Cybonto integrity leading to faulty performance. Additionally, certain feedback loops must exist for certain psychology or cognitive paths to "fire." For instance, an HDT may need to gather enough information about a situation from other HDTs and DTs before it can reason about

the situation. Hopefully, the proposed Cybonto Conceptual Framework will help with minimizing these external threats to validity.

Prior Work

Booker and Musman [59] indicated that human-in-the-loop cybersecurity responses are slow because cyberattacks happen at a higher speed than human decision-making. Therefore, we need autonomous agents of which behaviors are aligned with the defenders' understanding of related business aspects and preferences. The author framed the problem as a partially observable Markov decision problem, in which "Belief" is the probability of being in a particular state, provided the agents know some past actions and observations. Without using a cognitive system, the work demonstrates the usefulness of autonomous agents for the task of finding out good defense strategies under developing attacks.

According to Francia et al [60], predicting the outcomes of risky behaviors in cyberspace is challenging owing to sensitivity to initial conditions, occurrences of random events, and interactivity among different complex systems. The paper proposed agent-based modeling of entity behavior in cybersecurity as one solution. The study simulated different scenarios of computer virus spread. Simulation parameters are the sophistication of hackers' attacks, trust level, defenders' level of training, and quality of cyber defense. Although the study is a work in progress, it demonstrates the mechanisms and the benefits of having opposed autonomous agents interact with each other. From another angle, Metge et al [61] investigated the dynamic trust relationships among autonomous agents and human operators who are all on the same team. The paper emphasized the challenge of building the right autonomous agent's mental model, which is the first step in gaining human operators' trust. Autonomous agents need to be both able to provide sound solutions and to behave in ways that their human counterparts can trust.

Thomson et al [62] proposed ACT-R–based models as autonomous cybersecurity agents that can understand and augment human analysts. Interestingly, digital agents can detect bias in human teammates. The paper describes in adequate detail the working of ACT-R in 3 use cases of making sense of human decisions, cyber-deceptive signaling defense, and malware detection. In another study, Golovianko et al [63] used Pi-Mind and adversarial machine learning to clone image classification cognitive capabilities of human participants. The study also reviewed important concepts such as top-down cognitive twin cloning via explicit transfer of knowledge, bottom-up cloning via machine learning or deep learning, and individual and group cloning. Notably, the study considers autonomous agents as "cognitive clones" or "cognitive twins," all of which can act like the human counterparts in both business-as-usual situations and critical situations. The results illustrate more stable performances of cognitive twins in stressful situations.

Conclusions

DCTs and HDTs are gaining popularity, but they are not necessarily new concepts. A good body of prior works involves "autonomous agents" with various applications in security and cybersecurity. However, autonomous agents have been designed in specific ways for solving specific problems. HDTs are fundamentally different from autonomous agents. Most HDTs consist of a cognitive system and a noncognitive system, and most cognitive systems can combine cognitive reasoning (symbolic) with deep learning models (subsymbolic). Furthermore, HDTs and DTCs should be able to perform in a much wider set of situations than autonomous agents as DCTs are parts of HDTs that are in turn a part of the Metaverse strategy. Once massive noncognitive digital twin systems transition to the internet, adding human cognitive digital twins will be the only logical next step.

The vision of letting human digital twins "run free" in connected digital twin worlds (the Metaverse) and observing them is realistic and offers a new paradigm in knowledge mining. The Cybonto conceptual framework demonstrates how such an ecosystem can be leveraged for shaping proactive cybersecurity defense strategies. In the context of studying malicious cybersecurity behaviors, the key is building a digital human cognitive twin that models well malicious hackers' cognitive patterns. Specifically, cognitive reasoning with adequate granularity and a well-designed ontology allows us to observe, understand, and—more importantly—explain the HDTs' behaviors. Hence, the paper also proposes the Cybonto ontology as a recommendation on how current cognitive systems can be extended.

Notably, medical researchers may take Cybonto core ontology and fit it to their applications such as virtual patients for applied psychology training, automatic behavioral annotations, analysis of electronic health records, and virtual agents for community psychology experiments. Future work may involve further framework development, fine-tuning and expanding the ontology, human cognitive cloning, and building different practical HDTs.

Conflicts of Interest

None declared.

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Abbreviations

AC: authority centrality
BC: betweenness centrality
BFO: Basic Formal Ontology
DC: degree centrality
DCT: Digital Cognitive Twin
DT: Digital Twin
EC: Eigenvector centrality
HDT: Human Digital Twin
IGE: in-group environment
INE: internal environment
MF: Mental Functioning
SOE: societal environment
STIX: Structured Threat Information eXpression

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Original Paper

The Association of Shared Care Networks With 30-Day Heart Failure Excessive Hospital Readmissions: Longitudinal Observational Study

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Abstract

Background: Higher-than-expected heart failure (HF) readmissions affect half of US hospitals every year. The Hospital Reduction Readmission Program has reduced risk-adjusted readmissions, but it has also produced unintended consequences. Shared care models have been advocated for HF care, but the association of shared care networks with HF readmissions has never been investigated.

Objective: This study aims to evaluate the association of shared care networks with 30-day HF excessive readmission rates using a longitudinal observational study.

Methods: We curated publicly available data on hospital discharges and HF excessive readmission ratios from hospitals in California between 2012 and 2017. Shared care areas were delineated as data-driven units of care coordination emerging from discharge networks. The localization index, the proportion of patients who reside in the same shared care area in which they are

admitted, was calculated by year. Generalized estimating equations were used to evaluate the association between the localization index and the excessive readmission ratio of hospitals controlling for race/ethnicity and socioeconomic factors.

Results: A total of 300 hospitals in California in a 6-year period were included. The HF excessive readmission ratio was negatively associated with the adjusted localization index (β=–.0474, 95% CI –0.082 to –0.013). The percentage of Black residents within the shared care areas was the only statistically significant covariate (β=.4128, 95% CI 0.302 to 0.524).

Conclusions: Higher-than-expected HF readmissions were associated with shared care networks. Control mechanisms such as the Hospital Reduction Readmission Program may need to characterize and reward shared care to guide hospitals toward a more organized HF care system.

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KEYWORDS

patient readmission; quality assurance; health care; catchment area; health; community networks; regional medical programs

Introduction

Higher-than-expected heart failure (HF) readmission impacts approximately half of US hospitals every year, and almost every hospital has experienced it at least once in the period between 2012 and 2017. By 2030, HF is projected to affect at least 8 million people in the United States, with an incidence of 21 per 1000 people older than 65 years and an estimated cost of US $69.8 billion [1]. The number of patients with HF receiving HF care and requiring advanced HF therapies such as left ventricular assisted devices (LVADs) will increase exponentially [2]. Addressing higher-than-expected HF readmissions for patients with HF is needed as demand increases, with the aging population requiring improved care coordination mechanisms that promote a more organized HF care system [3].

HF is managed through a complex system that serves both affluent and vulnerable patient populations, and encompasses nonlinear interactions among primary care, general cardiology, specialized HF clinics, and tertiary and quaternary centers. The implementation of any control mechanism can produce unintended consequences if the complexity of the HF care system is not taken into consideration [4,5]. Systemwide control programs such as the Hospital Reduction Readmission Program (HRRP) [6] may be a first step toward organizing the HF care system. Nonetheless, they will continue to create unintended consequences and penalize hospitals for factors beyond their control [7] unless these programs specifically foster care coordination mechanisms capable of promoting organization for HF care's complex system.

Shared care integrates primary, secondary, and tertiary levels of care [8], and has been advocated as a necessary model to promote a more organized HF care system [9] such as the spoke-hub-and-node model [10]. Shared care has been studied among chronic diseases [11], including HF [12], but only recently has it been advocated for by international working groups as a way to organize HF care [9], particularly among patients with advanced HF [10] such as patients with LVAD support [13]. Shared care areas (SCAs) are data-driven units of care coordination captured from large-scale data on hospital discharges to patient residencies, and SCAs may explain variation in medical adherence to HF guideline-directed medical therapy [14]. The localization index (LI) of an SCA is the proportion of patients who reside in the same SCA they are admitted and is a measure of local care coordination commonly used to evaluate SCAs [15]. This study aims to evaluate the longitudinal association between higher-than-expected HF readmissions and the LI of SCAs both unadjusted and adjusted for racial/ethnic and socioeconomic factors.

Methods

This methods section was written according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) standard of writing.

Study Design, Study Setting, and Participants

This is an observational longitudinal study. All data used in this study are made publicly available by the HRRP and Office of Statewide Health Planning and Development (OSHPD). The study setting was hospitals in California during the period from 2012 to 2017. Participants were all in hospitals reported in the HRRP [6]. The eligibility criteria were as follows: at least 2 repeated measures of higher-than-expected HF readmission in the HRRP and availability of discharge data from the OSHPD [16]. These criteria enabled carrying out a longitudinal study that requires repeated measures and linking data from the HRRP with date from OSHPD. Between 233 and 237 hospitals in California were included depending on the year. Ethical approval was unnecessary because all data were at the hospital level and already made publicly available from both HRRP and OSHPD. All code, processed data, built networks, and data analysis resulting from this study are available on the Open Science Framework repository for this study [17].

Study Outcome

The main study outcome was hospital excessive readmission ratio (ERR), which is a risk-standardized 30-day readmission ratio that adjusts for a set of patient-specific covariates such as congestive HF, renal failure, and chronic obstructive pulmonary disease [18]. It is used by the HRRP to assess excess hospital readmissions and calculate hospital penalties [6]. The ERR is calculated by dividing the predicted readmissions by the expected readmissions. Using a hierarchical generalized linear model, both predicted and expected readmissions are estimated using an adjusted average intercept over all hospitals, but predicted readmissions, in addition, are estimated using a hospital-specific intercept deviation from the adjusted average intercept over all hospitals. Such methodology, well documented

in the Condition-Specific Readmission Measures Updates and Specifications Report from the Centers for Medicare & Medicaid Services [18], makes the ERR an appropriate instrument for comparing hospitals within and between years.

Study Variables

The main study variable was the LI, which represents the proportion of patient discharges from hospitals within the same SCA of which these patients live [19,20]. A higher LI represents a homogenous SCA with localized care coordination (ie, patients tend to receive care where they live). Other study variables were the proportions of residents who were Black, Hispanic, had poverty status, and had private insurance as determined by the American Community Survey [21].

Data Sources

The ERR data used in this study was made publicly available from the HRRP [6]. The ERR data of each year in the period from 2012 to 2017 (ie, fiscal year 2014 and 2019) was separately downloaded from HRRP and compiled into a single file. The Patient Origin/Market Share data was made publicly available from the OSHPD [16]. Patient Origin/Market Share data are aggregated numbers of emergency department (ED) discharges among zip codes of hospitals and patient residencies. Zip Codes were converted to the Zip Code Tabulation Areas (ZCTAs) using the Zip Code to ZCTA Crosswalk made publicly available by the Uniform Data System [22]. Demographic data was gathered for the state of California from the American Community Survey [21].

Uncovering Shared Care Areas and Localization Index From Hospital-Patient Discharge Data

Six yearly hospital-patient discharge networks were built from OSHPD hospital-patient ED discharges between 2012 to 2017. In a hospital-patient discharge network [15], a node is the ZCTA of a hospital or patient residency, and the link between two nodes (ie, ZCTAs) is the total number of ED discharges. For each yearly hospital-patient discharge network, SCAs were delineated using community detection algorithms. Each delineated SCA consists of a set of ZCTAs in which hospitals are embedded. A set of four diverse community detection algorithms were considered to decrease both variability and bias [23]. The algorithms were Louvain [24] with resolution equal to 1, Stochastic Block Model [25,26] with degree corrected, Infomap [27] with two levels, and Speaker-Listener Label Propagation [28] with postprocessing threshold equal to 0.5

Statistical Analysis

The ERR hospitals and the LI of SCAs were integrated at each year by linking the ZCTAs of hospitals and SCAs (Table S1 and Figure S1 in Multimedia Appendix 1). A longitudinal regression was specified in which the dependent variable ERR of a hospital at time *t* as a function of the LI of its SCA at time *t*. We used a generalized estimating equation (GEE) using a Gaussian family and an exchangeable working correlation structure to account for multiple observations of ERR from the same hospital across years and SCAs [29]. The estimated regression coefficients (beta) were used to measure unadjusted associations between the dependent and independent variables, and adjusted associations after controlling for racial/ethnic and socioeconomic confounders associated with HF readmission at the regional level [30]. The GEE was estimated using the Statsmodels Python package [31]. Additionally, hospitals were stratified based on quartiles of the LI and all covariates that were found statistically significant, and median values of ERRs and percentage of hospitals penalized were calculated for each quartile (Q1, Q2, Q3, Q4). We estimated 95% CIs using 10,000 bootstrap samples with replacement from each quartile, the estimation of CIs for medians using the Bootstrapped Python package [32].

Predicting Higher-Than-Expected Heart Failure Readmissions for Changes in Localization Index

The estimated GEE model was used to predict HF's ERRs assuming a range of changes in the LI in SCAs with distinct percentages of Black residents, the only statistically significant covariate. The differences in the LI between subsequent years were calculated for all hospitals. The 25th, 50th, and 75th percentiles were separately calculated for both positive (+q1, +q2, and +q3) and negative (–q1, –q2, and –q3) differences. The SCAs were stratified by quartiles of Black residents (Q1, Q2, Q3, and Q4). The ERR was predicted using the GEE model after each positive and negative percentile difference in the LI was applied to the stratified SCA data.

Results

Descriptive Statistics of Heart Failure Hospital Readmissions in the United States and California

The ERR is calculated every year by the HRRP for the approximately 2700 to 2900 hospitals in the United States, from which 233 to 237 hospitals are from California (Table 1). Overall, approximately half of US hospitals are penalized, and this percentage has not changed during the study period between 2012 to 2017. The ERR (and the percentage of hospitals penalized) of US hospitals have remained approximately constant during the study period, from 1.0013 (49.76%) in 2012 to 1.0016 (48.94%) in 2017. The ERR (and the percentage of hospitals penalized) of hospitals in California increased from 0.9914 (49.36%) to 1.0087 (56.12%). In 2017, the percentage of hospitals penalized in California (56.12%, 95% CI 49.75%-62.29%) is slightly higher than that among all hospitals in the United States (48.91%, 95% CI 47.06%-50.76%). Although not statistically significant, the ERR SD appears to be decreasing over the years.

Table 1. Descriptive statistics of excessive readmission ratio (ERR) and percentage of hospitals penalized in the United States and California.

Region	2012	2013	2014	2015	2016	2017
United States						
Hospitals, n	2864	2860	2825	2820	2827	2793
Hospitals penalized (%)	49.76	48.95	49.17	49.22	49.45	48.94
ERR	1.0013	1.0012	1.0010	1.0012	1.0018	1.0016
ERR SD	0.0844	0.0809	0.0803	0.0774	0.0776	0.0753
California						
Hospitals, n	233	233	233	233	237	237
Hospitals penalized (%)	49.36	48.50	56.22	55.79	51.90	56.12
ERR	0.9914	0.9963	1.0034	1.0057	1.0049	1.0087
ERR SD	0.0761	0.0778	0.0760	0.0731	0.0720	0.0703

Association of the Excessive Readmission Ratio and Localization Index

The results of the quartile analysis indicate that the ERR of hospitals was negatively associated with the LI (Table 2) as well as with the percentage of Black residents (Table 3). In 2017, for instance, the ERR of hospitals in SCAs with the lowest quartile (Q1) of the LI was 1.03 (95% CI 1.02-1.04) with 65.7% (95% CI 59.4%-72.0%) of hospitals penalized. In SCAs with the highest quartile (Q4) of the LI; however, the median ERR was 0.98 (95% CI 0.97-0.99) with only 43.1% (95% CI 35.3%-51.0%) of hospitals penalized. From 2012 to 2017, the disparities between the ERR and percentage of hospitals penalized among SCAs belonging to the lowest (Q1) and highest LI (Q4) quartiles has increased mainly because of increases in the ERR and percentage of hospitals penalized within SCAs in the lowest LI quartile (Q1). Similarly, in 2017, the ERR of hospitals in SCAs with the lowest quartile (Q1) of Black residents was 0.99 (95% CI 0.98-1.0) with 45.2% (95% CI 38.2%-52.2%) of hospitals penalized. In SCAs with the highest percentage of Black residents quartile (Q4), however, the median ERR was 1.03 (95% CI 1.02-1.04) with 67.6% (95% CI 60.7%-74.6%) of hospitals penalized. The percentage of Black residents is slightly higher in SCAs with lower localization (Table S4 in Multimedia Appendix 1). The results of the regression analysis (Figure 1 and Table 4) indicate that the ERR of hospitals was negatively associated with the adjusted and unadjusted LI of their SCAs (eg, ERRs were lower when hospitals were located in SCAs where more patients received care close to where they resided) according to both unadjusted (β=–.0717; P<.001) and adjusted (β=–.0495; P=.049) coefficients when the regression was controlled for racial/ethnic and socioeconomic covariates. The percentage of Black residents in the SCA was the only covariate with a statistically significant association according to the regression coefficient (β=.3892; P<.001). The results can be separately analyzed for each community detection algorithm (Table S3, Multimedia Appendix 1), and the Stochastic Block Model uncovered SCAs with the LI anomalously lower and was not considered in the final analysis. The results can be separately analyzed for each community detection algorithm for ERR (Table S5 in Multimedia Appendix 1), percentage of hospitals penalized (Table S6 in Multimedia Appendix 1), and the percentage of Black residents (Table S7 in Multimedia Appendix 1).

Table 2. Excessive readmission ratios (ERRs) for hospitals in California by the localization index (LI) quartile.

LI[a]	2012 (95% CI)	2013 (95% CI)	2014 (95% CI)	2015 (95% CI)	2016 (95% CI)	2017 (95% CI)
ERR[b]						
Q1	1.0 (0.99-1.01)	1.0 (0.99-1.01)	1.01 (1.0-1.02)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.03 (1.02-1.04)
Q2	1.0 (0.99-1.01)	1.01 (1.0-1.02)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.01 (1.0-1.02)	1.01 (1.0-1.02)
Q3	0.99 (0.97-1.0)	1.0 (0.98-1.01)	0.99 (0.98-1.0)	1.0 (0.99-1.0)	0.99 (0.98-1.0)	1.0 (0.99-1.02)
Q4	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.99 (0.98-1.0)	0.99 (0.98-1.0)	0.99 (0.98-1.0)	0.98 (0.97-0.99)
Hospitals penalized (%)						
Q1	53.24 (45.61-60.82)	50.58 (43.02-58.14)	62.09 (54.6-68.97)	67.0 (59.66-73.86)	60.63 (53.88-67.78)	65.69 (59.42-71.98)
Q2	53.13 (46.39-60.31)	52.75 (45.34-60.25)	67.07 (59.63-74.53)	58.85 (51.27-66.46)	54.1 (47.03-61.08)	58.17 (50.85-65.54)
Q3	45.02 (37.32-52.82)	50.82 (43.65-58.01)	49.48 (42.39-56.52)	51.79 (44.67-58.88)	48.68 (41.53-55.74)	54.00 (46.55-61.49)
Q4	45.32 (38.54-52.6)	40.53 (33.51-47.57)	47.78 (40.56-55.0)	45.79 (38.1-53.57)	43.61 (36.2-51.53)	43.14 (35.29-50.98)

[a]CIs estimated by 10,000 bootstrap samples with replacement.

[b]Quartiles Q1 (0-25th), Q2 (25th-50th), Q3 (50th-75th), and Q4 (75th-100th).

Table 3. Excessive readmission ratios (ERRs) for hospitals in California by percentage of Black residents in the shared care area.

LI[a,b]	2012 (95% CI)	2013 (95% CI)	2014 (95% CI)	2015 (95% CI)	2016 (95% CI)	2017 (95% CI)
ERR[c]						
Q1	0.96 (0.95-0.97)	0.97 (0.96-0.98)	0.97 (0.96-0.98)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.99 (0.98-1.0)
Q2	0.99 (0.98-1.0)	0.99 (0.98-1.01)	1.0 (0.98-1.01)	1.0 (0.98-1.01)	1.0 (0.99-1.01)	1.0 (0.99-1.02)
Q3	1.0 (0.99-1.01)	1.0 (0.99-1.01)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.01 (1.0-1.02)	1.01 (1.0-1.02)
Q4	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.03 (1.02-1.04)	1.04 (1.03-1.05)	1.03 (1.02-1.04)	1.03 (1.02-1.04)
Hospitals penalized (%)						
Q1	33.34 (26.11-40.56)	36.65 (29.44-43.89)	36.65 (29.44-43.89)	33.89 (27.22-40.56)	38.13 (31.18-45.16)	45.17 (38.17-52.15)
Q2	50.82 (43.24-57.84)	48.09 (41.08-55.14)	50.85 (43.78-57.84)	54.57 (47.03-61.62)	52.48 (45.41-59.46)	52.99 (45.95-60.0)
Q3	53.05 (45.73-60.98)	55.49 (47.56-63.41)	65.84 (58.54-73.17)	68.28 (60.98-75.0)	59.94 (52.69-67.07)	59.9 (52.69-67.07)
Q4	61.14 (53.53-68.24)	54.69 (47.06-61.78)	73.47 (66.47-80.0)	68.22 (61.18-75.29)	58.42 (50.87-65.9)	67.64 (60.69-74.57)

[a]LI: localization index.

[b]CIs estimated by 10,000 bootstrap samples with replacement.

[c]Quartiles Q1 (0-25th), Q2 (25th-50th), Q3 (50th-75th), and Q4 (75th-100th).

Figure 1. Central illustration: association of heart failure excessive readmission with shared care networks. Hospitals are embedded in shared care areas (SCAs), which are data-driven units of care coordination emerging from the discharge networks among hospitals. The localization index is the proportion of patient discharges from hospitals within the same SCA in which these patients live. The heart failure ERRs of hospitals are associated with the SCA localization index in which they are embedded.

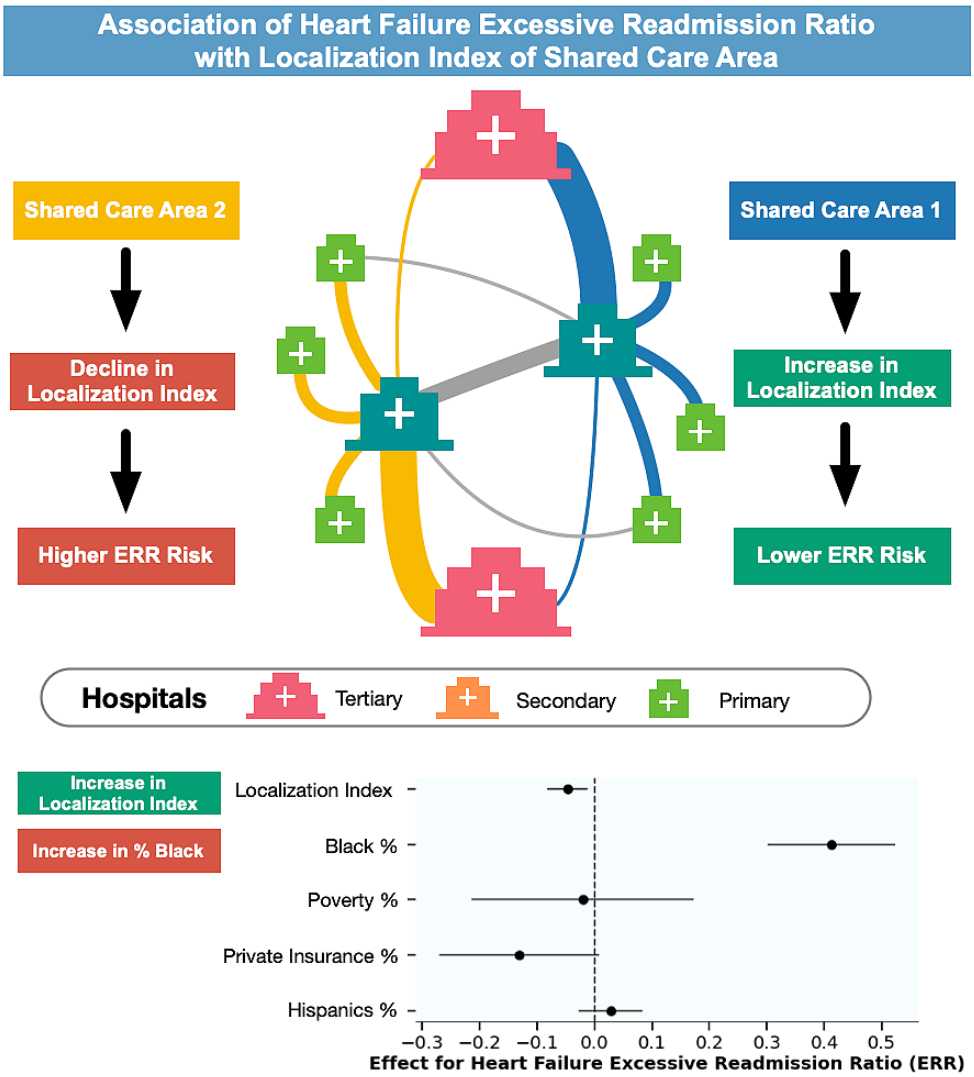


Table 4. Results of the generalized estimating equations regression for excessive readmission ratios.

Estimator	Coefficient (SE)	*z*	*P* value
Unadjusted model			
Intercept	1.0733 (0.014)	75.626	<.001
Localization index	–0.0722 (0.0170)	–4.2190	<.001
Adjusted model			
Intercept	1.1054 (0.067)	16.558	<.001
Localization index	–0.0474 (0.0180)	–2.6670	.008
% Black	0.4128 (0.0570)	7.2970	<.001
% poverty	–0.0208 (0.0990)	–0.2100	.83
% private insurance	–0.1317 (0.0710)	–1.8500	.06
% Hispanic	0.0278 (0.0290)	0.9710	.33

Predictions of Excessive Readmission Ratio Based on Changes in Localization Index

The predictions of ERRs and percentage of hospitals penalized based on changes in the LI (Table 5 and Figure 2) demonstrated the negative association with the LI of their SCAs as well as the positive association with the percentage of Black residents in the SCAs. The percentage range of Black residents in the stratified SCAs were 0.20% to 1.96% in Q1, 1.96% to 4.16% in Q2, 4.16% to 7.85% in Q3, and 7.85% to 17.6% in Q4. The quartiles in the LI for negative differences were –0.167 (–q3), –0.058 (–q2), and –0.015 (–q1); positive differences were 0.019 (+q1), 0.070 (+q2), and 0.179 (+q3). In Q1 and Q4, the estimated median ERR was 0.995 (95% CI 0.994-0.996) and 1.039 (95% CI 1.038-1.041), respectively, with 27.5% (95% CI 24.6%-30.4%) and 100% (95% CI 100%-100%) of hospitals penalized, respectively. If the LI decreases by –0.167 (ie, a –q3 LI change), the median ERR is predicted at 1.003 (95% CI 1.002-1.004) and 1.047 (95% CI 1.046-1.048) in Q1 and Q4, respectively, with 39.2% (95% CI 35.8%-42.4%) and 100% (95% CI 100%-100%) of hospitals penalized. Conversely, if the LI increases by 0.179 (ie, a +q4 LI change), the median ERR is predicted at 0.987 (95% CI 0.986-0.988) and 1.031 (95% CI 1.030-1.032) in Q1 and Q4, respectively, with 18.1% (95% CI 15.6%-20.8%) and 91.6% (95% CI 89.7%-93.4%) of hospitals penalized.

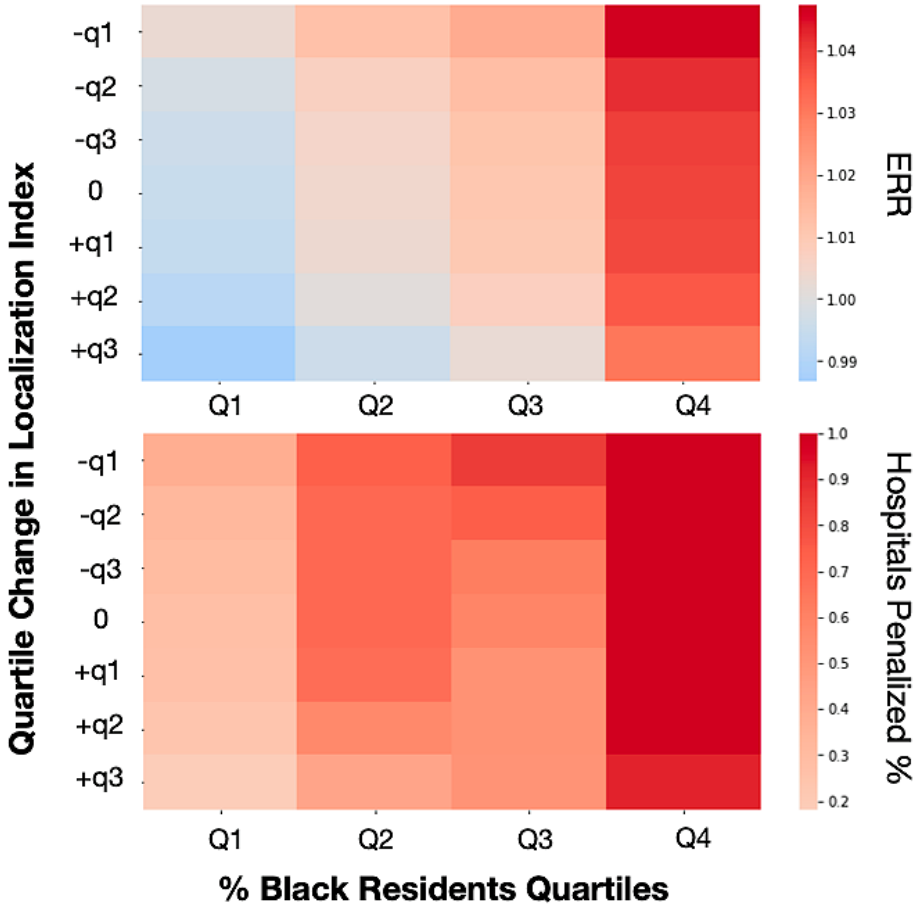
Table 5. Predictions of excessive readmission ratios (ERRs) and percentage of hospitals penalized based on changes in localization index (LI).

Change in LI[a]	% Black (Q1; 95% CI)[b]	% Black (Q2; 95% CI)[b]	% Black (Q3; 95% CI)[b]	% Black (Q4; 95% CI)[b]
ERR				
–q3	1.003 (1.002-1.004)	1.012 (1.011-1.014)	1.019 (1.018-1.02)	1.047 (1.046-1.048)
–q2	0.998 (0.997-0.999)	1.007 (1.006-1.008)	1.014 (1.013-1.015)	1.042 (1.041-1.043)
–q1	0.996 (0.995-0.997)	1.005 (1.004-1.006)	1.012 (1.011-1.013)	1.04 (1.039-1.041)
0	0.995 (0.994-0.996)	1.004 (1.003-1.006)	1.011 (1.01-1.012)	1.039 (1.038-1.041)
+q1	0.994 (0.993-0.995)	1.003 (1.002-1.005)	1.01 (1.009-1.011)	1.038 (1.037-1.04)
+q2	0.992 (0.991-0.993)	1.001 (1.0-1.002)	1.008 (1.007-1.009)	1.036 (1.035-1.037)
+q3	0.987 (0.986-0.988)	0.996 (0.995-0.997)	1.002 (1.001-1.004)	1.031 (1.03-1.032)
Hospitals penalized (%)				
–q3	0.392 (0.358-0.424)	0.736 (0.706-0.766)	0.856 (0.832-0.879)	1.0 (1.0-1.0)
–q2	0.323 (0.291-0.354)	0.707 (0.676-0.737)	0.744 (0.715-0.772)	1.0 (1.0-1.0)
–q1	0.299 (0.269-0.329)	0.704 (0.673-0.734)	0.624 (0.591-0.656)	1.0 (1.0-1.0)
0	0.275 (0.246-0.304)	0.704 (0.673-0.734)	0.592 (0.561-0.624)	1.0 (1.0-1.0)
+q1	0.273 (0.243-0.302)	0.686 (0.656-0.718)	0.524 (0.492-0.557)	1.0 (1.0-1.0)
+q2	0.242 (0.213-0.271)	0.574 (0.542-0.606)	0.525 (0.492-0.557)	1.0 (1.0-1.0)
+q3	0.181 (0.156-0.208)	0.432 (0.398-0.466)	0.519 (0.486-0.552)	0.916 (0.897-0.934)

[a]Changes in LI were measured as quartiles of negative differences (–q1, –q2, –q3), positive differences (+q1, +q2, +q3), and zero (no change).

[b]The quartile of % Black residents are Q1 (0 to 25th), Q2 (25th to 50th), Q3 (50th to 75th), and Q4 (75th to 100th).

Figure 2. Predictions of ERRs and percentage of hospitals penalized based on changes in localization index. The heart failure ERRs of hospitals are negatively associated with the localization index of the shared care areas (SCAs) in which they are embedded and positively associated with the percentage of Black residents within the SCA. The percentage of Black residents in SCAs were stratified into four quartiles: Q1 0.20%-1.96%, Q2 1.96%-4.16%, Q3 4.16%-7.85%, Q4 7.85%-17.6%. The quartiles in localization index differences were separately calculated for negative (–q1, –q2, –q3)=(–0.167, –0.058, –0.015) and positive (+q1, +q2, +q3)=(0.019, 0.070, 0.179) of localization index differences. ERR: excessive readmission ratio.



Discussion

Principal Findings

Regional variation in health care delivery is a ubiquitous phenomenon [3,19], and the HRRP may have differently impacted almost 3000 US hospitals depending on their state. The main finding in this study is that higher-than-expected HF hospital readmissions are associated with the share care networks in which hospitals are embedded. Specifically, hospitals within SCAs with a high LI are associated with lower ERRs than hospitals within SCAs with lower LIs. The LI represents the proportion of patient discharges from hospitals within the same SCA of which these patients live. The LI is widely used as a measure of care coordination and unwarranted health care variation [4,19], but to our knowledge, this is the first documentation of its association with HF higher-than-expected readmissions. In this study, the LI is ultimately derived from the shared care discharge networks. In SCAs with a high LI, discharges are localized with a lower proportion of discharges of patients from other SCAs. Not only has shared care been advocated as an appropriate model to organize HF care [9,10], but partnerships among community physicians and local hospitals have been identified as hospital strategies to reduce 30-day HF readmission [33]. Characterizing shared care networks provides a road map for hospitals to work together, improving their shared care network as a whole instead of focusing on their hospital penalties.

Though the HRRP is a nationwide effort to reduce higher-than-expected hospital readmissions, it has also created unintended consequences in the complex system of HF care by penalizing hospitals for issues beyond their control, leaving them without specific guidance on how to improve and focusing on punishment instead of process improvements [7]. Patients with HF should be managed as a continuum of care within the primary, secondary, and tertiary level of care, promoting timely patient referrals and delivering care within a strong working relationship [9]. Integrated HF care will improve care coordination that influences patient outcomes. The features identified that result in improved shared care include liaisons between levels of care and institutions, shared professional education, and medication optimization. Comprehensive pathways across primary, secondary, and tertiary care and institutions should be developed and implemented considering patients and health care providers in the design of these pathways [34].

The association of ERRs with shared care networks, however, seems to vary depending on the ethnic/racial and socioeconomic composition of SCAs. In this study, ERR is positively associated with the percentage of Black residents in the SCA. Ethnic/racial disparities may contribute to HF hospital readmissions [20,30,33,35], and HF readmission rates are consistently higher for Black patients [35-37]. In a previous case-control study [30], after matching maximum penalty hospitals as cases to their nearest nonpenalty hospitals as controls, the authors found that maximum penalty hospitals were more likely than controls to be in counties with low socioeconomic status.

The regional variation on the impact of the HRRP raises the following question: how much HF higher-than-expected readmissions are related to hospital-specific performance, and how much it is related to issues beyond the control of a hospital? Additionally, the increased association of the ERR with the LI in SCAs with increasingly higher percentages of Black residents raises the following question: how can improved shared care networks reduce HF disparities among underserved and marginalized groups? Our findings will hopefully motivate cluster randomized clinical trials [38] to evaluate how improved shared care models will reduce hospital readmissions and overall costs, increase adherence to guideline-directed medical therapy, and improve clinical outcomes such as survival and development of chronic conditions.

Limitations

The HRRP is a nationwide program, but our study only considered hospitals in California because large-scale hospital-specific discharge data at the ZCTA level is not publicly available to examine all US hospitals. Our finding only applies to higher-than-expected HF readmissions, and the generalization to conditions other than HF (eg, acute myocardial infarction, pneumonia, and chronic obstructive pulmonary disease) will require further investigation. The primary outcome used in our study, the ERR, is a ratio between two hospital-level regressions that can be used across heterogeneous hospitals but has little inherent variability. In its current version, our study neglects to model the interactions between SCAs, which deserves further investigation. Although our study assumes that the ERR can be used to compare different hospitals as it accounts for a plethora of factors associated with the hospital-level HF readmissions at the individual level, our findings should be interpreted at the hospital level.

Conclusions

Shared care models have been advocated for in HF care but have not been explicitly characterized and rewarded by nationwide control programs such as the HRRP or health systems. In this study, we evaluated the association of higher-than-expected HF readmissions with shared care networks by curating publicly available large-scale hospital-level data on HF ERRs from Medicare HRRP as well as hospital-patient discharges from OSHPD. HF ERRs of hospitals were associated with the LI of the SCAs in which they were embedded, even after controlling for socioeconomic disparities. The HRRP, health systems, and hospitals should characterize and reward models of shared care practices for promoting the necessary integration capable of producing a sustainable and equitable HF care system. The higher-than-expected HF readmission of hospitals was associated with the shared care networks in which hospitals were embedded and the ethnic/racial composition of their SCAs. Hospitals should collectively work to systematically improve their shared care networks for improved HF care.

Improved shared care networks of HF care could mitigate higher-than-expected HF readmissions, especially among underserved and marginalized groups, and translate into economic benefits. Implementation of this model will require collaboration between providers and hospital administrations. Future clinical trials will be needed to evaluate the impact of systematic implementation of improved shared care models of HF to improve higher-than-expected HF readmissions.

Acknowledgments

RH is an independent researcher in Seattle, United States.

Data Availability

All data used in this work is made publicly available by the Hospital Reduction Readmission Program and Office of Statewide Health Planning and Development.

Authors' Contributions

DP and MC participated in the design of the work, acquisition of data, and drafted the article. All authors participated in the analysis of the data, reviewed the manuscript, and authorized the manuscript in its current form.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental material.
[DOCX File , 233 KB - xmed_v3i2e30777_app1.docx]

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Abbreviations

ED: emergency department
ERR: excessive readmission ratio
GEE: generalized estimating equation
HF: heart failure
HRRP: Hospital Reduction Readmission Program
LI: localization index
LVAD: left ventricular assisted device
OSHPD: Office of Statewide Health Planning and Development
SCA: shared care area
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
ZCTA: Zip Code Tabulation Area

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Original Paper

Modeling Years of Life Lost Due to COVID-19, Socioeconomic Status, and Nonpharmaceutical Interventions: Development of a Prediction Model

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Abstract

Background: Research in the COVID-19 pandemic focused on the health burden, thereby largely neglecting the potential harm to life from welfare losses.

Objective: This paper develops a model that compares the years of life lost (YLL) due to COVID-19 and the potential YLL due to the socioeconomic consequences of its containment.

Methods: It improves on existing estimates by conceptually disentangling YLL due to COVID-19 and socioeconomic status. By reconciling the normative life table approach with socioeconomic differences in life expectancy, it accounts for the fact that people with low socioeconomic status are hit particularly hard by the pandemic. The model also draws on estimates of socioeconomic differences in life expectancy to ascertain potential YLL due to income loss, school closures, and extreme poverty.

Results: Tentative results suggest that if only one-tenth of the current socioeconomic damage becomes permanent in the future, it may carry a higher YLL burden than COVID-19 in the more likely pandemic scenarios. The model further suggests that the socioeconomic harm outweighs the disease burden due to COVID-19 more quickly in poorer and more unequal societies. Most urgently, the substantial increase in extreme poverty needs immediate attention. Avoiding a relatively minor number of 4 million unemployed, 1 million extremely poor, and 2 million students with a higher learning loss may save a similar amount of life years as saving 1 million people from dying from COVID-19.

Conclusions: Primarily, the results illustrate the urgent need for redistributive policy interventions and global solidarity. In addition, the potentially high YLL burden from income and learning losses raises the burden of proof for the efficacy and necessity of school and business closures in the containment of the pandemic, especially where social safety nets are underdeveloped.

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KEYWORDS

COVID-19; pandemic; socioeconomic status; mortality; nonpharmaceutical interventions; prediction model; low-income status; life expectancy; public health; income groups

Introduction

More than 3 million people have lost their lives to COVID-19 with estimates projecting up to 5 million deaths by August 2021 [1]. To contain the spread of the virus, governments worldwide mainly relied on nonpharmaceutical interventions (NPIs). These came with a heavy socioeconomic burden, however, especially for the poor. According to International Labour Organization (ILO) estimates in 2020, 8.8% of all working hours were lost (the equivalent to 255 million full-time jobs) [2]. For 2021, the shortfall is expected to correspond to 140 million full-time jobs. Remittances to poorer countries declined substantially. Extreme poverty could increase by around 100 million people (or more than twice as many under the less strict poverty line of US $3.20 per day) [3,4]. Prolonged school closures that temporarily affected up to 1.5 billion students will depress long-term economic recovery [5]. Whether the long-term socioeconomic harm outweighs the benefit to protect health in the short-term is therefore a key question in the pandemic.

Governments justify the use of NPIs by referring to their proportionality. Three component parts define the proportionality of NPIs. The first two concern their efficacy (ie, the suitability and necessity of particular measures). They largely belong to the realm of epidemiologists and virologists, and are therefore beyond the scope of this paper [6-8]. The third meaning concerns the proportionality of NPIs in the narrower sense. It asks whether they are reasonable given the collateral damage they induce. However, in the pandemic, at least two problems complicate such an assessment. Subjective risk perceptions tend to have significant distortions, rendering public citizen assessments of proportionality of limited reliability [9-11]. More importantly, no common measure exists to compare the immediate health threat from COVID-19 to the mostly indirect long-term socioeconomic harm from NPIs. The time lag with which the socioeconomic damage is realized also means that the question of proportionality can only be answered in full sometime in the future.

Furthermore, important moral and legal concerns exist against weighing lives against lives in the pandemic [12]. This is particularly true because, rather than being a great equalizer, the pandemic has exacerbated existing inequalities, leaving the same people most exposed to health and socioeconomic risks. Any such comparison must therefore primarily aim at gauging the need for proportional socioeconomic compensation and raising the burden of proof for suitability and necessity of NPIs, especially in the context of resource scarcity and severity of consequences (eg, extreme poverty). After all, people can be lifted from poverty but not be resurrected from the dead.

Against this background, the paper introduces a model to compare the damage to life from COVID-19 and the socioeconomic consequences of NPIs. The starting point of the considerations is that both acute infectious diseases such as COVID-19 and a low socioeconomic status (SES) may shorten an individual's life expectancy. Accordingly, it is possibly to assess the damage due to COVID-19 and NPIs in years of life lost (YLL). YLL refers to the gap between the age of death and the age to which a person could have lived. The approach complements but is distinct to other perspectives on the pandemic such as the burden of disease and value of life. The model rather contributes to the discourse on the relationship between health inequality and social justice [13,14]. This paper targets some of the key conceptual difficulties when attributing YLL to individual causes. Any such assessment can only be plausible estimates at best because validation of the model would require information on the share of the current socioeconomic fallout that will become permanent. Thus, the efforts at quantifying the model primarily serve for purposes of illustration.

Methods

The model starts from the basic assumption that proportionality can be expressed as a correspondence of YLL due to COVID-19 and the socioeconomic damage from the NPIs.

YLL Due to COVID-19 and SES

The first part of the section discusses the first part of the equation, that is YLL due to COVID-19. The second part of the section discusses the YLL due to SES.

The analysis takes as the starting point the only large cross-country evaluation of YLL due to COVID-19 spanning 81 countries. Pifarré i Arolas et al [15] estimated the global average per COVID-19 deaths at 16 YLL. If countries are grouped along the World Bank income group classification, the average for high-income countries in their estimate was at around 13 YLL and 19 YLL for middle- and low-income countries. The estimate is based on UN World Population Prospects' life tables for remaining life expectancy at the exact age of deaths. As the life tables are partly able to account for the systematic differences in life expectancy between global income groups, the higher YLL estimates for low- and middle-income countries reflect that COVID-19 deaths tend to occur at younger ages than in high-income countries.

However, for several reasons the life tables do not reflect the actual years a person would have lived had they not died of COVID-19. To date, no single methodology for estimating YLL exists, but it is common practice to use life tables that either assume an ideal life expectancy in a counterfactual disease- and poverty-free egalitarian world or draw on hazard ratios within the age bracket of the birth cohort [16,17]. As a result, the higher one moves in the age brackets of the life table, the more it reflects the life expectancy of the rich and healthy share of the population. The tables thus state an aspiration rather than providing information about the actual number of years an

individual would have lived in the absence of a specific cause of death.

Although such a normative approach is defendable for idealistic reasons, it has weaknesses in correctly attributing YLL to individual causes. YLL has the same determinants as life expectancy in general. The question therefore is to what extent YLL can be attributed to the immediate cause of death (eg, COVID-19) or in fact reflect more fundamental causes. Unfortunately, it is difficult to specify the relative causal influence of fundamental factors such as genetic disposition [18] and SES [19,20], the mechanisms through which they work such as health behaviors [21-23] and morbidities (eg, chronic diseases) [24,25], and the immediate causes of death (eg, infectious diseases). Temporal and causal complexity and a lack of reliable data further complicate such estimates [26,27].

Because correcting YLL estimates for individual health factors such as genetic disposition, health behaviors, and comorbidities entails extraordinary data requirements, it is unsuitable for most studies. It is suggested here that a still challenging but more viable strategy is correcting for socioeconomic differences in life expectancy. In other words, dropping the assumption of an egalitarian society and accounting for socioeconomic differences in life expectancy. This may improve YLL estimates in at least three ways: a potentially more precise estimate of the actual YLL while retaining the normative claim of not accepting a lower than ideal life expectancy, a more accurate attribution of YLL to its fundamental and immediate causes, and consequently better policy advice tailored to specific health and socioeconomic vulnerabilities. To that end, country-specific findings on socioeconomic differences in life expectancy should be combined with data on the socioeconomic profile of COVID-19 deaths (or where such data is lacking seroprevalence and hospitalization rates).

Socioeconomic differences in life expectancy in high-income countries usually amount to 5 to 10 years between groups with a low and high SES (eg, between the first and fifth quintile of the income distribution) [28]. They may, however, reach up to 15 to 20 years in poorer and more unequal societies or when using more fine-grained indicators of SES [19,29,30]. In the United Kingdom, for example, a country that collects relatively detailed socioeconomic data, life expectancy differs by 7.8 years between the first and the fifth quintile (and 9.4 years between the first and the highest decile) of the Index of Multiple Deprivation [31]. In Germany, differences in life expectancy between people with a low SES and those with a high SES is around 6.6 years [32]. Comparable data for low- and middle-income countries is scarce but higher overall life span variability and the leveling effect of socioeconomic progress suggest an even larger socioeconomic gap in life expectancy [33,34]. Brazil, for example, an upper middle–income country with persistent and high socioeconomic inequality was able to reduce life span inequality from 19 to 12 years between 1991 and 2010 with socioeconomic development explaining the vast majority of this development [35]. In many low- and lower middle–income countries, the lowest quintile of the income distribution often lives below the poverty line, which may result in even higher inequality in life expectancy [30]. Amid existing data uncertainties, this model assumes a socioeconomic gap in life expectancy between people with low and high SES of 5 to 15 years.

Regarding the socioeconomic distribution of COVID-19 deaths, studies consistently find that people with a low SES are significantly overrepresented. The United Kingdom reports the most credible data on socioeconomic deprivation. Here, the most deprived quintile accounts for 23% of COVID-19–related deaths [36]. In the United States, the poorest quintile has one-third more comorbidities, twice the case count and death rate, and accounts for one-third of COVID-19–related deaths (people with below median income account for two-thirds) [37,38]. Swedish data from the early periods of the pandemic put the share of deaths with a low SES at even 40% [39]. In Germany and Scotland, people with a low SES account for 40% and 50% of hospitalizations, respectively [40,41]. Awaiting relevant data from low- and middle-income countries, the model assumes a range of 20% to 40% for COVID-19 deaths with a low SES (Table 1).

Table 1. ∅ years of life lost due to socioeconomic status (SES).

Distribution of deaths by SES group (low/mid/high; %)	Socioeconomic gap in life expectancy (years)				
	5	7.5	10	12.5	15
20/60/20	2.5	3.8	5	6.3	7.5
30/60/10	3	4.5	6	7.5	9
40/50/10	3.3	4.9	6.5	8.1	9.8

Because the life tables for the COVID-19–YLL previously discussed assume that everyone is rich (and healthy), the average YLL per person must be corrected for the combined effect of the socioeconomic gap in life expectancy and the socioeconomic distribution of COVID-19 deaths. Table 1 summarizes the stylized findings across various scenarios.

For example, in a country like the United Kingdom where approximately 23% of COVID-19 deaths have a low SES and 60% a medium SES, and the socioeconomic gap in life expectancy is around 7.8 years, the 11.2 YLL estimated in Pifarré i Arolas et al [15] would need to be corrected downward by 4.1 YLL to 8.1 YLL. In other words, 4.1 YLL do not occur due to COVID-19 but can be attributed to a low SES:

For a country with a distribution of 40% and 50% with low and middle SES, respectively, and a socioeconomic gap in life

expectancy of 15 years, the YLL estimate due to COVID-19 would have to be corrected downward by 9.8 YLL. Such distribution may be more likely in low- and lower middle–income countries where the informal economy accounts for 50% to 90% of employment. Together with informal housing (ie, slums), this is an important driver of COVID-19 incidence and deaths [42-44]. The correction would reduce the average 19 YLL due to COVID-19 in this income group to 9.2 YLL.

In sum, the idealistic estimates from the UN life tables of 12 to 19 YLL need to be corrected downward by around 25% to 50%, depending on how egalitarian the life expectancy and distribution of COVID-19 deaths are in a country. This correction only partially accounts for comorbidities, which are indeed lower but not absent in people with a high SES. Correcting for comorbidities in previous studies resulted in a further reduction by 1 to 3 YLL [45]. To account for this, the model uses 8 YLL per COVID-19 deaths as its standard parameter and 6 YLL and 10 YLL as an alternative specification.

Six hypothetical scenarios (W1-6) with different numbers of COVID-19 deaths are constructed (see Table 2). Current empirical projections for the global pandemic estimate up to 6 million deaths by December 2021 and twice as many excess deaths [1]. With slow vaccine rollout in most parts of the world and uncertain protection against new virus variants, it cannot be ruled out that this number multiplies over the following years. Additionally, a less stringent global response or a more deadly virus could have yielded substantially higher numbers of death.

Table 2. Total years of life lost (YLL) due to COVID-19.

Scenario	COVID-19 deaths (millions)	Average YLL per COVID-19 death (millions)		
		∅6	∅8	∅10
W1	5	30	40	50
W2	7.5	45	60	75
W3	10	60	80	100
W4	30	180	240	300
W5	50	300	400	500
W6	70	420	560	700

YLL Due to NPIs

The model also draws on the socioeconomic gap in life expectancy to ascertain the potential YLL from loss in SES (eg, due to unemployment or forgone education). However, it would almost certainly be an overestimate to infer that a loss in SES group directly translates into an equivalent reduction of the individual life span. As previously noted, a host of factors determine life expectancy, which means that only a part of it is in fact malleable. While exact causal weights are still to be determined, the model can draw on a number of studies that made considerable headway into estimating the individual contribution of factors such as income and education to the socioeconomic gap in life expectancy. In the European mean, low income explains around 10% to 20% of an average 5-year gap in life expectancy between educational groups [46]. For disability-adjusted life expectancy, it is around 20% of an 8.5-year gap in life expectancy between low and high educational groups [47]. Educational and occupational status also account for around 20% of the 10-year gap in life expectancy between SES groups [48,49]. Taken together, the model therefore assumes that key SES factors such as income and educational status may each account for about 20% of the socioeconomic gap in life expectancy.

To date, little credible data exists that could confirm whether these findings can travel easily from European high-income countries to the rest of the world. There are reasons to believe that socioeconomic determination of life expectancy is higher in low- and middle-income countries. In poorer countries, morbidity and mortality are generally higher, but health behaviors account for a smaller share of the socioeconomic differences in life expectancy [25,50]. Education also tends to entail higher-income premiums [51] but, like health services, is often not universally supplied and depends on personal income. While this is unlikely to reflect exact causalities, the Socio-Demographic Index of the Global Disease Burden Project accounts for 85% of international differences in average healthy life expectancy by building the geometric mean of lagged per capita income, education of the population aged ≥15 years, and the fertility rate of women aged ≥25 years (as a proxy for the standing of women in society) [52]. Against this background, it seems plausible that in middle- and low-income countries factors such as income and education may each account for 30% and more of the socioeconomic differences in life expectancy.

Based on these findings, it is possible to construct a rough estimate of YLL due to loss in SES, depending on the size of the socioeconomic gap in life expectancy (5-15 years) and the degree of socioeconomic determination (20%-40%; Table 3). The YLL vary between 0.5 in a rather egalitarian high-income country and a 3 YLL in a highly unequal low-income country. Given that in the latter case a loss in status group often entails falling into poverty, this seems a rather conservative estimate.

Table 3. $YLL^{I,E}$ (per capita) for decline in socioeconomic status.

Socioeconomic determination	Socioeconomic gap in life expectancy (years)				
	5	7.5	10	12.5	15
High income (20%)	0.5	0.8	1	1.3	1.5
Middle income (30%)	0.8	1.1	1.5	1.9	2.3
Low income (40%)	1	1.5	2	2.5	3

In the proportionality model that has been developed, the two main causes of loss in SES group and components of the socioeconomic damage (YLL_{SES}) in the pandemic are income loss (YLL_I) and forgone education (YLL_E). The main factors behind *permanent* income loss are unemployment, reduction of working hours, and economic inactivity. Forgone education may result from unrealized secondary or tertiary education due to dropping out or a lack of qualification or financial means for higher education:

Educational loss in the pandemic further differentiates in two components: the most unfortunate cases where income loss or temporary school closures result in students permanently forgoing a higher educational bloc depriving them of secondary or tertiary education (YLLe1) and the average income losses from school closures that affect the vast majority of students (YLLe2). Past examples show that even short episodes of temporary school closures have a measurable average impact on income in later life. The first pandemic-related school closures may reduce lifetime earnings by 1% to 4%, depending on the subsequent ability for learning compensation [53,54]. Adding the second round of school closures at the turn of the year 2020/2021 and considering that longer closures add exponentially, current losses in lifetime earnings may amount to 2% to 8%. For simplicity, the model assumes an average of 5% reduced lifetime earnings (or about one-eighth of a decline in SES group).

For many low- to middle-income countries, this is likely to be an underestimate, given that school closures were on average longer and entail higher dropout rates and higher income premiums [55,56].

Proportionality Model

In the proportionality model the loss of life years in these scenarios is then juxtaposed with the socioeconomic damage in the pandemic. The main idea is to calculate the number of people for which the loss in SES would have to become permanent for the amount of YLL to be equivalent.

To that end, the individual components of socioeconomic damage are distributed among subgroups of the globally affected population (Ng):

$$N_g = n_e + n_i + n_p \textbf{(8)}$$

- Workers(n_ii) ≈ 3,492,000,000 (from ILO)
- Students(n_ee) ≈ 1,500,000,000 (from UNESCO)
- Extremelypoor(n_p) ≈ 640,000,000 (World Bank)

Learning loss is divided into two subgroups. Those students with average learning and subsequent income loss from school closures YLLe2 and the worst hit students that forgo a 3- to 4-year higher learning block YLLe1 (ie, additional dropouts due lack of funding or qualification for higher education). Because students with a high SES may have more capacities to compensate for learning losses, it is assumed that two-thirds of the students worldwide (0.9 billion) had average learning and subsequent income loss due to school closures.

$$YLL_{E2} = 0.66 \cdot n_e \cdot YLL_{e2} \textbf{(9)}$$

The resulting value is subtracted from the overall YLL due to COVID-19. The remaining damage is then distributed among the students with a learning block loss (YLL_{E1}), people with an income loss (YLL_I), and those that fall into extreme poverty as a result (YLL_P).

$$YLL_{COV} - YLL_{E2} = YLL_{E1} + YLL_I + YLL_P \textbf{(10)}$$

Each group carries a weighted burden that reflects group size and the social gradient (α, ,γ). Income losses account for slightly more than half (0.54) and forgone education (0.23) and poverty (0.22) each for slightly less than one-quarter of all YLL. For the global average, the factor of socioeconomic determination is set at 0.3 and 0.4 for the extremely poor. The average socioeconomic gap in life expectancy is set at 7.5 years.

With these shares it is possible to individually calculate the total number of workers (Xi), students (Xe), and extremely poor (Xp) for whom the socioeconomic damage in the pandemic would have to become *permanent*.

Results

The standard model specifications aim to reflect the global average (8 YLL per COVID-19 death, a 7.5-year socioeconomic gap in life expectancy, and a socioeconomic determination factor of 0.3). Tables 4 and 5 read as follows. Each row displays the total number of workers, poor, and students for which the socioeconomic damage would have to become *permanent* for the YLL to be equivalent of those attributable to COVID-19.

Values are negative when the average socioeconomic damage from school closures (YLLe2) is higher than the YLL due to COVID-19. A separate column on the right provides the common percentage share, which by definition is identical for all groups (eg, 1% of all workers, extremely poor, and students).

Because the YLL from YLLe2 alone amount to an equivalent of approximately 20 million COVID-19 deaths, although the individual burden distributed over 900 million students is relatively small, a second table displays the outcomes excluding YLLe2.

Table 4. Equivalent permanent socioeconomic damage with standard specifications.

Scenario	COVID-19 deaths (millions)	∅8 years of life lost			
		Income loss (millions)	Extremely poor (millions)	Education loss (millions)	Share (%)
W1	5	–47.9	–8.8	–20.6	–1.4
W2	7.5	–38.3	–7.1	–16.4	–1.1
W3	10	–28.6	–5.3	–12.3	–0.8
W4	30	48.7	9	20.9	1.4
W5	50	126	23.2	54.1	3.6
W6	70	203.3	37.5	87.3	5.8

Table 5. Equivalent socioeconomic damage (excluding school closures).

Scenario	COVID-19 deaths (millions)	∅8 years of life lost			
		Income loss (millions)	COVID-19 poor (millions)	Education loss (millions)	Share (%)
W1	5	19.3	3.6	8.3	0.6
W2	7.5	29	5.3	12.5	0.8
W3	10	38.7	7.1	16.6	1.1
W4	30	116	21.4	49.8	3.3
W5	50	193.3	35.6	83	5.5
W6	70	270.6	49.9	116.2	7.7

To put the model estimates in perspective, current projections by major international organizations can contextualize the findings. It should be noted, however, that the main outcomes of interest will only be available years if not decades from now because, to have a significant effect on life expectancy, a loss in SES has to become permanent. Regarding education loss, the negative values in the first three rows of Table 5 suggest that YLL from temporary school closures outweighs the YLL due to COVID-19 in the currently most probable scenarios. Only in scenarios W4-6 would an increase in students that will forgo a whole 3- to 4-year educational block be proportional (eg, because of them not qualifying for further education or dropping out into the labor market is uncertain). Table 6 shows that, even excluding the effect of YLLe2, the socioeconomic damage in scenarios W1-3 is likely to be disproportionate to the YLL due to COVID-19. Already in September 2020, UNESCO warned that at least 24 million students could drop out of school due to school closures (>W3) [57]. One year later, 168 million students worldwide have missed out on learning for almost an entire year, and another 214 million missed more than 9 months. For 140 million children, the first day of school has been indefinitely postponed [58]. One in three countries is not taking measures to compensate for learning losses [59]. The number of children that will forgo a whole education bloc is thus likely to be above even the worst-case scenarios. Another way to put it is that children are bearing a disproportionate share of the socioeconomic consequences of NPIs.

Table 6. Proportional socioeconomic damage across different model specification.

	SOD[a]: 0.2 and ∅YLL[b]: ∅6			SOD: 0.3 and ∅YLL: ∅8			SOD: 0.5 and ∅YLL: ∅10		
	GAP[c]: 5	GAP: 7.5	GAP: 10	GAP: 7.5	GAP: 10	GAP: 12.5	GAP: 10	GAP: 12.5	GAP: 15
W1	–3.4%	–2.3%	–1.7%	–1.4%	–1.0%	–0.8%	–0.7%	–0.6%	–0.5%
W2	–2.9%	–2.0%	–1.5%	–1.1%	–0.8%	–0.7%	–0.5%	–0.4%	–0.3%
W3	–2.5%	–1.6%	–1.2%	–0.8%	–0.6%	–0.5%	–0.3%	–0.2%	–0.2%
W4	1.3%	0.8%	0.6%	1.4%	1.0%	0.8%	1.3%	1.0%	0.8%
W5	5.0%	3.3%	2.5%	3.6%	2.7%	2.2%	2.8%	2.2%	1.9%
W6	8.7%	5.8%	4.4%	5.8%	4.4%	3.5%	4.4%	3.5%	2.9%

[a]SOD: socioeconomic determination of life expectancy.

[b]YLL: year of life lost.

[c]GAP: socioecomonic difference in life expectancy.

Another group bearing an even more disproportionate share of the pandemic burden are the extremely poor. The World Bank estimates their number has increased by approximately 100 million [3]. As the impact of the pandemic continues to worsen in low- and lower middle–income countries, the initial increase is expected to persist. This is three and two times the proportional YLL damage in the worst-case scenarios of Tables 4 and 5, respectively (>W6). Income loss is also likely to remain disproportionate even if the long-term loss in jobs will settle significantly below 100 million (>W3/W4). The ILO estimates that in 2020 working hours equivalent of 255 million full-time jobs were lost [60]. In 2021, working hours will still be 4.4% below the projection for the no-pandemic scenario. Lower middle–income countries experienced the strongest decline. The 2020 estimate divides into 30 million people affected by forgone job growth, 131 million by reduced working hours, and 114 million by employment loss. The last group is divided into 33 million unemployed and 81 million people economically inactive of which the latter are unlikely to recover anytime soon, if ever.

For a second set of results, the standard model specifications were adapted to reflect different country conditions (see Table 6). The three columns on the left assume conditions more similar to a typical high-income country. The factor of socioeconomic determination is set at 20%; the average per capita YLL due to COVID-19 at 6 YLL; and the socioeconomic gap in life expectancy varies between 5 YLL (South Europe), 7.5 YLL (Central, Western Europe), and 10 YLL (Eastern Europe, United States). The three middle columns show two variations of the standard specification with a higher socioeconomic gap in life expectancy (10 and 12.5 years) to account for more unequal and lower-income countries. The three columns on the right assume conditions that may be more characteristic of low-income countries with a higher level of socioeconomic determination (40%), a high loss of per capita life years due to COVID-19 (10 YLL), and a wide socioeconomic gap in life expectancy (10-15 years). Again, two tables were produced including and excluding YLLe2. For reasons of readability, the tables present the changing values only as the common percentage share of people affected with income loss, extreme poverty, and foregone education.

The different model specifications obtain two main results. One at the cross-country level and one at the within-country level. First, the differences in parameters tend to largely even out across the different model specifications. The first three scenarios remain disproportionate in low-, middle-, and high-income countries, meaning the socioeconomic fallout outweighs the COVID-19–related YLL. The results also largely hold when dropping the average damage from school closures (YLLE2; Table 7). Larger differences only occur in scenario W4-6. At the extreme ends of the model specifications, the proportionality of the socioeconomic damage differs by a factor of 3 (2.9%-8.7%), reflecting the steeper social gradient in low-income countries. The second main result is that, at constant YLL per COVID-19 death, the socioeconomic damage becomes disproportionate much faster in more unequal societies. In more egalitarian high-income countries, twice the socioeconomic damage is proportional than in the most unequal ones. In middle- and low-income countries, these differences are less pronounced but remain significant.

Table 7. Proportional socioeconomic damage across different model specification (excluding school closures).

	SOD[a]: 0.2 and ∅YLL[b]: ∅6			SOD: 0.3 and ∅YLL: ∅8			SOD: 0.4 and ∅YLL: ∅10		
	GAP[c]: 5	GAP: 7.5	GAP: 10	GAP: 7.5	GAP: 10	GAP: 12.5	GAP: 10	GAP: 12.5	GAP: 15
W1	0.9%	0.6%	0.5%	0.6%	0.4%	0.3%	0.4%	0.3%	0.3%
W2	1.4%	0.9%	0.7%	0.8%	0.6%	0.5%	0.6%	0.5%	0.4%
W3	1.9%	1.2%	0.9%	1.1%	0.8%	0.7%	0.8%	0.6%	0.5%
W4	5.6%	3.7%	2.8%	3.3%	2.5%	2.0%	2.3%	1.9%	1.6%
W5	9.3%	6.2%	4.7%	5.5%	4.2%	3.3%	3.9%	3.1%	2.6%
W6	13.1%	8.7%	6.5%	7.7%	5.8%	4.6%	5.4%	4.4%	3.6%

[a]SOD: socioeconomic determination of life expectancy.

[b]YLL: year of life lost.

[c]GAP: socioecomonic difference in life expectancy.

Discussion

Principal Results

This paper sets out to narrow in on the difficult question of proportionality between the health and socioeconomic fallout in the pandemic. To do so, it first made the case that dropping the assumption of a poverty-free and egalitarian society can make estimates of YLL due to COVID-19 about 25% to 50% more accurate. To put it differently, up to half of the YLL extracted from life tables may in fact be socioeconomic differences in life expectancy. Because SES is associated with morbidity and mortality more generally, the approach may yield analytic benefits beyond the current pandemic. Ecological data of the SES for the population of interest may partly proxy for a lack of individual-level data on the prevalence of morbidity and other risk factors.

The application to the pandemic highlights the difficult trade-offs involved in the short- and long-term protection of health. While NPIs target immediate health concerns, the long-term socioeconomic damage is likely to entail a steep cost to life, especially among the poor and children, that requires immediate attention in the aftermath of the pandemic. In countries that lack the necessary resources to compensate for the socioeconomic damage in the pandemic, more drastic NPIs such as business and school closures should only be implemented as a last resort. The tentative results further suggest that avoiding a relatively minor number of 4 million people with income loss, 1 million extremely poor, and 2 million students with a higher learning loss can save a similar amount of life years as saving 1 million people from dying from COVID-19. The extent of the socioeconomic damage further suggests that decision makers took measures in expectancy of a worst-case scenario (W6). Interestingly, the question of proportionality has otherwise been rather similar across different income groups, largely because the social gradient and the associated loss of life is steeper for both COVID-19 and the NPIs. Levels of within-country inequalities may, however, be a key concern for estimating the proportionality of the NPIs. This is especially true because a wider socioeconomic gap in life expectancy signals a weaker social safety net that could compensate for losses.

Limitations

The approach comes with a number of important limitations. The assumptions on the extent of socioeconomic determination of the life expectancy and the size of the socioeconomic gap in life expectancy in low- and middle-income countries require a more thorough basis in empirical data that to date is missing. Furthermore, the model does not account for the nonlethal health impacts in the pandemic (eg, “Long-Covid,” psychosocial harm, or overwhelmed hospitals). Future research could include such information using quality-adjusted estimates such as the healthy life expectancy. The model also does not account for the COVID-19–related disease burden on economic activity. Issues of the relative causal weight of NPIs have been largely put aside. Harsher NPIs are sometimes invoked to justify reducing the socioeconomic damage in the pandemic. However, existing research into the relationship has thus far been unable to disentangle the causal role of voluntary behavioral change, formal and informal NPIs, and the objective disease burden in reducing economic activity. NPIs may only account for about one-third of the variation in COVID-19 mortality and around 20% of reduced business activity [8,61]. Against this background, the model has assumed that causal uncertainties on both sides of the equation may eventually even out. Future research should carefully assess issues of causal weight and direction.

Conclusions

The application to the pandemic highlights the difficult trade-offs involved in the short- and long-term protection of health. While NPIs target immediate health concerns, the long-term socioeconomic damage is likely to entail a steep cost to life, especially among the poor and children, that requires immediate attention in the aftermath of the pandemic. In countries that lack the necessary resources to compensate for the socioeconomic damage in the pandemic, more drastic NPIs such as business and school closures should be weighed carefully.

Conflicts of Interest

None declared.

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Abbreviations

ILO: International Labour Organization
NPI: nonpharmaceutical intervention
SES: socioeconomic status
YLL: years of life lost

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Original Paper

Cognitive Factors Associated With Public Acceptance of COVID-19 Nonpharmaceutical Prevention Measures: Cross-sectional Study

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Abstract

Background: During the COVID-19 crisis, protests against restrictions emerged and rule violations increased, provoking peaks in new positive cases, forcing authorities in France to impose fines to slow down the spread of the disease. Due to these challenges, subsequent implementations of preventive measures in response to COVID-19 recurrences or other pandemics could present difficulties for decision makers. A better understanding of the factors underlying the public acceptance of COVID-19 nonpharmaceutical preventive measures may therefore contribute greatly to the design of more effective public communication during future pandemics.

Objective: The aim of this study was to evaluate the acceptance of COVID-19 nonpharmaceutical prevention measures in France. The specific objectives were (1) to examine the public's acceptance of COVID-19 nonpharmaceutical prevention measures and (2) to assess the association of the public's acceptance of these prevention measures and their perception of COVID-19.

Methods: Data were collected from 2004 individuals through an online survey conducted 6-8 weeks after the first lockdown in France. For objective 1, participants were asked the extent to which they supported 8 COVID-19 nonpharmaceutical preventive measures using a 4-point Likert scale. For objective 2, COVID-19–related perceptions were assessed using a 5-point Likert scale from an adapted version of Witte's Extended Parallel Process Model. Sociodemographic and environmental variables were also collected. The public's acceptance factors were estimated using an unweighted least squares factorial analysis, and their associations with perceptions of COVID-19, expressed as rate ratios (RR) and 95% CIs, were estimated using generalized linear Poisson regression models. Statistical analyses were performed using the SPSS statistical package.

Results: The acceptance rate reached 86.1% for individual protective measures, such as making masks mandatory in public open spaces, and 70.0% for collective restrictions, such as isolating the most vulnerable people (1604/2004, 80%) or forbidding public gatherings (n=1590, 79.3%). The least popular restrictions were closing all schools/universities and nonessential commerce such as bars and restaurants (n=1146, 57.2%). Acceptance of collective restrictions was positively associated with their perceived efficacy (RR 1.02, 95% CI 1.01-1.03), fear of COVID-19 (RR 1.04, 95% CI 1.03-1.05), and perceived severity of COVID-19 (RR 1.04, 95% CI 1.03-1.06), and negatively with age >60 years (RR 0.89, 95% CI 0.81-0.98). Acceptance of individual protective

measures was associated with their perceived efficacy (RR 1.03, 95% CI 1.03-1.04), fear of COVID-19 (RR 1.02, 1.01-1.03), and perceived severity of COVID-19 (RR 1.03, 1.01-1.05).

Conclusions: Acceptance rates of COVID-19 nonpharmaceutical measures were rather high, but varied according to their perceived social cost, and were more related to collective than personal protection. Nonpharmaceutical measures that minimize social costs while controlling the spread of the disease are more likely to be accepted during pandemics.

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KEYWORDS

Extended Parallel Process Model; COVID-19; lockdown; public acceptance; nonpharmaceutical measures; Likert scale; France

Introduction

Background

The COVID-19 pandemic has affected many countries, with more than 10 million cases worldwide and more than 500,000 deaths as of July 1, 2020 [1]. Several restrictions were implemented to prevent further spread of the disease in the early stages of the pandemic. Confinement, the restriction of individuals to their homes, was one of the restrictions enforced in many countries [2], including France beginning on March 17, where surveillance of COVID-19 cases was implemented on January 10, 2020 [3]. In addition, global and local health authorities used media campaigns to inform individuals about the spread of the virus, the number of daily cases and deaths, and recommended actions to prevent infections [4,5]. The preventive measures include regular handwashing, social distancing, avoiding crowded places, and covering the mouth and nose, among others.

The lockdown was lifted in France on May 11, 2020, after a dramatic decrease in the number of cases and deaths, but mobility restrictions had some major adverse consequences [6]. The ensuing reductions in social (collective training sessions or sport events) and physical (barred access to exercise facilities or parks) opportunities to exercise had a direct negative effect on health behaviors and well-being [7-11]. The lockdown also had a detrimental impact on various aspects of psychological health (eg, posttraumatic stress disorder, anxiety, and depression [12,13]), especially in high-density and socially deprived neighborhoods [14] and among people with pre-existing chronic conditions [15]. Social distancing, self-isolation, and travel restrictions have led to a reduced workforce across all economic sectors and caused many jobs to be lost. Schools were closed and the need for commodities and manufactured products decreased [16]. As a result, protests against restrictions emerged and rule violations increased, provoking peaks in new positive cases [17], forcing authorities to impose fines to slow down the spread of COVID-19 [18]. Due to these challenges, subsequent implementations of nonpharmaceutical measures in response to COVID-19 recurrences or other pandemics could present difficulties for decision makers [19]. A study examining acceptance of different scenarios showed that lockdown length affected respondents' reactions much more strongly than intensity or flexibility [20]. Additional analyses showed that half of the respondents rejected any further extensions or intensifications, while 20% would endorse long-term strategies if necessary.

Study Rationale

Beliefs and risk perceptions associated with the disease (perceived personal vulnerability and perceived severity of the disease) have a major influence on the acceptance and uptake of and adherence to required restrictions [21-26]. This study was based on the Extended Parallel Process Model (EPPM). During the first lockdown in France, we investigated COVID-19 fear, risk perception, and trust in recommended measures based on the EPPM [27], which is one of the latest developments among theories that explain the role of fear in persuasion. The following constructs are central to the EPPM: fear, threat (with its two components: perceived severity of and perceived susceptibility to the illness), efficacy (comprising self-efficacy and response efficacy), and two types of responses (danger control and fear control). As nonpharmaceutical interventions play a considerable role in the control and prevention of pandemics such as the COVID-19 pandemic, it is necessary to better understand the factors underlying their public acceptance.

Specific Objectives

The objectives of this study were (1) to measure the public's acceptance of COVID-19 nonpharmaceutical measures and (2) to assess the association of the public's acceptance of these measures and their perception of COVID-19.

Methods

Study Design

Data were collected from a 2-week cross-sectional survey administered 6-8 weeks after the first lockdown (June 25-July 5, 2020) among adults residing in France.

Participants and Procedures

The respondents were recruited among Arcade Research panelists, who agreed to participate regularly in surveys of customer attitudes and experiences. The respondents to this survey were enrolled on the basis of a stratified sampling method to reflect the distribution of the French general population regarding sex, age, occupation, and region.

Ethical Considerations

The research protocol was registered by the École des Hautes Études en Santé Publique (EHESP) School of Public Health Office for Personal Data Protections and approved by the Institutional Review Board of the Méditerranée Infection University Hospital Institute (reference number: 2020-022).

Measurements

Acceptance of Public COVID-19 Nonpharmaceutical Measures

The dependent variable for the analyses was support of the following eight restrictive measures implemented (or likely to be implemented) by national governments to contain the COVID-19 outbreak: (1) make face masks mandatory in public closed spaces; (2) make face masks mandatory in public open spaces; (3) isolate vulnerable people (eg, older adults); (4) forbid public gatherings (eg, fairs, markets); (5) implement mobility restrictions for nonessential workers; (6) introduce a stay-at-home order for nonessential workers; (7) close all schools/universities; and (8) close nonessential commerce (eg, bars, restaurants). For each of them, the participants were asked to rate their acceptance on a Likert-type response scale, which ranged from 1 ("totally disagree") to 4 ("totally agree"), and for which the meaning of each value was explicitly indicated [28]. To facilitate the treatment of the data, agreements obtained from these 8 items were added to generate a cumulative score that enabled the research team to assess participants' acceptance of proposed nonpharmaceutical measures.

Sociocognitive Factors

To assess participants' beliefs and expectations related to the COVID-19 epidemic, we used a range of constructs and variables from Witte's EPPM. Items related to these constructs were adapted to the COVID-19 pandemic and translated into French. EPPM factors were estimated using an unweighted least squares factorial analysis, followed by a Promax rotation, and five factors were extracted accordingly [8]: (1) efficacy of preventive measures (eg, *actions recommended by scientists are effective at preventing COVID-19*), (2) lack of fear control (eg, *the risk of being infected is frightening me*), (3) perceived severity of COVID-19 (eg, *I believe that COVID-19 is extremely harmful*), (4) perceived susceptibility to COVID-19 (eg, *it is possible that I will get COVID-19 in the next few weeks*), and (5) cognitive avoidance (eg, *When I go shopping, I tend to avoid thinking about the risk of being infected*).

Sociodemographic and environmental variables were also collected, such as age in years (divided into groups: 18-39 years, 40-59 years, and ≥60 years), gender (self-reported sex), occupational status (active, unemployed, or retired), persons in household (≥3, 2, or 1), living density (urban, more than 100,000 people; urban, 20,000-100,000 people; urban, 2000-20,000 people; rural), chronic disease (yes/no), and perceived health (very poor, poor, good, very good).

Data Analysis

Categorical data were expressed as frequencies (n) and percentages (%), while numerical data were expressed as mean (SD), and compared with 1-way ANOVA. EPPM raw scale scores were transformed to a 0-100 scale: ([raw score – lowest possible raw score]/possible raw score range) × 100. Acceptance factors were estimated using an unweighted least squares factorial analysis, followed by a Promax rotation, a nonorthogonal (oblique) solution in which the factors are allowed to be correlated. This method provides accurate and conservative parameter estimates when using ordinal data [29]. This item reduction method established which of the 8 items belonged to domains or conceptual areas and which items should be maintained. Items are deleted if they loaded on 2 or more factors, or if they exhibited a correlation coefficient of less than 0.40 with their own factor. Internal consistency reliability was assessed by computing Cronbach α, considered satisfactory if ≥.70 [30]. Interscale correlations were computed with the nonparametric Spearman correlation test. Since the study outcomes were count variables (number of accepted measures), generalized linear Poisson regression models were used to estimate the rate ratios (RRs) of acceptance as a function of sociodemographic variables and scores of COVID-19 perceptions, as assessed by the EPPM. Estimates in univariate analysis (model 1) were expressed as RRs with 95% CIs. Significant estimates from model 1 were analyzed in a multivariate model (model 2). The goodness of fit of the multivariate model was assessed using the value/df for the deviance statistics. This value should be near 1.0 for a Poisson regression. Statistical analyses were performed using the SPSS statistical package (version 19; IBM Corp).

Results

Participant Characteristics

Of the 2004 individuals who completed the survey (Table 1), half were women (1012/2004, 50.5%), 66% (1329/2004) were professionally active, and 76% (1532/2004) were living in urban environments. The mean age was 46.9 (SD 15.9) years, and was similar between men (mean 46.4, SD 16.3) and women (mean 47.4, SD 15.5; *P*=.18)

More than 1 in 5 participants (404/2004, 20.5%) reported financial difficulties related to COVID-19, and 3 in 10 had a chronic disease (n=615, 30.7%). Nearly 9 in 10 respondents (n=1796, 89.6%) perceived their health state as "good" or "very good."

Table 1. Participants' characteristics (N=2004).

Variables	Values
Gender, n (%)	
Male	992 (49.5)
Female	1012 (50.5)
Age group (years) , n (%)	
≥60	518 (25.8)
40-59	750 (37.1)
18-39	736 (36.7)
Professional status , n (%)	
Active	1329 (66.3)
Retired	427 (21.3)
Unemployed	248 (12.4)
People in the household , n (%)	
≥3	825 (41.2)
2	723 (36.1)
1	456 (22.8)
Population density , n (%)	
Urban, more than 100,000 people	385 (19.2)
Urban, 20,000-100,000 people	520 (25.9)
Urban, 2000-20,000 people	627 (31.3)
Rural zone	472 (23.6)
Chronic disease, n (%)	615 (30.7)
Perceived health , n (%)	
Poor/very poor	208 (10.4)
Good/very good	1796 (89.6)
Financial difficulties , n (%)	
Yes, related to COVID-19	404 (20.2)
Yes, unrelated to COVID-19	480 (24)
None	1120 (55.9)
EPPM[a] scores, mean (SD)	
Efficacy	73.8 (17.4)
Fear control	54.5 (26)
Severity	73.5 (23.1)
Vulnerability	42.7 (22.4)
Avoidance	48.9 (22.9)

[a]EPPM: Extended Parallel Process Model.

Public Acceptance of Nonpharmaceutical COVID-19 Measures

The majority of the study population approved of all 8 proposed measures (Table 2). The items with the highest approval ratings were "make masking mandatory in public closed spaces" (1783/2004, 89.0%) and "make masking mandatory in public open spaces" (n=1667, 83.2%), and the items with the lowest approval ratings were "closing all schools/universities" (n=1286, 64.2%) and "closing nonessential commerce such as bars and restaurant (n=1146, 57.2%).

Unweighted least squares exploratory factorial analysis, followed by a Promax rotation, was performed on the 8 items. Eigenvalues for the first 3 factors were 4.58, 1.05, and 0.63, respectively; this suggested a 2-factor solution explaining 62.5% of the common variance of the data. Factor 1 included 6 items

related to collective restrictions and was interpreted as expressing acceptance of collective restrictions, whereas factor 2 included the 2 items related to mandatory mask wearing and was interpreted as expressing acceptance of individual protective measures. The factors showed satisfactory internal validity (Cronbach α was 0.88 for factor 1 and 0.87 for factor 2). The interscale correlation coefficient (r=0.61) showed that these factors were related but distinct. On average, more than 80% of the study population agreed with individual protective measures (make masking mandatory in public closed spaces: 1783/2004, 89%; make masking mandatory in public open spaces: n=1667, 83.2%) and 74% agreed with collective restrictions, with some variations—from 80% (n=1604) for "isolate vulnerable people" to 57.2% (n=1146) for "close nonessential commerce such as bars and restaurants." More than 80% (n=1628) of participants accepted the 2 proposed individual protective measures and 9.1% (n=182) rejected them both, while 41.1% (n=823) accepted the 6 proposed collective restrictions and 6.1% (n=122) rejected all of them (Table 3).

Regarding COVID-19 perceptions, as assessed by the EPPM, efficacy (mean 73.8, SD 17.4) and severity (mean 73.5.1, 23.1) had the highest scores on a 100-point response scale, followed by lack of fear control (mean 54.5, SD 26.0), cognitive avoidance (mean 48.8, SD 22.9), and perceived vulnerability (mean 42.8, SD 22.4). Differences between T-scores were significant, except for efficacy and severity.

Table 2. Numbers, percentages, and factor loadings for the 2-factor solution of the acceptance of 8 nonpharmaceutical COVID-19 measures (N=2004).

Item	Totally agree/agree, n (%)	Totally disagree/disagree, n (%)	Factors	
			F1	F2
Make mask mandatory in public closed spaces	1783 (89)	221 (11)	N/A[a]	0.95
Make mask mandatory in public open spaces	1667 (83.2)	337 (16.8)	N/A	0.81
Isolate vulnerable people (eg, older adults)	1604 (80)	400 (20)	0.56	N/A
Forbid mass gatherings (eg, fairs, markets)	1590 (79.3)	414 (20.7)	0.59	N/A
Mobility restrictions for nonessential workers	1482 (74)	522 (26)	0.74	N/A
Stay at home order for nonessential workers	1314 (65.6)	690 (34.4)	0.85	N/A
Close all schools/universities	1286 (64.2)	718 (35.8)	0.80	N/A
Close nonessential commerce (eg, bar, restaurant)	1146 (57.2)	858 (42.8)	0.82	N/A
Eigenvalue	N/A	N/A	4.58	1.05
Percentage of explained variance	N/A	N/A	52.6	9.9
Cronbach α	N/A	N/A	0.88	0.87

[a]N/A: not applicable.

Table 3. Respondents (N=2004) agreeing with proposed collective COVID-19 nonpharmaceutical prevention measures.

Number of measures accepted	Respondents, n (%)
0	122 (6.1)
1	149 (7.4)
2	186 (9.3)
3	209 (10.4)
4	239 (11.9)
5	276 (13.8)
6	823 (41.1)

Association Between Public's Acceptance of Nonpharmaceutical Measures and COVID-19 Perceptions

Estimate of acceptance of collective restrictions in univariate analysis (Table 4) increased with household number and level of efficacy, fear, perceived severity, perceived susceptibility, and cognitive avoidance and decreased with age older than 60 years and retired occupational status. In multivariate analyses, this estimate increased with elevated level of efficacy, fear, and perceived severity and decreased with age older than 60 years.

Estimate of acceptance of individual protective measures in univariate analysis (Table 5) increased with level of efficacy, fear, perceived severity, and perceived susceptibility. In multivariate analyses, this estimate increased with higher level of efficacy, fear, and perceived severity. However, the goodness of fit for the multivariate model indicated an underdispersion of the data that warrants caution when interpreting the results.

Table 4. Rate ratios and 95% CIs of the acceptance of collective restrictions (N=2004), Poisson regression.[a]

Variables	Univariate, rate ratio (95% CI)	Multivariate[b], rate ratio (95% CI)
Gender		
Female	1.03 (0.98-1.07)	N/A[c]
Male	1	N/A
Age in years		
≥60	*0.89 (0.84-0.94)*	*0.89 (0.81-0.98)*
40-59	0.97 (0.92-1.02)	0.96 (0.91-1.01)
18-39	1	1
Professional status		
Active	1.01 (0.94-1.07)	1.02 (0.96-1.09)
Retired	*0.91 (0.85-0.99)*	0.98 (0.88-1.09)
Unemployed	1	1
Population density		
Urban, more than 100,000	1.00 (0.94-1.07)	N/A
Urban, 20,000-100,000	1.04 (0.98-1.10)	N/A
Urban, 2000-20,000	1.04 (0.98-1.10)	N/A
Rural zone	1	N/A
Household size		
≥3	*1.11 (1.05-1.18)*	1.04 (0.99-1.11)
2	1.03 (0.97-1.09)	1.03 (0.97-1.09)
1	1	1
Chronic disease	1.00 (0.95-1.05)	N/A
Perceived health		
Poor/very poor	0.96 (0.89-1.03)	N/A
Good/very good	1	N/A
Financial difficulties		
Yes, related to covid	1.07 (1.02-1.13)	N/A
Yes, unrelated to covid	1.01 (0.96-1.07)	N/A
None	1	N/A
EPPM[d] scores		
Efficacy	*1.03 (1.02-1.04)*	*1.02 (1.01-1.03)*
Lack of fear control	*1.06 (1.05-1.07)*	*1.04 (1.03-1.05)*
Severity	*1.08 (1.07-1.09)*	*1.04 (1.03-1.06)*
Vulnerability	*1.05 (1.04-1.06)*	1.01 (0.99-1.02)
Avoidance	*1.02 (1.01-1.03)*	1.00 (0.99-1.02)

[a]Significant results (P<.05) are marked in italics.

[b]Goodness of fit for the multivariate model (value/df for the deviance)=1.08.

[c]N/A: not applicable.

[d]EPPM: Extended Parallel Process Model.

Table 5. Rate ratios and 95% CIs of the acceptance of individual protective measures (N=2004), Poisson regression.[a]

Variables	Univariate, rate ratio (95% CI)	Multivariate[b], rate ratio (95% CI)
Gender		
Female	1.04 (0.97-1.11)	N/A[c]
Male	1	N/A
Age group (years)		
≥60	1.08 (0.99-1.17)	N/A
40-59	1.04 (0.96-1.12)	N/A
18-39	1	N/A
Professional status		
Active	1.02 (0.92-1.13)	N/A
Retired	1.09 (0.97-1.23)	N/A
Unemployed	1	N/A
Population density		
Urban, more than 100,000 people	0.95 (0.86-1.06)	N/A
Urban, 20,000-100,000 people	0.99 (0.90-1.09)	N/A
Urban, 2000-20,000 people	1.01 (0.92-1.10)	N/A
Rural zone	1	N/A
Number of household		
≥3	1.04 (0.95-1.14)	N/A
2	1.04 (0.95-1.14)	N/A
1	1	N/A
Chronic disease	1.07 (0.99-1.15)	N/A
Perceived health		
Poor/very poor	0.96 (0.86-1.07)	N/A
Good/very good	1	N/A
Financial difficulties		
Yes, related to covid	0.98 (0.90-1.07)	N/A
Yes, unrelated to covid	1.01 (0.963-1.09)	N/A
None	1	N/A
EPPM[d] scores		
Efficacy	*1.04 (1.03-1.05)*	*1.03 (1.03-1.04)*
Lack of fear control	*1.04 (1.03-1.05)*	*1.02 (1.01-1.03)*
Severity	*1.07 (1.05-1.08)*	*1.03 (1.01-1.05)*
Vulnerability	*1.03 (1.01-1.04)*	1.00 (0.98-1.02)
Avoidance	1.00 (0.98-1.02)	N/A

[a]Significant results are marked in italics.

[b]Goodness of fit for the multivariate model (value/df for the deviance)=0.34.

[c]N/A: not applicable.

[d]EPPM: Extended Parallel Process Model.

Discussion

Principal Results

Acceptance rates in our study population reached, on average, 86.1% for individual protective measures (such as mandatory face mask wearing), and 74.0% for collective restrictions, such as isolate vulnerable people (80%), forbid public gatherings (79.3%), and mobility restrictions for nonessential workers (74.0%). The least popular restrictions were closing of nonessential commerce such as bars and restaurants (57.2%). Acceptance of collective restrictions was positively associated with the level of efficacy, fear, and perceived severity, and negatively with age older than 60 years. Acceptance of individual protective measures was associated with level of efficacy, fear, and perceived severity.

Data were collected after the first lockdown in France, in a period when COVID-19 cases and deaths were minimal. Most restrictions implemented to help combat COVID-19 have been lifted; although strict hygiene and social distancing methods remained in place, life returned to some level of normality. However, global and local health authorities continued to use various media to inform the public about the epidemic and to promote a range of health protective behaviors to prevent infections [4,5]. In this in-between stage of the COVID-19 pandemic, our participants still perceived COVID-19 as a severe disease, and the recommended measures as highly efficient to prevent infection. This indicates a “danger control” process, in which individuals are motivated to take action to lessen the threat. Additionally, the “lack of fear control” and vulnerability scores indicated a strong reaction to the ongoing fear appeal communication about COVID-19, even if people did not consider themselves to be highly vulnerable [8].

Comparisons With Prior Studies

Although individual protective measures were rather consensual in our study population, collective restrictions had more mixed acceptance rates—ranging from 80%-57%. One possible explanation is that these measures were assessed in light of their restrictive nature [31], socioeconomic consequences (eg, unemployment, bankruptcy of businesses, mobility restrictions), and/or psychological burden (eg, anxiety, depression) [32]. For instance, the stay-at-home order for nonessential workers was linked to health anxiety, financial worry, decreased physical activity, isolation, and loneliness [9,33]. Similarly, closing all educational settings (schools and universities) jeopardized students’ education and well-being [34-36], while closing bars and restaurants led to massive unemployment in the food and hospitality sector during the first lockdown. This would be in line with a European Union report documenting a substantial increase in people’s economic anxiety in the months following the COVID-19 outbreak, especially in those European Union countries hit hardest in economic terms [37], and with a survey conducted in the aftermath of the first quarantine periods showing that unemployment and poverty/social inequality were close behind COVID-19 in the global concerns ranking [38]. Conversely, isolating vulnerable people [39], forbidding mass gatherings, and restricting the mobility of nonessential workers had higher acceptance rates, as these targeted restrictions may reduce COVID-19 spread and deaths with more limited social costs.

The relationship observed between vulnerability and acceptance of collective and individual protective measures became nonsignificant when entered together with efficacy, lack of fear control, and perceived severity in the multivariate models. This indicates that the acceptance of collective restrictions was more related to collective than personal protection, likely to protect others [21] and restore the situation back to normal. The acceptance of collective restrictions was nevertheless lower among participants aged >60 years, who are more likely than others to be targeted and isolated from the rest of society [40]. Other indicators of vulnerability (chronic disease, perceived health) were unrelated to acceptance rates, perhaps because older age was the main identified factor linked to COVID-19 mortality during the first outbreak [41].

Limitations

The results of this study must be viewed in light of its main limitations. First, the cross-sectional design does not allow causal inferences about relationships between variables to be determined. Furthermore, missing data precluded the investigation of EPPM appraisal in the total study sample, and some novel measures such as “location tracking” [19] or “COVID-19 passport” were omitted. Second, personality variables such as anxiety trait and pessimism may have a pivotal influence on appraisals and were not assessed. Finally, data were collected in a cohort including a small proportion of individuals with deprived socioeconomic backgrounds, which may limit the generalizability of our results. The large size of our cohort and the inclusion of diverse professions and socioeconomic groups nevertheless offered an interesting opportunity to assess the acceptance of COVID-19 nonpharmaceutical measures in the general population.

Conclusion

The aim of this study was to evaluate the acceptance of COVID-19 nonpharmaceutical measures and, more specifically, to measure the public’s acceptance of these measures and their association with COVID-19 perceptions. Our findings suggest that acceptance rates of COVID-19 nonpharmaceutical measures were rather high, but varied according to their perceived social costs, and seemed to be more related to collective than personal protection. Altogether, it appears that the nonpharmaceutical measures that minimize social costs while controlling the spread of the disease are more likely to be accepted and therefore more sustainable during pandemics.

Data Availability

The data underlying this article are available in Open Science Framework [42].

Authors' Contributions

AC, DC, KGM, and JR contributed to the conception and design of the study and interpreted the data and drafted the final manuscript. KGM suggested the theoretical framework. AC performed the statistical analysis and wrote the first draft of the manuscript. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EPPM: Extended Parallel Process Model
RR: rate ratio

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Original Paper

Exploring the Reasons for Low Cataract Surgery Uptake Among Patients Detected in a Community Outreach Program in Cameroon: Focused Ethnographic Mixed Methods Study

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Abstract

Background: Vision 2020: The Right to Sight, was one potential way to deal with the barriers surrounding cataract surgery and improve access to eye care. To this effect, the Magrabi International Council of Ophthalmology (ICO) Cameroon Eye Institute (MICEI) has performed more than 1000 sight-restoring cataract surgeries among patients referred from outreach camps. However, quite a good number of patients diagnosed with cataracts during community screening camps fail to present for surgery. This study sought to explore some of the challenges to accepting cataract surgery among community-diagnosed patients with cataract, patients operated for cataract, and community members.

Objective: The study objective was 5-fold: (1) to assess the level of awareness about cataract and available treatment, (2) to explore barriers to cataract surgery uptake, (3) to assess people's perception about the outcome of cataract surgery, (4) to understand people's perception about free cataract surgery, and (5) to explore reasons for outright refusal of cataract surgery.

Methods: This was a focused ethnographic study from December 2018 through February 2019 in 3 different communities of the Center Region of Cameroon, in which patients with cataract were diagnosed. The study sample was composed of patients operated for cataract, those diagnosed with cataract, key informants, and community members. Focus group discussions (FGDs), personalized in-depth interviews, and a short demographic questionnaire were used to collect data. Data were analyzed using a Microsoft Excel spreadsheet and Stata 14 (StataCorp). Data were presented using tabular and graphical methods.

Results: A total of 29 subjects (19 men) with a mean age of 54.5 (SD 14.5) years took part in the study. The most prominent barriers to cataract surgery were found to be cost (25/29, 86%) and fear of surgery (17/29, 59%). It was also noted by 41% (12/29)

of subjects that those who do not take up cataract surgery turn to traditional medicine. Other barriers included the lack of awareness of available treatment (6/29, 21%), no perceived need (5/29, 17%), cultural beliefs and superstition (4/29, 14%), and negligence (4/29, 14%).

Conclusions: We found cost (25/29, 86%) and fear (17/29, 59%) to be the main barriers. Belief in traditional medicine and superstition were the main drivers of fear. The implementation of a tiered pricing system, counseling training for key informants, incentives for the referral of patients with cataract, mass media engagement, advocacy, training and active involvement of traditional doctors as key informants, acquisition of a 4×4 outreach van, and motorbikes for camp organizers were some of the recommendations based on our results.

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KEYWORDS

ophthalmologic surgical procedures; access to health care; ophthalmology; patient-centered care; ethnography; health knowledge; attitudes; practice

Introduction

According to VISION 2020: The Right to Sight, African countries needed a cataract surgical rate of at least 2000 per million population to eliminate avoidable blindness by 2020 [1,2]. The Magrabi International Council of Ophthalmology (ICO) Cameroon Eye Institute (MICEI) [3], in attempting to expand high-quality and subsidized cataract surgeries through free community eye screening camps, saw a backlog of 40.9% (604/1477) of diagnosed cataracts. Figure 1 shows the backlog of community-diagnosed cataracts for 2018.

The global burden of blindness increased by 10.8% between 2010 and 2019 [4]. This burden was worse in sub-Saharan Africa owing to limited eye care personnel [5,6]. Studies have shown that the prevalence of moderate to severe bilateral visual impairment among those aged 50 years and above is approximately 10.9% (95% CI 8.3-14.3) [7]. Cataracts are considered the leading cause of blindness among the ≥50-year age group, and 55% of those blind individuals are women [8]. Although approximately 80% of blindness is preventable with either a simple sight-restoring surgery or a pair of eyeglasses, many people, particularly older individuals in the community, continue to be needlessly blind [9]. The Universal Eye Health Global Action Plan (UEH GAP 2014-2019) was aimed at a world in which no one is needlessly blind and those with irreversible blindness can achieve their full potential by integrating eye health into national health plans [4,10-12]. The fact remains that low- and middle-income countries are disproportionately affected with 90% of the global burden borne by African countries and with vulnerable low-income individuals particularly being the hardest hit [13].

The Universal Health Coverage effectiveness coverage index for Cameroon is 42 [14] and 70% of the total health spending per capita (US $60, range, US $47-75) is an out-of-pocket expense [15]. This may explain why Cameroon has one of the highest burdens of moderate to severe visual impairment in the world [16], with almost a quarter of a million persons reported to be blind and approximately 720,000 individuals with visual impairment [16]. Age remains a major predictor and as such, the burden of visual impairment in Cameroon increases with age [17]. There is limited evidence regarding the health-seeking behavior of different communities toward eye care in Cameroon. Studies conducted (most of which were hospital-based and dating more than a decade) have focused on visual impairment, causes, and functional difficulties [18-22]. We found a single community-based study related to self-reported visual impairment [9]. There is the staggering belief in Cameroon that those with health concerns report to the hospital, but evidence suggests that Cameroonians generally report to health facilities when their health conditions have worsened [23,24].

Despite having a National Eye Care Program (Programme national de lutte contre la cécité), there is currently a very small government budget compared to needs specifically allocated to eye care as reported in many other sub-Saharan countries [25]. Lack of integration of eye care into the public health strategy, unavailability of well-trained personnel, and concentration of those trained in major city centers [26,27] coupled with inappropriate infrastructure limit access to eye care among high-income individuals. This is further compounded by the poor transport network, ignorance of available services, and cultural beliefs [28]. This limits the cataract surgical rate of Cameroon—which is the number of cataract operations performed per million population per year—to 758, which is far below the recommended 2000 (target) [29]. Eye care delivery in Cameroon is hospital-based and the evidence on best practices, for which particular groups of persons they are intended, and under what contextual factors they are delivered is generally lacking [30]. The above-highlighted challenges leave the prevalence of cataract blindness in the community very high among the elderly population, thereby making traditional medicine an important alternative [31].

The establishment of MICEI led to the introduction of the Aravind eye care delivery model [32-34] in Cameroon. This program involves community screening targeted to the ≥50-year age group, providing free voluntary transport referral to the clinic and back to the community for those diagnosed with cataract, offering sight-restoring cataract surgery, a bed, feeding, and postoperative medications. Figure 2 shows the community screening camp's workflow.

Figure 1. Community-diagnosed cataract backlog in 2018.

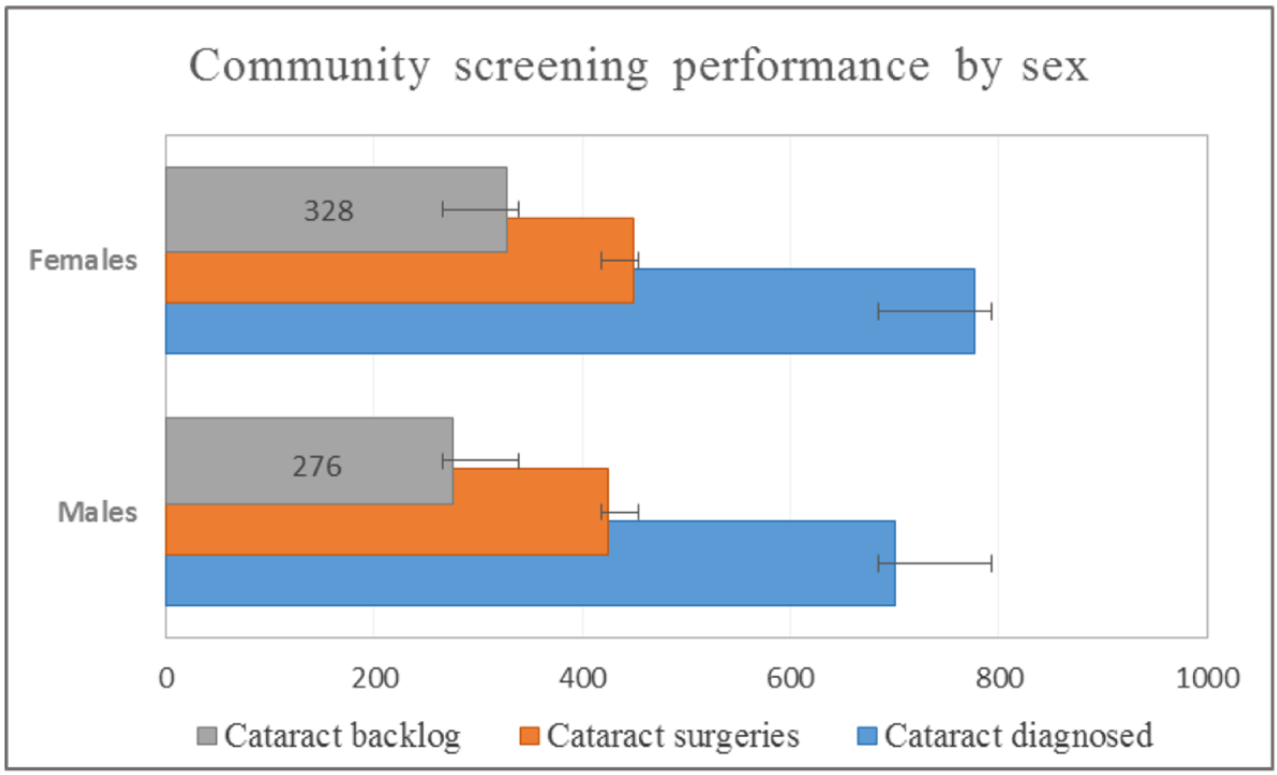
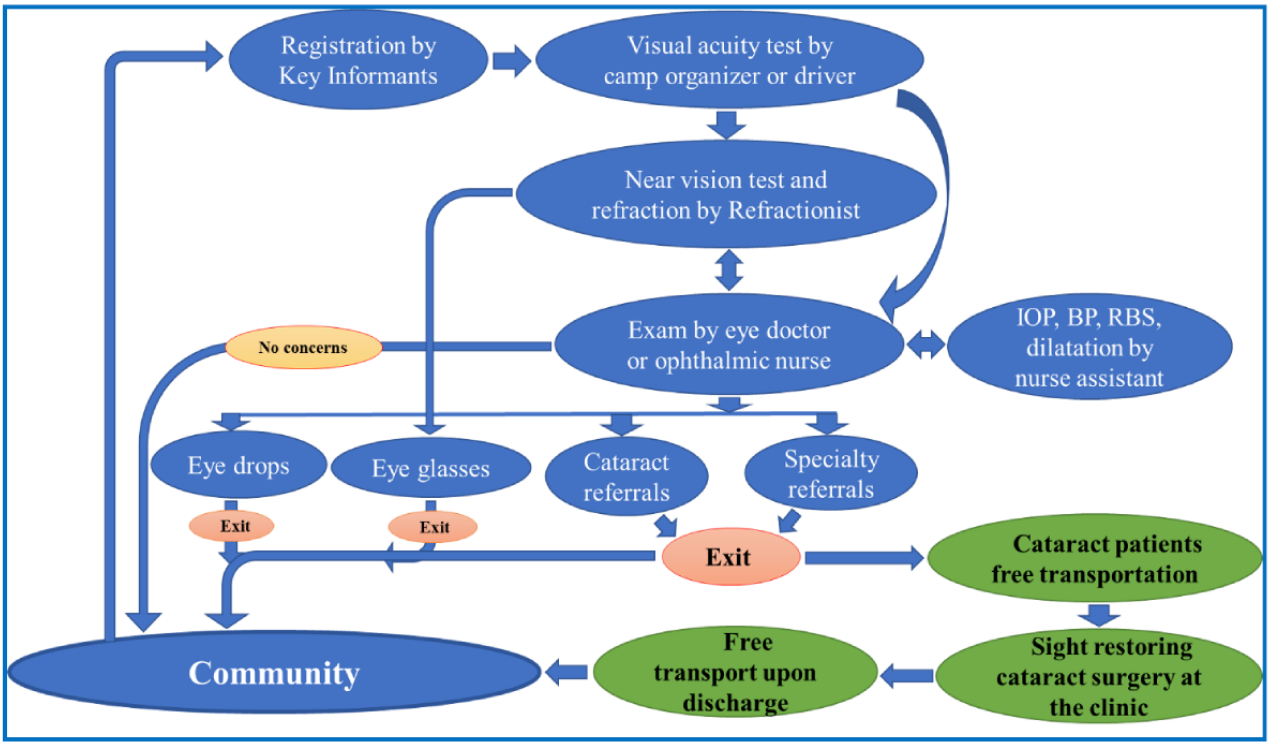


Figure 2. Magrabi International Council of Ophthalmology Cameroon Eye Institute's community ophthalmic screening camp workflow. BP: blood pressure, IOP: intraocular pressure, RBS: random blood sugar.



A similar community-based tiered system is operational in Nigeria [35,36] either by the government or private clinics, Ethiopia [37], and in the Democratic Republic of the Congo [38]. Patients admitted for surgery may be operated on site, as is the case in Nigeria. Community screening programs specific to cataract surgery may also take the form of operationalizing memoranda of understanding with donor organizations. This includes, for example, the Seeing Is Believing project (SiB) [39], the Hilton Cataract Initiative [40], and the Cameroon Cataract Bond [41,42].

We aimed at understanding the challenges associated with accessing cataract surgery. The study objectives were to (1)

assess the level of awareness about cataracts and available treatment, (2) explore barriers to cataract surgery, (3) assess the community's perception about the outcome of cataract surgery, (4) understand people's perception surrounding free cataract surgery, and (5) understand the reasons for outright refusal of cataract surgery.

Methods

Study Design

This was an ethnographically oriented mixed methods study [43-45] involving informal discussions, outreach document analysis, field visits, field notes, focus group discussions (FGDs), in-depth interviews, and questionnaires. We focused the ethnography [46] on investigating the challenges surrounding decisions to take up cataract surgery.

Ethnographic Rationale

Ethnography [47,48] in health care is a context-specific and field-based approach to understanding patient behavior within the complexity of their family and community cultures [49,50]. Ethnography is a recommended approach for multisite studies aimed at capturing diverse perspectives [51]. Evidence also suggests that ethnography can be focused [52,53] to address specific issues or questions. This approach was particularly important because we wanted to understand not only the reasons for the low uptake of cataract surgery among patients with cataract but also the role of family members and the community as a whole in the making of such decisions [46,54]. Studies have used similar methods in exploring user experiences in health care [55,56].

Research Team and Reflexivity

The research team comprised (1) the principal investigator (PI), (2) a research assistant recruited purposely for the study, (3) a trained key informant, and (4) a driver. While subjects were known to the research key informant, a few might have seen the driver during screening camps. The PI, who was familiar with qualitative research methods, drilled the research assistant and the driver on the study and data collection procedures prior to the study. The key informant was briefed about the study over the telephone but only knew about the questions during FGDs. Both the PI and the driver administered open-ended questions during FGDs while the PI took on the personalized interviews. The key informant assisted with translation during FGDs and only assisted in personalized interviews on the basis of need.

Setting and Context

This study took place in 3 underprivileged communities in which MICEI has organized outreach screening campaigns. MICEI is a 73-bed capacity lone subspecialty clinic and training institute dedicated to eye care in Cameroon and environs, with a daily traffic of 300 outpatient visits [3]. The clinic is home to 7 ophthalmologists, 7 ophthalmic nurses, an optometrist, a low vision expert, 75 allied eye health personnel, and 2 cataract operating rooms [57].

The 3 ethnographic study sites were predominantly French-speaking communities located in the Lekié Division of the Center Region of Cameroon including Elig-Mfomo in the Elig-Mfomo Sub-Division, Nkalngaha in the Evodoula Sub-Division and Lenouk in the Monatélé Sub-Division. The Lekié Division is inhabited by half a million population dispersed across 700 villages. Life is subsistent and highly reliant on agriculture, with cocoa as the main cash crop [58].

The population of the Center Region of Cameroon is approximately 4.5 million. There are 8 other eye clinics (general ophthalmology) within the region including the (1) University Teaching Hospital, (2) Central Hospital, (3) General Hospital, (4) Military Hospital, (5) Gyneco-obstetric Hospital, (6) Etoug-Ebé Presbyterian Hospital, (7) Essos Hospital Center-NSIF, and the (8) Obala Sub-Divisional Hospital.

Sampling Strategy

Study Site Selection

Ahead of the study, an assessment of the community outreach program showed a backlog of 42.13% (495/1175) of all diagnosed cataracts. We compared the number of people with cataract diagnosed in each community visited in 2018 to the number of those who received surgery. Since the aim was to improve the cataract acceptance rate through the emic and etic perspectives [59], a study exercise of outreach reports together with informal conversations with colleagues provided insights on the communities with extremely poor and best cataract surgery acceptance rates.

Recruitment of Participants

A total of 29 subjects were recruited from a sampling frame of both operated and unoperated patients with cataract as well as the members of each selected community. For good representation, each community sample constituted 3 direct subjects (1 operated and 2 unoperated patients with cataract) and 7 indirect subjects (1 family head or breadwinner of the operated patient, 1 family head or breadwinner of an unoperated patient with cataract, a village head, a traditional healer, a trained key informant, a trained frontline health worker, and an influential community member). Both the operated and the unoperated patients with cataract were purposefully selected from the clinic's database of operated and diagnosed patients with cataract followed by a snowball sampling technique, with the help of key informants. A purposive sampling technique was used to identify key informants from the sampling frame of the MICEI's trained key informants from the preselected study sites. The inclusion criteria were (1) being diagnosed in a screening camp organized by the clinic, (2) being diagnosed in the selected community, (3) being a resident within the community and environs, and (4) having undergone surgery at the MICEI. The exclusion criteria were (1) site inaccessibility, (2) inability to provide informed consent, and (3) inability to communicate.

Ethical Considerations

A study protocol was developed and informally approved by the institutional review board (IRB) of the MICEI. Written informed consent was sought from all participants in accordance with the tenets of the Helsinki Declaration of 1975 [60]. This study adhered to the Critical Appraisal Skills Program [61,62].

Subjects were briefed prior to data collection, on the need to maintain anonymity. Research materials were translated into the French language as the study sites were predominantly French-speaking communities. Participants received reimbursement for their transport fares. All blind subjects with cataract were invited for free cataract surgery. All questions were translated into the local Eton or Manguissa languages (subsets of the Beti ethnic group) for those who neither understood nor could express themselves in the official languages. All the concerns of subjects were addressed before the start of data collection.

Data Collection Procedure

An interview guide (Multimedia Appendix 1) and a short demographic questionnaire were developed and reviewed by the IRB in a research protocol ahead of field visits. We consulted with colleagues to define the questions that preoccupied the community eye health unit, and then we used a realist approach [63] to develop the interview guide based on a framework of the defined questions as main themes. Interview guide questions included "What do you know about cataract?" "What would you say hinders people from taking cataract surgery?" "What do people say when those who had cataract surgery return to the community?" "What is your opinion about free and paid cataract surgery?" and "Why do you think some people do not want cataract surgery?" All data were collected in the French language, and translations were made into local languages and vice versa. Data collection was organized into 3 FGDs (N=30), 30 personalized interviews, and 30 short sociodemographic questionnaires. Data were collected on December 28, 2018, for Nkalngaha, January 3, 2019, for Elig-Mfomo, and February 7, 2019, for Lenouk. One participant was absent, thereby reducing the sample to 29 subjects.

Document Review

Data on which sites were to be selected were obtained through document analysis of the community outreach unit at the base clinic. It took the form of a desk exercise followed by a deliberation meeting between the PI and colleagues. The review was based on outreach, operating theater, and medical record reports from January through September 2018. Data from the reports generated by the 3 departments were matched for consistency. We then calculated the cataract backlog by comparing the number of operated patients with diagnosed ones. This was used to produce time-series graphs per outreach site in Microsoft Excel.

FGDs

All subjects took part in a community-based FGD at each of the 3 study sites. Focus groups were a cross-section of the communities from which they were drawn. The duration of FGDs, which took place at a venue arranged by participants, ranged 30-42 minutes. FGDs were conducted by both the driver and the PI using open-ended questions. Participants took turns to express their views and experiences without time restrictions. The PI moderated unnecessarily lengthy discussions and used probes until saturation was reached. Saturation was observed when there was silence with no further contributions. The key informant switched between the moderate role (by translating into the local language and vice versa) and an "observer as a participant" role during FGDs [64].

Personalized Interviews

All participants were invited to a personalized interview with the PI at the end of each FGD. Interviews were conducted further away from FGDs to enhance autonomy. The key informant assisted with translation where necessary. The overall duration of personalized interviews was 66 minutes on average.

Demographic Questionnaire

The data on demographic variables were also collected by the research assistant at the end of personalized interviews. All 29 subjects took part in the survey. The place for administering the short questionnaire was decided at the convenience of participants.

Field Backup Notes

The research assistant who served as a complete observer (passive participant) took backup notes during FGDs on the basis of observed and nonverbal communication of subjects as well as any phenomenon of interest, using eye-to-eye and soul-to-soul approaches.

Data Collection Tools

An interview guide was used to conduct the FGDs and personalized interviews. Digital recordings of FGDs and interviews were performed using an Android tablet (SAMSUNG Galaxy Note 10.1). A short paper questionnaire was used to capture data on age, sex, marital status, residence, education, and occupation. Field and backup notes were collected on A4 papers. The distances of participants' villages from the clinic were computed using Google and OpenStreetMap [65].

Data Processing and Analysis

Data Preparation

Digital recordings of FGDs and personalized interviews were assessed after each field visit for quality and saved against a date and study site. Captured demographic data were entered into a Microsoft Excel spreadsheet prior to analysis. Audio recordings were severally listened to vertically and horizontally for familiarization. Based on this intimacy, the data were transcribed and translated into the English language. For the easy discovery of phrases of interest in the data, investigation, and analysis, we adopted a heuristic coding approach [66] starting with questions, including "What do you know about cataract?" (Code 1), "What would you say hinders people who want surgery from taking cataract surgery?" (Code 2), "What do people say when those who had cataract surgery return to the community?" (Code 3), "What is your opinion about free and paid cataract surgery?" (Code 4), and "Why do you think some people do not want cataract surgery?" (Code 5).

Data Analysis

Quantitative Analysis

The quantitative data analysis of this study started with the outreach unit review process whereby we compared the monthly reports of community screening camps. This was trimmed down to the 3 sites with the poorest performances by comparing the

monthly cataract diagnosed lists established at the end of each camp against the monthly operating theater reports of those who received surgery, for the period of January to September 2018. Demographic survey data were analyzed using Stata 14 (StataCorp).

Thematic Analysis

The inductive and deductive methods, known to be effective in exploring users' views [67], were used to analyze qualitative data. An inductive approach and predefined framework [68] were used to focus the thematic analysis on research objectives and interview guide [69]. FGD and interview data were transcribed and analyzed thematically [70] using Microsoft Excel. Through a heuristic process [66,71], multiple rounds of going through the transcribed data and field notes permitted the identification of phrases linked to the originally established question codes. These were then arranged into themes in accordance with question codes by means of cut and paste. Further investigation into these themes (deduction) led to the breakdown of these themes into subthemes, which provided insights into the different pieces of information required for each question. These pieces were analyzed by focusing on content and context with the intention of creating new knowledge about individual perceptions, how they are interrelated, and their relation to the environment [66]. Each subtheme (coded datum) was attributed a descriptive code [72] that depicted the datum's intent and essence.

Data Transformation

In this study, contextualized qualitative data were transformed by giving numerical meaning to quotes (scoring) [73] on the basis of "popularity coding" for robust presentation and visualization [74]. Although some have criticized the quantification of qualitative data [75], our proposed theme and subtheme "popularity coding" approach is based on the argument that the finality of data analysis is to meaningfully represent data and arrive at conclusions that mirror the data [76]. Besides, the coding in thematic analysis, as well as logistic regression techniques, still represent the use of numerical values in qualitative data. We depicted the relative importance attached to particular words and experiences based on how often they appeared in the text. These were then assigned numerical values and reported as frequencies.

Trustworthiness, Validity, and Reliability

The use of focused ethnography [52,53] led to the diversity of captured data and rendered it as close to reality and specific to communities as possible. Prompts proposed by Dixon-Woods et al [77] were used to ensure quality. Trustworthiness in the results was ensured by establishing a link and maintaining harmony between the data and the analysis through a back-and-forth approach, by continually listening to the audios and reading the transcribed data intermittently to ensure coherence, intimacy, incubation, and reflexivity [66]. The triangulation of data from FGDs and personalized interviews from 3 different communities increased the internal validity of our results. Intermittently withdrawing from the data analysis and enthusiastically returning to the transcriptions led to inspirational fresh immersion, incubation, and reflexivity, which improved the way data were analyzed and interpreted [78]. Notwithstanding the challenges of measuring reliability in qualitative research [79], specific reporting guidelines were used to maintain reliability and ensure that the results are reproducible.

Results

Results Overview

We report the study findings using the Critical Appraisal Skills Program [61,62], the Standards for Reporting Qualitative Research [80], as well as the recommendations of Gertner et al [51] for reporting studies with ethnographic approaches.

Participant Characteristics

Table 1 shows the demographic characteristics of participants. Altogether 29 subjects from 3 different communities (Evodoula, Elig-Mfomo, and Monatélé Sub-Divisions) were recruited to the study from December 2018 through February 2019. The age of the subjects ranged 30-81 years with a mean age of 54.5 (SD 14.5) years. Male subjects constituted 66% (19/29) of the total sample. Subjects came from 7 different villages with an average distance of 82.5 km and a drive time of 2 hours 23 minutes from the eye clinic (Table 2).

Table 1. Participant demographic characteristics (N=29).

Category	Direct (n=9), n (%)	Indirect (n=20), n (%)	Total, n (%)
Focus group			
Focus group discussion 1	3 (33)	6 (30)	9 (31)
Focus group discussion 2	3 (33)	**7** (35)	10 (35)
Focus group discussion 3	3 (33)	7 (35)	10 (35)
Age (years)			
<40	—[a]	3 (15)	3 (10)
40-49	2 (22)	10 (50)	12 (41)
50-59	3 (33)	2 (10)	5 (17)
60-69	2 (22)	1 (5)	3 (10)
70-79	1 (11)	2 (10)	3 (10)
≥80	1 (11)	2 (10)	3 (10)
Reported sex			
Male	5 (55)	14 (70)	19 (66)
Female	4 (44)	6 (30)	10 (35)
Marital status			
Married	6 (67)	13 (65)	19 (66)
Cohabiting	1 (11)	4 (20)	5 (17)
Single	—	—	—
Divorced/widowed	2 (22)	3 (15)	5 (17)
Residence			
Nkalngaha (Evodoula)	3 (33)	6 (30)	9 (31)
Elig-Mfomo	3 (33)	7 (35)	10 (35)
Lenouk (Monatélé)	2 (22)	4 (20)	6 (21)
Monatélé urban	—	1 (5)	1 (3)
Akougouda (Monatélé)	1 (11)	—	1 (3)
Nkol-Evida (Monatélé)	—	1 (5)	1 (3)
Nkolngal (Monatélé)	—	1 (5)	1 (3)
Employment			
Yes	—	3 (15)	3 (10)
No	9 (100)	17 (85)	26 (90)
Education			
None	1 (11)	3 (15)	4 (14)
Primary	3 (33)	9 (45)	12 (41)
Ordinary secondary	4 (44)	5 (25)	9 (31)
Advanced secondary	1 (11)	2 (10)	3 (10)
Graduate	—	1 (5)	1 (3)
Postgraduate	—	—	—

[a]—: not reported.

Table 2. Distance from the eye clinic.

Village	Distance (km)	Drive time (hours:minutes)
Average values	82.5	2:23
Nkalngaha (Evodoula)	44	1:15
Elig Mfomo	33	1:04
Lenouk (Monatélé)	100	2:52
Monatélé urban	91.2	2:36
Kougouda (Monatélé)	111.2	3:09
Nkolevida (Monatélé)	101.2	2:56
Nkolngal (Monatélé)	97	2:50

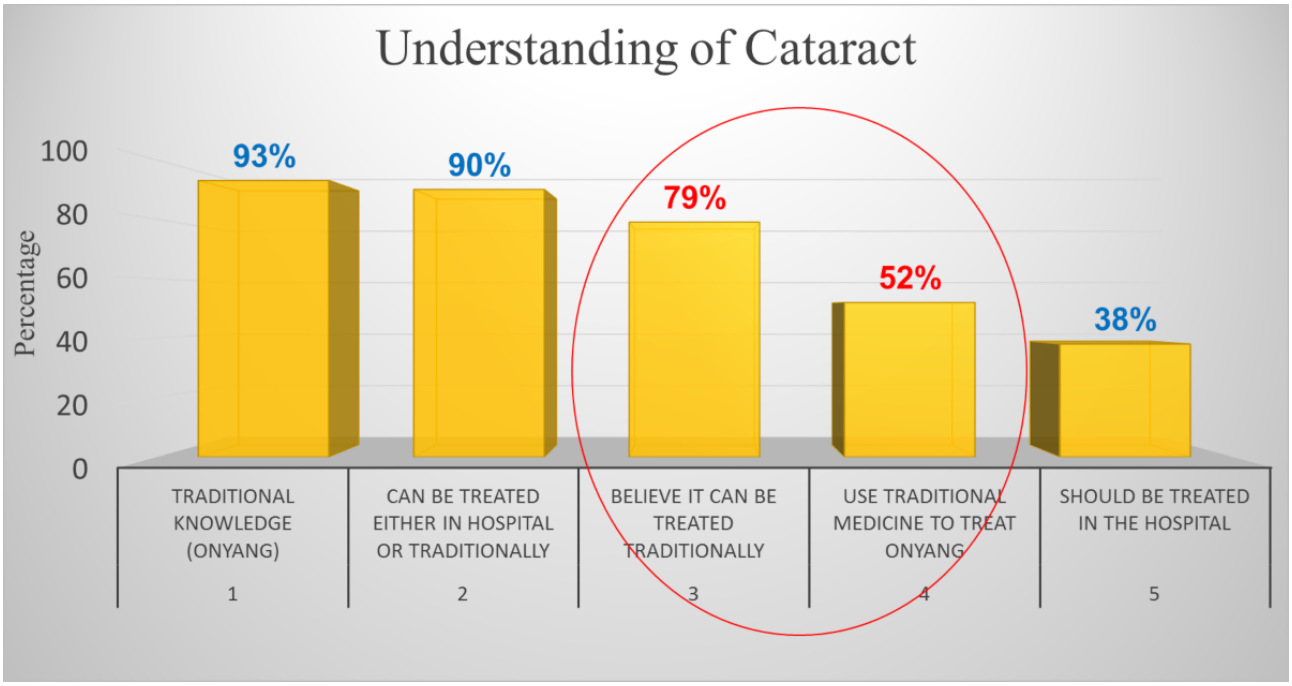
Knowledge And Awareness About Cataract

Subjects perceived cataract as a disease that affects the eye and can be called by many names depending on the community. Up to 93% (27/29) of participants knew cataract either as "Onyang," "Oquan-à-dis," or "Ndem-à-dis." According to them, "Onyang" was any visible white spot or substance in the eye that can either be treated traditionally or in the hospital. Further, sight loss to them meant that someone has the disease that affects the eye (cataract). Subject 2 in focus group 2 said, "Cataract is a disease that kills the eye, when it grows the eye dies." Only 38% (11/29) mentioned the hospital as the appropriate place to seek treatment for cataracts, as can be seen in Figure 3.

The experience of Subject 6 attests to the fact that "Onyang" can be cured traditionally as indicated below:

> *It is something that develops in the iris and it is white. I can treat it but if it is more than me, I send the person to the hospital*. [Indirect, Subject #6, FG1]

Figure 3. Participant-reported understanding of cataract.



Perceived Barriers to Cataract Surgery

Barriers to cataract surgery, which emerged from FGDs common to all 3 communities included the cost of surgery, fear, and hospital reputation, particularly owing to a history of cataract surgeries with poor outcomes from other clinics. A comparison of the FGDs with personalized interviews showed that 86% (25/29) and 59% (17/29) of subjects noted that lack of money and fear of surgery were, respectively, the main barriers to their accessing cataract surgery. Further, 21% (6/29) of subjects also reported a lack of awareness of available treatment. Curiously, up to 41% (12/29) of subjects reported that those who fail to take up surgery turn to traditional medicine, which itself is a major barrier. Figure 4 shows the barriers that emerged from the transcripts.

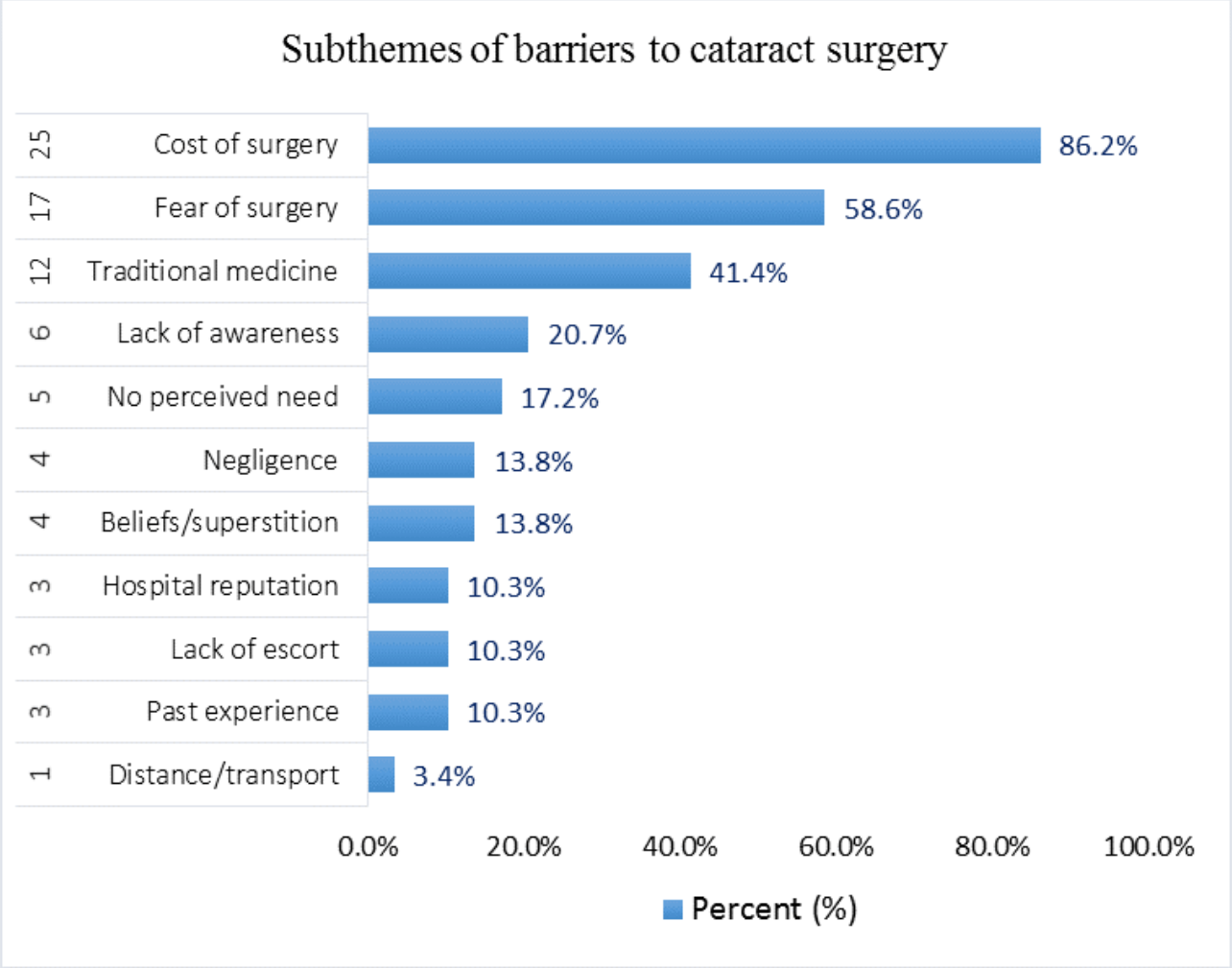
The following excerpts demonstrate that people attend the hospital when their health situation has worsened:

> *…. It is Onyang in Etone [famous tribe]. When you have Onyang, they can use traditional medicine, it works with the Beti [famous ethnic group] but sometimes it fails, after that, you can go to the hospital*. [Indirect, Subject #2, FG2]

> *We used to go to herbalists […]. Like the ones of Papa, we tried to put traditional medicines, it did not work, we called, the first person came it did not work, the other one said 'if I put the medicine two times it does not work then it is not at my level'*. [Direct, Subject #2, FG3]

In addition to traditional medicine as an alternative to treating cataracts in these communities, 28% (8/29) of interviewed subjects also reported that these patients stay at home, while only 13.8% (4/29) of subjects reported that patients sought care from other health facilities after failing to take up cataract surgery. One of the reasons why people sought traditional medicine was a lack of awareness of available treatment. One of the subjects said, "…we treat it with our leaves in the bush, herbs, we did not know that it can be operated" [FGD 3 extract].

Figure 4. Subthemes that emerged as barriers to cataract surgery.



Perception About Operated Patients With Cataract

In general, positive feedback from the community when operated patients with cataract returned from the eye clinic was acknowledged across all 3 FGDs. This was also confirmed by most subjects during personalized interviews. It was reported that many are seen dancing when those operated for cataract returned to these communities, as shown in the following quotes:

> *They [community members] start doing propaganda, 'such and such a person was at the hospital, he has been treated and now can see well' […]. Many people congratulate the hospital staff […], they give positive comments.* [Direct, Subject #3, FGD1]

> *After your campaign, I saw a mother dancing at the center [health center] saying 'I could not see but now I can see.' those who did not go said 'weeh!! [Exclamation], we have missed'*. [Indirect Subject #6, FGD2]

Approximately 86% (25/29) of interviewed subjects acknowledged that the community feedback is positive and that people are happy when those operated for cataract return into the community. Most of the patients reported that some are happy and others are not. The 5 main reasons that emerged from the data relating to why people might not be happy included lack of money to also undergo surgery (8/29, 28%), hatred and jealousy of those who were operated (4/29, 14%), regret (3/29, 10%), and the inability to continue managing the assets of those who were blind (7%). The following excerpts highlight some of the reasons:

> *Everybody says 'it is good, people eat 3 times a day [at MICEI], there is a bed, dresses'. People complain*

> *because they do not have the XAF25,000 (US$42.86) for surgery.* [Indirect, Subject #8, FG2]
>
> *… what is sure is that the person who was blind and is now seeing is like a witch or wizard, as if he has done some magic, has taken the eyes of a sheep to use. People will start commenting that eyes have been purchased and given to you.* [FGD3 extract]

Perception of Free Cataract Surgery

Subjects' perception that people were positive about free cataract surgery dominated in 2 of the 3 FGDs. The discussion in one focus group weighed on the fact that free cataract surgery raises suspicion and fear as shown in the following extract:

> *It is suspected in the community because we know that what is free later becomes expensive. Also, we do not have confidence in such operations because there could be other motives.* [Direct Subject #7, FG3]

Members of some of the FGDs, however, believed that suspicion and fear should not be a major call for concern since surgery is aimed at helping people regain sight. In FGD 2, for instance, subjects reported that paid cataract surgery will only be appreciated by those who can afford to pay the requested contribution, while in FGD 3, members thought that people are generally more comfortable to pay when surgery is subsidized than when it is free. The main reason behind not being happy for paid cataract surgery was the lack of means as 41% (12/29) of subjects related their unhappiness to cost when they see those who underwent cataract surgery return into the community rejoicing.

In total, 79% (23/29) of subjects reported that they would be happy with free cataract surgery and that the community will be positive about it as well. One of the interviewees said, "I ask if true and I run for it" (Direct, Subject #1, FG1).

Perceived Reasons for Refusing Cataract Surgery

In addition to participants' lived experiences in accessing cataract surgery and their perception of free cataract surgery were other perceived challenges even if they were to be made free of charge. While during FGD 1, subjects thought that refusal of free cataract surgery could be attributed to ignorance, both FGD 2 and FGD 3 revealed that refusal may result from age, fear, cultural beliefs, and superstition. Concurrent with in-depth interviews, the most prominent reasons for outright refusal of cataract surgery were fear (9/29, 31%) and cultural beliefs and superstition (8/29, 28%). Other reasons included age (4/29, 14%), poor experience (3/29, 10%), ignorance (3/29, 10%), and postsurgical follow-up costs (2/29, 7%).

> *Some people traditionally cannot be operated, sometimes age, fear. Before they used to take people to [...], [an eye clinic: name removed], they will leave here seeing well, when they come back they are blind.* [Indirect, Subject #8, male FGD2]
>
> *… myself, I was operated on. […] but when I got home, my village brothers started quarreling with me saying 'OK, we shall then see since you said you have gone to the hospital […]'. They are doing everything to put us uncomfortable [sorcerers], also do everything to save us [MICEI].* [FG3 Discussion extract, Direct Subject]

Regarding possible remedies to improve the uptake of cataract surgery, 24% (7/29) of subjects suggested the continuation of screening campaigns, 14% (4/29) suggested community education and awareness, and 14% (4/29) suggested counseling, including the use of postsurgical cataract ambassadors.

Discussion

Principal Findings

We found in this study that the barriers to cataract surgery included A (Awareness, Age), B (Beliefs or superstition, Bad experience), C (Cost), D (Distance), E (Escort), and F (Fear) among others. Even though 93% (27/29) of subjects knew cataract as "Onyang," "Oquan-à-dis," or "Ndem-à-dis" and as a disease that leads to blindness if not treated, up to 79% (23/29) of subjects believed cataract can be treated traditionally. In addition to seeking traditional treatment (12/29, 41%), cost (25/29, 86%) and fear of surgery (17/29, 59%) were the most acknowledged and leading barriers to cataract surgery. We also found that while most people were happy with free cataract surgery (23/29, 79%), cultural beliefs and superstition was a major driver of people's fear of cataract surgery and lack of resilience.

Interpretation of Results

We found in this study that 93% (27/29) of the study subjects knew about cataract as a potentially blinding eye disease, which was only a little lower than the 98% rate reported among 4 districts in Kerala, India [81]. Apart from a very large sample size of 2000, India has a long-standing history of community eye care delivery. Further, the 38% (11/29) of subjects who reported that cataracts should be treated in hospital was in line with the 37.2% reported by Lakshmipriya [81]. Our results of 97.6% awareness were higher than the 85.6% reported among subjects from 5 districts in Ghana, perhaps owing to differences in settings and methodology [82]. The 21% (6/29) lack of awareness of available treatment found in this study was lower than the 30% (33/109) awareness reported in East Nusa Tenggera in Indonesia [83], principally owing to differences in methodology as their study was hospital-based. The 93% awareness rate found in this study was only slightly lower than the 99.7% reported among a cross-section of 767 surveyed subjects in the Lomé neighborhood in Togo [84]. The rate of awareness of 94.9% among subjects in Takeo, Cambodia, was in accordance with the 93% awareness rate reported in this study [85].

The fact that up to 93% of subjects in our study knew that cataract is a blinding disease did not, however, completely translate into them knowing what cataract is. Their understanding of cataract in their local language could range from any visible vision-related problem to a white scar in the eye, depending on the tribe. This is similar to a study in Brazil in which 79% of subjects perceived a cataract as a scar that gradually covers the eye [86].

We report an 86% (25/29) cost-related barrier in this study as the leading barrier to cataract surgery, which is almost twice

that (49.2%, 65/132) reported by Fadamiro and Ajite [87] among subjects in Ekiti State, Nigeria. This study was carried out much earlier and over a longer period (2012-2014). The difference in time, settings, and methodology could have led to this disparity. Cost, as a leading barrier to cataract surgery reported in our study, was concordant to that reported among elders in the Nuwara Eliya District, Sri Lanka [88], as a leading barrier to eye care services. Kumar et al [89] reported that 88.9% of surveyed subjects attending an outpatient unit in Uttar Pradesh, India, complained about the cost of cataract surgery and 59.1% complained about the fear of losing sight. These results were similar to the 86% and 59% rates we found for cost and fear, respectively. Our report about cost as a leading barrier was also in line with the reported results by Tafida and Gilbert [90] in a study among subjects in the Jigawa State of northern Nigeria. A study in the English-speaking region of Cameroon found that cost was reported by 52.9% of participants as the major barrier to the uptake of surgery [9]. This was much lower than the 86% we found, principally because their study was a survey based on a questionnaire. Our results about cost as a leading barrier were not very different from the results (91%) reported among 66 subjects in Ghana [91]. Cost of surgery was also among the 3 main barriers to cataract surgical services uptake reported in Benin [92]. This study found that 86% of subjects reported lack of funds as the main barrier to cataract surgery, similar to the 79% reported among 157 subjects in Kilimanjaro, Tanzania [93].

This study found that 59% (17/29) of subjects had fear as one of the leading barriers to cataract surgery, which was similar to the 55.9% reported by Gilles et al [94] within the same setting. The proportion of those who reported fear (59%) as a major barrier to cataract surgery in our study was more than double of that (24.2%) reported in India [95], which could have been because interviews were limited to patients with cataract as opposed to ours and owing to the level of awareness, which should normally be higher in India. Our results about fear of surgery were almost 5 times the 12.57% (8/58) value reported in a similar study in Ghana [91]. Even though the study also made use of 3 FGDs and personalized interviews, their sample was limited to the operated and blind patients with cataract and the study was conducted more than a decade ahead of this study. A study among patients with cataract and key informants in Andhra Pradesh, India, also reported fear as a major barrier to the uptake of cataract surgery [96]. Fear of surgery was also reported by 9.2% of the 2076 surveyed subjects in rural Myanmar [97], which was far below our reported results probably because they used a closed-ended questionnaire with a much larger sample, and was conducted more than a decade earlier as well.

A study in the predominantly English-speaking Southwest Cameroon found that visually impaired patients seek traditional medicine before ever visiting the hospital [9], which was similar to what we found in this study. A study among 60 patients with cataract (operated and blind) in Kilimanjaro, also reported how subjects first sought traditional medicine prior to accepting cataract surgery [98].

In addition to perceived barriers, this study also found that awareness about cataract as a disease that can be cured traditionally also presents as a barrier to accepting cataract surgery. The following excerpt demonstrates this:

> *…. It is Onyang in Etone [famous tribe]. When you have Onyang, they can use traditional medicine, it works with the Beti [famous ethnic group] but sometimes it fails, after that, you can go to the hospital.* [Indirect, Subject #2, FG2]

This study reported that the benefits of cataract surgery extended beyond those operated on as the community joined them in celebration when they return to the community. A study in Bangladesh and Kenya also reported how the impact of cataract surgery extended beyond those operated upon [99]. The externalities of successful cataract surgery were also reported among 83 caregivers in Vietnam, whose happiness and life satisfaction among others significantly improved [100]. There is little evidence about the community's perceived impact of cataract surgery. Much of the reported evidence about the postcataract surgical experience is centered around quality of life [101-103].

This study found that 79% of interviewed subjects were happy with free cataract surgery if ever offered. This was lower than the 90% reported among 90 subjects in the Kwale District, Kenya [104]. This difference could have occurred because not only was their sample size larger and had a better male to female ratio (40:50), but also their study was limited to operated and blind patients with cataract (visual acuity≤6/18). Per our results, interviewees who admitted being comfortable with free surgery (79%) were fewer than the 95.2% of 152 patients with cataract who expressed the desire for free cataract surgery in Ghana [105]. The perception of free cataract surgery in some rural communities in Cameroon only compounds the already existing perception of dying on the operating table as reported by Rotchford et al [106]. A high proportion of subjects in this study reported that free cataract surgery was suspected in the community. This was similar to the views expressed among interviewed subjects in Kilimanjaro, suggesting that providing free cataract surgery may not necessarily increase uptake [93].

Our results revealed that fear was the most prominent reason why people outrightly refused cataract surgery. This was concordant with the results reported in Kwale District [107]. Although we did not explore further to find out what constituted subjects' fear, there is evidence in our results (according to Subject 8 in FGD2, for example) that this could be due to reported poor outcomes of previous surgeries from other clinics.

A study with a much larger sample in Ghana (n=152) also found fear to be the major reason for refusing free surgery [105], similar to our findings. Fear has also been reported to be a major predictor of free cataract surgery refusal in Kenya, principally stemming from rumors [107]. Findings from 46 patients who refused surgery in Paraguay showed that refusal was mainly associated with transport cost and distance from the clinic [108] as opposed to the findings of this study. Their study was based on telephone interviews following a rapid assessment of avoidable blindness survey. A hospital-based study within the same setting also found fear (55.9%) to be the leading reason for refusing free cataract surgery [94]. Fear was also reported

among 41 subjects as one of the 3 leading reasons for not taking up eye surgery in rural Eswatini [109].

Refusal of cataract surgery in some communities was more associated with supernatural beliefs, as shown in the following example portraits:

Subject P: He is an operated cataract patient aged 81, widower, and living with the daughter. There is a feeling of belief in superstition when he talks. His expressions relate to experiences of those living with cataracts and the operated *"You already know, in, Africans like promising evil to their brothers […], all that we have as sickness in the hospital we Africans have transformed overnight, that means one can decide to throw the sickness on you like SIDA like cataract then you find yourself with the disease whereby the scientists, big doctors will find it difficult […], while the person responsible will also be aggravating the problem"*.

Subject M: The explanation of their experience portrays the joy that those operated bring to the community but also the lack of money, fear of surgery, age, and transport cost as potential barriers, *"Others are happy, those who do not have money admire those who had surgery. Others say they cannot take surgery because they are old, their small veins will be cut and they will go blind. Others complain of distance, that it is far and that the cost is high going to Obak [MICEI's location]"*.

Strengths and Limitations

This is the first ethnographic study in Cameroon, which was aimed at uncovering the challenges faced by community-diagnosed patients with cataract in accessing cataract surgery. As opposed to assumed conditions in other study designs [110,111], the holistic and naturalistic approach of focused ethnography helped to collect detailed qualitative field data that can readily be integrated into practice [46]. The use of both FGDs and personalized interviews led to internal validity. Placing patients, their families, and communities at the forefront of this study was vital for patient-based eye care delivery [112].

This study has 3 main limitations. The study was limited to the Lékié Division, and perhaps the results could have presented more diverse opinions if the focus groups were drawn from different divisions. The sample's male-female ratio was 1.9:1, which could have led to most of the responses and opinions being skewed toward male subjects. The inaccessibility of some sites reduced the ethnographic diversity.

Conclusions

This study aimed to explore the challenges in accessing cataract surgery among community-diagnosed patients with cataract and the wider community. We found that cost (25/29, 86%) and fear (17/29, 59%) were the main barriers to cataract surgery compounded by a strong belief in traditional medicine and superstition. These results apply to settings (1) reliant on hospital-based delivery models (2) with a disintegrated eye care delivery from the public health strategy and (3) with little or no health coverage.

This study highlights the overriding need to integrate eye care into the public health strategy and rethink the primary eye care conundrum in Cameroon. Despite evidence in the capacitation of the eye health workforce, the current evidence regarding the integration of eye care into Cameroon's primary health care is very limited [113]. The current need for renewed knowledge regarding barriers to cataract surgical uptake is indispensable in defining the priorities for primary eye care delivery in Cameroon. Our results reveal that the patient-reported barriers to cataract surgery of those attending eye clinics may not necessarily be the experience reflecting the communities they come from.

This study also shows that because the opinions of indirect subjects represent a major influence over the decisions of the direct subjects to accepting cataract surgery among older people, the decision mechanism is complex as this appears to be a social construct [98].

The following recommendations would therefore be useful: (1) implement a tiered pricing policy and reduce the number of postsurgical visits, (2) consider traditional doctors or healers as major stakeholders and include them in the community health volunteer training program at the clinic, (3) develop a plan for the engagement of mass media for regular awareness raising, (4) train patient counselors and improve cataract surgical outcomes to manage fear, (5) develop and implement advocacy programs including regular community eye talks and aligning eye care delivery with government-led community programs, (6) implement a fee-for-referral service for trained key informants, front line health workers, and traditional doctors, (7) acquire a 4×4 vehicle dedicated to outreach and motorbikes for camp organizers, and (8) deploy ArcGIS and related applications to improve the planning of awareness.

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Data Availability

Data will be made available upon request.

Authors' Contributions

MM developed the study protocol, collected and analyzed the data, and drafted the manuscript. HEN assisted with approval from the institutional review board and provided oversight of the implementation. Both authors reviewed and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group discussion and interview guide.
[DOCX File , 20 KB - xmed_v3i2e35044_app1.docx]

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Abbreviations

FGD: focus group discussion
ICO: International Council of Ophthalmology
IRB: institutional review board
MICEI: Magrabi ICO Cameroon Eye Institute
PI: principal investigator
SiB: Seeing Is Believing

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Original Paper

Satisfaction With Health Care Services at the Pediatric Specialist Clinic of the National Referral Center in Malaysia: Cross-sectional Study of Caregivers' Perspectives

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Abstract

Background: The concept of customer satisfaction is gaining hold in all corporate sectors worldwide, and a satisfaction survey is used as a tool to discover service problems and as a chance for customers to rate their experience with health care services. A high degree of patient satisfaction with the services given has been found in numerous studies conducted in Malaysian public health care facilities. However, there is limited information available on caregiver satisfaction with pediatric clinics run by the Ministry of Health (MoH) of Malaysia.

Objective: This was the first research performed at a public hospital's pediatric clinic, which was the first hospital to adopt the public-private-partnership model under the MoH, with the aim of discovering the prevalence and factors affecting the satisfaction of caregivers at the national referral center.

Methods: Cross-sectional research using the standard self-administered SERVQUAL questionnaire was conducted among caregivers accompanying their children to the clinic. The questionnaire consists of 16 paired statements to evaluate their expectations and experiences with the clinic services.

Results: A total of 459 caregivers were involved in this study with a majority aged between 30 and 39 years (n=254, 55.4%). Caregivers from the Indian community (adjusted odds ratio [AOR] 2.91, 95% CI 1.37-6.18) and lower income groups (AOR 2.94, 95% CI 1.87-4.64), and those with lower educational backgrounds (AOR 3.58, 95% CI 1.19-10.72) were more likely to be

satisfied with the quality of pediatric clinic services. Housewives/househusbands (AOR 0.48, 95% CI 0.25-0.90), on the other hand, appeared less likely to be satisfied with the services provided during their visit to the clinic. Looking at overall patient satisfaction, 50.5% (n=232) of caregivers demonstrated satisfaction with the quality of services, compared to 49.5% (n=227) of dissatisfied respondents.

Conclusions: This paper suggests that, although most caregivers are satisfied with the services, greater emphasis must be placed on delivering reliable service in response to the MoH's mission to provide quality and integrated people-centered health services in Malaysia.

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KEYWORDS

pediatrics; caregivers; health care services; public hospital; Malaysia; public-private-partnership; children

Introduction

Consumer satisfaction plays an increasingly important role in reforming health care quality and delivery in general across the United States and Europe [1]. The Integrated People-Centered Health Services is a global strategy by the World Health Organization that proposes a vision focused on providing people-centered and integrated health care services. This is a vision described as: "A future in which all people have access to health services that are provided in a way that responds to their personal preferences, are coordinated around their needs and are safe, effective, timely, efficient and of an acceptable quality, throughout their life course" [2]. Quality health care, in part, means meeting the needs of patients [3]. As the main stakeholders in a health care system, patients' satisfaction reflects the expectations and general experience of health care services provided to them [4].

Patient satisfaction serves as an objective indicator of experiences, health outcomes, and trust with the health care system, representing whether the care provided has satisfied the patient's needs and expectations [5]. Besides, it is an evaluation of the services provided by health care providers, which are influenced by both the level of expectations and the patient's experience [6]. It is also possible to monitor the quality of care that could pave ways toward improving health care delivery [7]. Research suggests that satisfied patients are more prepared to seek medical guidance, comply with therapies, fulfill appointments, and refer other patients to a physician [8,9]. Research carried out in India indicates that surveys of patient satisfaction also act to hold doctors responsible [10]. In addition, the advent of increased competitiveness in the health care sector has led to the development of facilities that are committed to meeting the needs of patients. Highly ranked institutions in terms of service quality have better customer retention, lower expenses for bringing in new customers, increased profitability, and higher customer satisfaction [11-14].

The Ministry of Health (MoH) of Malaysia began its quality assurance program in the 1980s and has implemented many initiatives to improve the quality of health care delivery and enhance customer satisfaction, which includes the Client's Charter and the acculturation of corporate values among employees who are caring, professional, and exercise teamwork [15]. Malaysia has provided impressive health benefits for its population through low-cost health care funded primarily by general revenue and taxes collected by the federal government [16].

The government has continuously committed itself to health care equity and accessibility, with the public health sector financing almost 95% of the cost of treatment and subsequently providing access to health care for more than 90% of its population [17]. Malaysians are also granted free access to consultations, treatment, and medications, as both inpatients and outpatients, for a nominal registration fee of Malaysian ringgit (RM) 1.00 (US $0.33) in all public health care facilities in the country [18]. This long-standing public policy has instilled a sense of entitlement among Malaysians that health care services in Malaysia should be free or cost the very least [16].

Many studies conducted at public health care facilities in Malaysia have shown a high level of patient satisfaction with the services provided [19]. However, to our best knowledge, no studies have been conducted on caregivers' satisfaction in MoH pediatric outpatient clinics or facilities. This study, therefore, aims to ascertain the prevalence and factors influencing satisfaction and to identify areas of dissatisfaction among caregivers at the Paediatric Specialist Clinic of Tunku Azizah Hospital. This newly established hospital is a tertiary facility and a national referral center for the pediatric and women population.

Methods

Participants

This cross-sectional study was conducted at the Tunku Azizah Hospital, Kuala Lumpur, Malaysia. Participants were caregivers to children seen with an appointment at the clinic. Exclusion criteria were foreign nationals, refusal to participate, cognitively unsound, caregivers who could not read, and patient visiting for the first time. Only participants who met the eligibility criteria and agreed to participate in the study were enrolled.

The minimum sample size required was 364, which was calculated using the Raosoft (2004) online sample size calculator with a 95% confidence level, 0.5 SD, margin of error (CI) of 5%, and population size of 6714 (the monthly patient average). A total of 600 questionnaires were distributed to the clinic, and we received 502 responses, giving a rate of 83.7%. Of these 502 responses, 43 were unusable and were excluded from this study, and the remaining 459 (91.4%) questionnaires were

analyzed. Some 2238 patients were registered for an appointment at the clinic during this data collection period.

Data Collection and Ethical Considerations

This study was conducted at the hospital's Paediatric Specialist Clinic by convenience sampling using a self-administered structured questionnaire. Every third registering caregiver was identified and given the questionnaires after seeing the doctor and while waiting for the date of their next consultation. Upon completing the questionnaire, participants were instructed to put it into an enclosed envelope. The sealed envelope is then passed to the nurse at the clinic counter.

Participants were recruited for 7 working days from September 3 to 12, 2019, upon receiving approval from the Medical Research and Ethics Committee (Research registration number NMRR-19-2191-49475[IIR]; MREC approval reference KKM/NIHSEC/P19-1924[5]). The goals and advantages of the study were explained in a verbal and written form attached to the questionnaires. Participants were assured of confidentiality in their involvement and that this would not have an effect on their treatment. They were reassured that their personal data would not be stored or used in any way possible and that their responses would only be used to enhance healthcare services. Informed consent was obtained from parents or guardians who agreed to participate. Following this study, only the data collection, findings and conclusions of this research have been published and any personal information collected from the participants is subject to confidentiality.

The principal researcher and two nurses were responsible for this data collection. This was part of a hospital-level survey assessing satisfaction among caregivers attending the clinic using the SERVQUAL instrument. SERVQUAL was initially developed for use in the marketing industry [20]. The SERVQUAL model is also known as a gap analysis model and is the most excellent tool for evaluating the quality of services [21]. The analysis of gaps is based on the difference between service quality expectations and perception. It was modified, translated, and validated in line with the Malaysian health care setting [22].

There are nine dimensions in this SERVQUAL tool, which includes the five original characteristics: tangibles, reliability, responsiveness, assurance, and empathy. Service outcomes and three other dimensions were included, including the core values of the MoH corporate culture: caring service, teamwork, and professionalism [23]. The current SERVQUAL tool that is used by the MoH is phrased in two languages (Malay and English).

The first part of the survey, which addressed the demographics of the respondents, was modified to include demographics of pediatric patients visiting the clinics. Sociodemographic data included independent variables such as the caregiver's age, gender, race, marital status, education, employment sector, and household income level. These followed by age and gender of the child (patient), relationship with the caregiver, subspecialty that is being visited, waiting time, and the main problem encountered at the clinic during their visit.

The second section included the SERVQUAL tool, which contains 16 statements related to the respondents' expectations on quality of service and 18 statements concerning their perception (experience) with the quality of service delivered. A 5-point Likert scale was used, ranging from "strongly disagree" (1) to "strongly agree" (5), with no verbal labels for scale points 2 through 4.

Statistical Analysis

The data were coded, entered in Excel (Microsoft Corporation), and analyzed using SPSS version 21 (IBM Corp). Primary data on 459 responses were analyzed to examine satisfaction with services provided at the clinic. Sociodemographic characteristics of caregivers and patients and patient's clinic visits were analyzed using descriptive analysis.

Each component from the satisfaction questionnaire was analyzed using a chi-square test. To describe caregivers' and patients' demographic profiles, a descriptive model with frequencies and percentages were developed. The median score of expectations and perceptions of caregivers and the mean gap scores for 16 paired items were evaluated. The difference in the mean values of perception and expectation for each component determined the caregiver's satisfaction. This methodology assesses service quality by measuring the discrepancy (gap) between caregivers' perceptions and expectations (service quality = P – E). "P" reflects the perception of the caregivers, and "E" refers to expectations of service delivery before encountering the actual service [24,25]. If the difference is negative, then there is dissatisfaction. To evaluate the mean satisfaction gap for each dimension, the mean gaps from all statements pertaining to a dimension is summed and then divided by the number of statements in that dimension.

Scores of four and five were considered to be satisfied, and the percentages were determined, while the other scores were considered to be dissatisfactory for the expectations and perception components. The Wilcoxon signed ranked test was used to make a comparison of distributions of expectations and perceptions. A logistic regression model was used to estimate the odds ratio (OR) and 95% CI for overall satisfaction level. The mean was computed for all gap scores of 16 paired statements, and an average of zero and higher is considered satisfied. P=.04 was considered to be statistically significant.

Results

The sociodemographic characteristics of respondents and patients are summarized in Table 1. The whole study population was made up of 144 men and 315 women, with a substantial number of those aged 30 to 39 years (n=254, 55.4%). A total of 343 (74.7%) of the 459 respondents were Malays, while 408 (88.9%) of the total participants were married. A total of 231 (50.3%) of the respondents had completed a tertiary education, while 136 (29.6%) worked in the private sector. It is also worth noting that respondents with a lower household income account for more than half of the total or 266 (57.9%). Parents made up 432 (94.1%) of the caregivers who took part, and 236 (52.4%) of the patients were younger than 60 months.

Table 2 shows the characteristics of patient clinic visits, demonstrating that 211 (46%) of them had four or more appointments with the clinic. A total of 304 (66.2%) patients

were seen by pediatric medical subspecialties, whereas 230 (50.1%) patients were seen in less than 60 minutes.

Table 1. Sociodemographic characteristics of caregivers and patients (N=459).

Characteristics	Male (n=144), n (%)	Female (n=315), n (%)	Total (N=459), n (%)
Age (years)			
18-29	20 (13.9)	55 (17.5)	75 (16.3)
30-39	71 (49.3)	183 (58.1)	254 (55.4)
≥40	53 (36.8)	77 (24.4)	130 (28.3)
Race			
Malay	107 (74.3)	236 (74.9)	343 (74.7)
Chinese	16 (11.1)	39 (12.4)	55 (12.0)
Indian	17 (11.8)	27 (8.6)	44 (9.6)
Others	4 (2.8)	13 (4.1)	17 (3.7)
Marital status			
Single	7 (4.9)	19 (6.0)	26 (5.7)
Married	135 (93.7)	273 (86.7)	408 (88.9)
Divorced/widowed	2 (1.4)	23 (7.3)	25 (5.4)
Education background			
No formal education	1 (0.7)	3 (1.0)	4 (0.9)
Primary education	6 (4.2)	13 (4.1)	19 (4.1)
Secondary education	68 (47.2)	137 (43.5)	205 (44.7)
Tertiary education	69 (47.9)	162 (51.4)	231 (50.3)
Occupation sector			
Public sector	48 (33.3)	78 (24.7)	126 (27.5)
Private sector	55 (38.2)	81 (25.7)	136 (29.6)
Self-employed	26 (18.1)	33 (10.5)	59 (12.8)
Housewife/househusband	5 (3.5)	84 (26.7)	89 (19.4)
Others	10 (6.9)	39 (12.4)	49 (10.7)
Household income[a,b] RM[c]			
<3852	72 (50.0)	194 (61.6)	266 (57.9)
3852-8319	58 (40.3)	104 (33.0)	162 (35.3)
≥8320	14 (9.7)	17 (5.4)	31 (6.8)
Relationship with patient			
Parents	136 (94.4)	296 (94.0)	432 (94.1)
Others	8 (5.6)	19 (6.0)	27 (5.9)
Patient's age (months)	272 (100.0)	187 (100.0)	459 (100.0)
<60	137 (50.4)	99 (52.9)	236 (51.4)
60-119	86 (31.6)	41 (21.9)	127 (27.7)
120-179	37 (13.6)	37 (19.8)	74 (16.1)
≥180	12 (4.4)	10 (5.4)	22 (4.8)

[a]Based on the Household Expenditure Survey (2014) published by the Malaysian Department of Statistics.

[b]US $1=RM 4.23

[c]RM: Malaysian ringgit.

Table 2. Characteristics of patient's clinic visit (N=459).

Characteristics	Male (n=272), n (%)	Female (n=187), n (%)	Total (N=459), n (%)
Frequency of visit			
2	101 (37.1)	73 (39.0)	174 (37.9)
3	51 (18.8)	23 (12.3)	74 (16.1)
≥4	120 (44.1)	91 (48.7)	211 (46.0)
Subspecialty visited			
Pediatric medical	173 (63.6)	131 (70.1)	304 (66.2)
Pediatric surgical	99 (36.4)	56 (29.9)	155 (33.8)
Waiting time (minutes)			
<60	138 (50.7)	92 (49.2)	230 (50.1)
60-119	61 (22.4)	38 (20.3)	99 (21.6)
120-179	50 (18.4)	44 (23.5)	94 (20.5)
≥180	23 (8.5)	13 (7.0)	36 (7.8)

Table 3 shows a comparison of expectation, perception, and satisfaction for each statement. This analysis shows that the respondents had a very high expectation for "staff politeness" (Q8), which was followed by "staff competency" (Q7) and "cleanliness of public toilets" (Q15). The lowest expectation was given for the "visual appeal of facilities" (Q2). However, it is interesting to note that the perception score fared slightly better for this statement. In terms of perception, the caregivers had the best experience with "staff politeness" (Q8), "staff work discipline" (Q13), and "cleanliness of public toilets" (Q15). On the contrary, the perception score was the lowest for "staff providing services at promised time" (Q3) and "appropriate waiting time" (Q16). The highest satisfaction gap was observed with the "appropriate waiting time" (Q16) followed by the "staff providing services at the promised time" (Q3), and the lowest satisfaction gap was for the statement "visually appropriate physical facilities" (Q2).

Table 4 depicts a comparison of expectation, perception, and satisfaction for each dimension. The "outcome" dimension had the most expectation from the caregivers, then by the "assurance" dimension. The lowest expectation was scored for the "caring service" dimension. The caregivers' perception was highest for the "outcome" dimension as well. The "reliability" dimension had the lowest perception score and the widest satisfaction gap. The "tangibles" dimension, on the other hand, had the smallest satisfaction gap.

Crude and adjusted ORs (AORs) with 95% CIs of the factors associated with the overall satisfaction of caregivers with the quality of services provided are demonstrated in Table 5. The OR was adjusted to the 11 factors listed in Table 5. Caregivers from the Indian community (AOR 2.91, 95% CI 1.37-6.18) and lower household income groups (AOR 2.94, 95% CI 1.87-4.64) were approximately three times more likely to express higher levels of satisfaction with pediatric clinic service quality. Besides, respondents from lower educational backgrounds (AOR 3.58, 95% CI 1.19-10.72) were almost four times as likely to be satisfied with the services they received. However, housewives/househusbands (AOR 0.48, 95% CI 0.25-0.90) seemed less likely to be satisfied with the services provided during their visit to the clinic.

Looking into the overall satisfaction of the patients with the quality of service encountered at the Paediatric Specialist Clinic, it can be derived that 50.5% (n=232) of caregivers demonstrated satisfaction with the quality of services, as opposed to 49.5% (n=227) of the respondents being unsatisfied.

Table 3. Comparison of distribution for expectation, perception, and satisfaction for each statement.

Measurement statements[a]	Expectation		Perception		Satisfaction gap, mean (95% CI)	*Z* statistic[b]	*P* value[b]
	Score 4-5[c] (%)	Median (IQR)	Score 4-5[c] (%)	Median (IQR)			
Q1	92.2	5 (1)	88.9	5 (1)	–0.21 (–0.27 to –0.14)	–6.08	<.001
Q2	89.8	5 (1)	90.0	5 (1)	–0.07 (–0.13 to 0.00)	–1.98	.049
Q3	92.6	5 (1)	78.2	4 (1)	–0.39 (–0.48 to –0.30)	–8.29	<.001
Q4	93.7	5 (1)	87.8	4 (1)	–0.26 (–0.33 to –0.19)	–6.94	<.001
Q5	93.0	5 (1)	81.3	4 (1)	–0.36 (–0.44 to –0.28)	–7.88	<.001
Q6	93.7	5 (1)	89.3	5 (1)	–0.21 (–0.27 to –0.14)	–5.84	<.001
Q7	95.0	5 (1)	89.1	5 (1)	–0.26 (–0.33 to –0.19)	–6.88	<.001
Q8	95.2	5 (1)	91.3	5 (1)	–0.21 (–0.28 to –0.15)	–6.36	<.001
Q9	93.2	5 (1)	88.0	4 (1)	–0.27 (–0.34 to –0.19)	–6.68	<.001
Q10	92.4	5 (1)	88.7	4 (1)	–0.23 (–0.31 to –0.16)	–6.27	<.001
Q11	94.3	5 (1)	89.8	5 (1)	–0.24 (–0.31 to –0.17)	–6.53	<.001
Q12	93.7	5 (1)	89.3	5 (1)	–0.22 (–0.29 to –0.15)	–6.12	<.001
Q13	94.8	5 (1)	90.4	5 (1)	–0.24 (–0.30 to –0.17)	–6.83	<.001
Q14	94.3	5 (1)	88.7	4 (1)	–0.27 (–0.34 to –0.20)	–7.26	<.001
Q15	95.0	5 (1)	90.4	5 (1)	–0.24 (–0.31 to –0.17)	–6.44	<.001
Q16	92.8	5 (1)	79.3	4 (1)	–0.48 (–0.57 to –0.39)	–9.35	<.001

[a]Refer to Multimedia Appendix 1 for measurement statements.

[b]Wilcoxon signed rank test.

[c]Caregivers scoring 4 and 5.

Table 4. Comparison of distribution for expectation, perception, and satisfaction for each dimension.

SERVQUAL dimensions[a]	Expectation		Perception		Satisfaction gap, mean (95% CI)	*Z* statistic[b]	*P* value[b]
	Score 4-5[c] (%)	Median (IQR)	Score 4-5[c] (%)	Median (IQR)			
Tangibles	90.4	5.00 (0.67)	84.7	4.33 (1.00)	–0.17 (–0.22 to –0.12)	–6.15	<.001
Reliability	90.4	5.00 (0.67)	75.4	4.33 (1.00)	–0.35 (–0.44 to –0.30)	–9.69	<.001
Responsiveness	92.6	5.00 (1.00)	81.7	4.50 (1.00)	–0.28 (–0.35 to –0.21)	–7.58	<.001
Assurance	93.7	5.00 (0.67)	85.6	4.67 (1.00)	–0.25 (–0.31 to –0.19)	–8.07	<.001
Empathy	91.7	5.00 (1.00)	86.1	4.50 (1.00)	–0.25 (–0.32 to –0.18)	–6.96	<.001
Outcome	94.3	5.00 (1.00)	89.8	5.00 (1.00)	–0.24 (–0.31 to –0.17)	–6.53	<.001
Caring service	89.1	5.00 (0.71)	77.8	4.43 (1.00)	–0.27 (–0.33 to –0.22)	–8.73	<.001
Teamwork	92.6	5.00 (1.00)	86.3	4.50 (1.00)	–0.24 (–0.30 to –0.18)	–7.32	<.001
Professionalism	90.6	5.00 (0.75)	77.6	4.50 (1.00)	–0.27 (–0.33 to –0.21)	–8.87	<.001

[a]Refer to Multimedia Appendix 1 for dimension statements.

[b]Wilcoxon signed rank test.

[c]Caregivers scoring 4 and 5.

Table 5. The odds ratio (OR) and 95% CI of factors associated with the level of caregiver's satisfaction (N=459).

Characteristics	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	*P* value
Gender			
Male	1 (reference)	1 (reference)	N/A[b]
Female	1.21 (0.82-1.80)	1.41 (0.89-2.21)	.14
Age (years)			
18-29	1 (reference)	1 (reference)	N/A
30-39	1.19 (0.71-1.99)	1.51 (0.85-2.69)	.16
≥40	1.02 (0.58-1.80)	1.45 (0.74-2.82)	.28
Race			
Malay	1 (reference)	1 (reference)	N/A
Chinese	0.70 (0.39-1.25)	0.69 (0.37-1.29)	.25
Indian	2.81 (1.40-5.64)	2.91 (1.37-6.18)	.005
Others	1.93 (0.70-5.34)	1.67 (0.56-4.97)	.36
Education background			
High education	1 (reference)	1 (reference)	N/A
Low education	3.74 (1.36-10.24)	3.58 (1.19-10.72)	.02
Occupation sector			
Public sector	1 (reference)	1 (reference)	N/A
Private sector	1.24 (0.76-2.02)	1.00 (0.59-1.69)	.98
Self-employed	1.66 (0.89-3.10)	1.23 (0.62-2.46)	.56
Housewife/househusband	0.93 (0.54-1.60)	0.48 (0.26-0.92)	.03
Others	1.39 (0.72-2.70)	0.71 (0.33-1.56)	.40
Household income			
Medium income	1 (reference)	1 (reference)	N/A
Low income	2.71 (1.81-4.06)	2.94 (1.87-4.64)	<.001
High income	1.48 (0.68-3.21)	1.51 (0.67-3.39)	.32
Frequency of visit			
2	1 (reference)	1 (reference)	N/A
3	1.27 (0.74-2.20)	1.22 (0.67-2.20)	.52
≥4	1.01 (0.68-1.51)	1.14 (0.73-1.78)	.57
Subspecialty visited			
Pediatric medical	1 (reference)	1 (reference)	N/A
Pediatric surgical	0.95 (0.64-1.40)	0.94 (0.61-1.46)	.80
Waiting time (minutes)			
<60	1 (reference)	1 (reference)	N/A
60-179	0.59 (0.37-0.92)	0.63 (0.39-1.03)	.07
≥180	0.66 (0.40-1.09)	0.67 (0.39-1.15)	.15
Relationship with patient			
Others	1 (reference)	1 (reference)	N/A
Parents	0.49 (0.22-0.12)	0.67 (0.26-1.72)	.40
Patient's age (months)			
<60	1 (reference)	1 (reference)	N/A

Characteristics	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	*P* value
60-179	0.98 (0.64-1.49)	0.83 (0.52-1.34)	.45
≥180	0.78 (0.48-1.26)	0.64 (0.36-1.12)	.12

[a]Adjusted for 11 factors: gender, age, race, educational background, occupation sector, household income, frequency of visit, subspecialty visited, waiting time, relationship with patient, and patient's age.

[b]N/A: not applicable.

Discussion

Tunku Azizah Hospital is the first public-private-partnership (PPP) project in Malaysia under the MoH, using the private finance initiative (PFI) model. This facility was initially known as the Kuala Lumpur Women and Children Hospital but was renamed in January 2020 to commemorate the present Queen. The hospital started operations in phases from February 2019, and the Paediatric Specialist Clinic was the first to offer its services to the public. To our best knowledge, this is the first paper that discusses the factors affecting overall caregivers' satisfaction and identifies areas of dissatisfaction in a pediatric clinic run by MoH in Malaysia.

As can be seen from the results of the analysis, there was a negative satisfaction gap in all dimensions, suggesting that none surpassed the expectations of the caregivers. This result is also consistent with another study carried out in Singapore [26] using a similar instrument. Negative gaps are commonly predicted, as expectations for optimum service are rarely met.

Overall, 50.5% (n=232) of caregivers were satisfied with the pediatric clinic and the quality of services provided during this study period. This result is in contrast with another study by Aniza et al [27] that was conducted at the Paediatric Clinics of the University of Kebangsaan Malaysia Medical Center that had a 90.5% satisfaction rate. Such a finding may be due to the higher expectations that caregivers had with a newly opened health care facility.

There was evidence that respondents with lower educational levels and household income, and those of the Indian community have better satisfaction with health care services at the clinic. Several authors have found that demographic characteristics, such as gender, age, and education, were strongly linked to respondent's satisfaction. Although satisfaction levels were not significantly associated between age and gender in this study, their prevalence in other studies was significant, where males were found to be more satisfied than female respondents [28,29]. Another study indicated that gender did not have a significant impact on the satisfaction rate in their findings [30]. Even if age does not appear to be associated with satisfaction levels in some research [31], one study found that the average satisfaction rate improved with the increase in age and that the satisfaction rate was the most feasible with those older than 55 years [32].

This study found a statistically significant inverse association between the level of education and the satisfaction of caregivers, which is comparable to other studies, indicating that respondents who were less educated were more satisfied than those with higher education [33-35]. This result could be due to higher standards set by the educated group, as they believed they were more acquainted with the care they would obtain. Besides, those with higher education levels are pragmatic and able to see the services objectively, and they were dissatisfied when the level of services did not meet their expectation [24]. Similar to other research done, this study also shows that a lower income group has shown more satisfaction toward the services at the clinic [18]. This group of caregivers consisted of more than half of the total respondents and were more concerned about the costs associated with health care delivery. Thus, they were more satisfied with the services at this outpatient facility accessible at a low cost of RM 1.00 (US $0.33). In this study, caregivers from the Indian ethnic minority were more satisfied, as opposed to the other ethnic groups. This is different from another study that pointed out that the minority ethnicity reported lower satisfaction and less positive experiences with health care services [36].

One interesting observation from this study is that the housewives/househusbands had a relatively lower satisfaction level at the clinic, which is similar to another published study [37]. This could be due to the different commitments they have made, and they anticipate that the appointment will be completed in a short period of time.

In this research, all statements and dimensions revealed negative satisfaction scores indicating that none met the expectations of the caregivers. However, caregivers' experiences from this study point out that the staff in the clinic had shown politeness and good work discipline, and that the public toilets were clean. Caregivers were the least satisfied with the waiting time and had concerns with services not being provided at the promised time. A study conducted in France also suggested dissatisfaction among patients with waiting times [38]. The MoH had a target of 90-minute waiting times. Nevertheless, almost half of the patients (median waiting time) were seen by doctors in less than 60 minutes or at an average of 83 minutes for all cases.

The respondents also pointed out better than expected experience with the visual appeal of the health care infrastructure. As this facility is a PPP project, it has integrated certain nonconventional elements into its architecture and design that reflect sociocultural, economic, professional, and aesthetic priorities. This reflects and reinforces contemporary concepts of patienthood and caring, and projects the implementation of patient-centeredness.

Caregivers' satisfaction with services can be assessed based on the following service attributes as highlighted by Parasuraman et al [20]. The five original SERVQUAL dimensions are defined as reliability (the ability to perform the promised service dependably and accurately), responsiveness (willingness to help customers and provide prompt service), assurance (employees' knowledge and courtesy, and their ability to inspire trust and

confidence), empathy (caring, individualized attention given to customers), and tangibles (the appearance of physical facilities, personnel, and written materials). An additional four dimensions (service outcome, caring service, teamwork, and professionalism) were included in the MoH version of SERVQUAL.

Caregivers had the highest expectation for service outcomes, and they also had the best experience with the outcome of their visits to the outpatient clinic, which indicates that they were pleased with the consultations or treatments they got. However, the "reliability" dimension needs to be substantially enhanced, as this had the most substantial satisfaction gap. The care providers should focus on reducing the waiting time in the clinic and mobilizing resources to enhance customer satisfaction further. While the "tangibles" dimension had the lowest satisfaction gap over all other dimensions, it is equally important to clean, maintain, and gleam the building premises. Maintaining the building premises is essential to maintain the properties and protect the inhabitants of the building. Proper building maintenance ensures that the building and the environment remain secure, clean, and safe to function.

There were some limitations to this study. First, we carried out our study at a tertiary, national referral center run by consultants, trained specialists, and postgraduate trainees, which differs from those in primary public clinics, which are mostly run by medical officers without postgraduate qualifications. Therefore, the results of our study cannot be generalized to reflect the performance of other clinics in this region. Since the questionnaires used were self-administered, patients who were illiterate were not recruited. Besides, convenience sampling, while unavoidable, is another drawback to this research due to the high probability of bias in sampling. Hence, the findings may not be generalized to the broader population. Additionally, not all aspects of the services, such as pharmacy and prescription drugs, have been evaluated in this study. These factors have been found to influence patient satisfaction significantly [39,40]. This study was also carried out at a relatively new facility, which could have resulted in a positive satisfaction bias among some respondents.

We believe that future surveys with questionnaires should avoid using all positively expressed statements to assess service quality. It would mitigate the overall bias if there were a combination of positive and negative framed statements [41]. Additionally, other aspects of services, such as registration, pharmacy, and prescription drugs, should be considered to gauge the complete experience of caregivers while visiting health facilities. Value-driven outcome tools that measure quality and include both nationally accepted and validated measures, as well as local physician- and patient-defined outcome measures, should also be considered [42].

The purpose of this paper is to demonstrate how caregivers' perspectives are influenced by various aspects of clinic services, as well as to assess the differences between what they expect and what they experience when engaging with a public health care facility. The study looked at data from a survey that measured caregiver opinions across several dimensions and found that the service outcome dimension was assigned the highest weight, and the pediatric clinic met expectations. In addition, respondents from lower income groups, Indian ethnicity, and those with less education were more appreciative of the services offered.

Regardless, consistent measures must be put in place to increase customer satisfaction, which will strengthen health care delivery standards. The incorporation of patient-centered care as a strategic investment goal, as well as the development and implementation of constructive, organized strategies that involve frontline clinicians in the process of improving caregiver satisfaction, will benefit hospital management. Routine satisfaction assessments should be conducted using improvised questionnaires or other tried-and-true methods to identify unsatisfactory domains that require substantial improvements. These measures will ensure that the services provided are in line with the MoH's mission of providing quality integrated, people-centered health care to the masses. Future studies may be able to compare additional hospitals that use the PFI model, as well as provide more information about the variations discovered in this study.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Measurement statements and dimensions concerning the satisfaction questionnaire used in the study.
[PDF File (Adobe PDF File), 585 KB - xmed_v3i2e33025_app1.pdf]

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Abbreviations

AOR: adjusted odds ratio
MoH: Ministry of Health
OR: odds ratio
PFI: private finance initiative
PPP: public-private-partnership
RM: Malaysian ringgit

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Original Paper

Google Trends as a Predictive Tool for COVID-19 Vaccinations in Italy: Retrospective Infodemiological Analysis

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Abstract

Background: Google Trends is an infoveillance tool widely used by the scientific community to investigate different user behaviors related to COVID-19. However, several limitations regarding its adoption are reported in the literature.

Objective: This paper aims to provide an effective and efficient approach to investigating vaccine adherence against COVID-19 via Google Trends.

Methods: Through the cross-correlational analysis of well-targeted hypotheses, we investigate the predictive capacity of web searches related to COVID-19 toward vaccinations in Italy from November 2020 to November 2021. The keyword "vaccine reservation" query (VRQ) was chosen as it reflects a real intention of being vaccinated (V). Furthermore, the impact of the second most read Italian newspaper (vaccine-related headlines [VRH]) on vaccine-related web searches was investigated to evaluate the role of the mass media as a confounding factor. Fisher r-to-z transformation (z) and percentage difference (δ) were used to compare Spearman coefficients. A regression model $V=f(VRH, VRQ)$ was built to validate the results found. The Holm-Bonferroni correction was adopted (P^*). SEs are reported.

Results: Simple and generic keywords are more likely to identify the actual web interest in COVID-19 vaccines than specific and elaborated keywords. Cross-correlations between VRQ and V were very strong and significant (min r^2=0.460, P^*<.001, lag 0 weeks; max r^2=0.903, P^*<.001, lag 6 weeks). The remaining cross-correlations have been markedly lower (δ>55.8%; z>5.8; P^*<.001). The regression model confirmed the greater significance of VRQ versus VRH (P^*<.001 vs P=.03, P^*=.29).

Conclusions: This research provides preliminary evidence in favor of using Google Trends as a surveillance and prediction tool for vaccine adherence against COVID-19 in Italy. Further research is needed to establish the appropriate use and limits of Google Trends for vaccination tracking. However, these findings prove that the search for suitable keywords is a fundamental step to reduce confounding factors. Additionally, targeting hypotheses helps diminish the likelihood of spurious correlations. It is recommended that Google Trends be leveraged as a complementary infoveillance tool by government agencies to monitor and predict vaccine adherence in this and future crises by following the methods proposed in this paper.

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KEYWORDS

COVID-19; epidemiology; Google Trends; infodemiology; infoveillance; Italy; public health; SARS-CoV-2; vaccinations; vaccines; social media analysis; social media

Introduction

Google Trends is an online website created by Google LLC that allows the user to examine the popularity of exact search queries (keywords) in Google Search across specific regions, time lapses, and languages. Google Trends has often been used by the scientific community to conduct infodemiological and epidemiological analyses [1,2]. In particular, this infoveillance approach—aimed at studying distribution and determinants of information in an electronic medium, specifically the internet, or in a population, with the ultimate aim to inform public health and public policy—has been applied to various disciplines, including but not limited to psychology, economics, veterinary medicine, and pharmacy [3-7]. However, past studies have been often criticized for not providing sufficient documentation to guarantee the full reproducibility of the methods [8]. Moreover, some authors have shown severe limitations in its use as a surveillance tool, including anomalies in results and mass media influence [9,10]. Nonetheless, Google Trends remains a currently irreplaceable tool for infoveillance. In particular, its simplicity and efficiency make analyses much faster than other systems, such as investigating user posts via application programming interface and machine learning [10]. In this regard, various strategies have been proposed in the literature to address its weaknesses [10-12]. Taking the latter into account, in this brief paper, Google Trends is used to investigate vaccine adherence in Italy against COVID-19. Indeed, COVID-19 vaccines are essential to contain the infection, limiting the spread of new variants of concern and substantially reducing the severity of the disease [13]. For instance, the latest report from the Italian Medicines Agency highlighted a low risk associated with vaccines despite high protection against COVID-19 [14]. Even considering Omicron's more elusive variant of concern, the rates of hospitalizations, patients in intensive care units, and deaths are 10, 27, and 25 times higher for the unvaccinated, respectively [15]. At present, monitoring of vaccine adherence is epidemiologically essential, especially considering the growing no-vax movement [16]. Furthermore, the use of effective and efficient infoveillance techniques is also necessary for any future health crises. Therefore, this research proposes an approach capable of targeting the hypotheses and eliminating the anomalies of Google Trends, thus reducing the likelihood of running into spurious correlations and having statistically uncertain outcomes. Specifically, the ability to predict the COVID-19 vaccination trend in Italy based on vaccine-related web queries is examined.

Methods

Procedure Summary

The hypothesis to be verified is that the COVID-19 "vaccine reservation" query (VRQ) can predict the trends of national and regional vaccinations (V). To achieve this scope and quantify the impact of mass media on web queries, cross-correlations between VQR, V, and COVID-19 vaccine–related headlines (VRH) of the Italian newspaper "La Repubblica" were searched. In particular, "La Repubblica" was chosen for its large readership and its online historical database (which allows the user to easily search for published articles containing a list of specific keywords). Besides, an appropriate regression model $V=f(VRH, VRQ)$ was also constructed.

Data Collection

The keyword "prenotazione vaccino" (vaccine reservation) was selected since it clearly expresses the desire to administer the dose of a vaccine. Synonyms of the word "prenotazione" (reservation) have been searched on the Treccani.it online dictionary. However, the synonym queries had a much lower relative search volume (RSV). Besides, even adding them to the original keyword through the "+" operator, the trends remained highly similar. Since the combination of queries makes it more likely that anomalies will appear in the data sets, a single query was chosen. The goodness of VRQ in identifying the web interest in COVID-19 vaccine queries is reported in the Results section. The Google Trends parameters have been set as follows: region: Italy; period: November 1, 2020, to November 27, 2021; category: all categories; and search type: web search. The "period" parameter has been changed to "Past 5 years" when performing a historical time series analysis. The "region" parameter was changed from "Italy" to "[the name of the region concerned]" when analyzing regional trends. The "interest over time" data sets were downloaded in ".csv format." Following the previous methods, the keywords "disdire vaccino + cancellare vaccino + evitare vaccino + non vaccinarsi + green pass falso + comprare green pass" (revoke vaccine + cancel vaccine + avoid vaccine + do not get vaccinated + fake green pass + buy green pass) were searched to investigate users' web interest in methods of not getting vaccinated. The first keyword searched was "disdire vaccino." The other terms have been selected by consulting various possible synonyms in the Treccani.it online dictionary and Google Trends–related queries. The final exact queries searched on Google Trends are reported as references [17,18]. Regarding national vaccinations, the data set was downloaded from the "GitHub" platform [19]. The keyword "vaccino, vaccini, astrazeneca, pfizer, moderna, johnson&johnson, vaxzevria, comirnaty, pikevax" was searched in the historical archive of the newspaper "La Repubblica" [20]. In particular, this query includes the generic and proper names of the COVID-19 vaccines administered in Italy during the investigated period. The number of articles containing the aforementioned keyword was counted from week to week until it covered the period November 2020 to November 2021. The filter has been set to "ricerca avanzata" (advanced search) and "almeno una [parola]" (at least one [word]). This newspaper was chosen since it represents the second most widely read newspaper in Italy and provides the most detailed news database

online. Furthermore, a previous publication showed similar news trends across primary Italian mass media during COVID-19 [21]. Such a result aligns with the theory of news competition and increasing returns-to-scale, which prompts profit-motivated media to publish on hot topics (as of interest to a broad audience) [22]. For these reasons, the author of this paper considered the source "La Repubblica" sufficient to represent the Italian media clamor about vaccines.

Ethical Considerations

This study does not involve human participants or animals. All Google Trends data is anonymized. Therefore, the research does not require approval from a committee.

Statistical Analysis

The shape of the data distribution was assessed both graphically and through the Shapiro-Wilk test. Since the data sets were not normal (P<.001) and above or below threshold correlations were not of interest, we adopted the Spearman correlation (R) [23]. To check the discrepancy between two time series, quantifiers such as percentage difference (used to compare the average RSV of two simultaneous series and indicated with "δ") and percentage increase (used to compare the average RSV of two consecutive series and indicated with "Δ") were exploited. The statistical significance of the discrepancies between average values was measured through the Welch t test (t), which is also valid for large nonnormal data sets [24,25]. When two contiguous time series were compared, a graphic check was carried out to guarantee the absence of seasonality and trends. All data sets were normalized to 100 by multiplying individual values by the constant "100/data set maximum value." The "Lag week" was defined as the number of weeks by which a time series was shifted to obtain the maximum correlation with another time series. By doing so, it was possible to estimate the predictive power of one time series over another and the latency between them. Finally, a multiple regression was used to build the function Y=f(VRH, VRQ) to evaluate the impact of VRH and VRQ on V [26]. SEs for the regression coefficients are reported. Based on previous literature, any causal correlations between the media clamor and web searches should be sought within a maximum lag range of 3 weeks (from –3 to 3) [9,11,21,27,28]. Indeed, the web interest in a topic must arise around the media hype peak to be considered a direct consequence or cause of the latter. Regarding the pairs (VRH, V) and (VRQ, V), the lag acceptability range was fixed at 0 to 8 weeks since it can take up to 2 months from vaccine booking to administration. Fisher r-to-z transformation (z) was used to compare Spearman coefficients. Since the search for cross-correlations is highly exploratory, the Holm-Bonferroni correction was adopted ($m=50$ hypotheses). The original P values have been reported alongside the adjusted ones (P*)—when P*>.001—to allow the reader to interpret the data independently.

Mass Media Clamor as a Confounding Factor

As previously discussed, there is solid evidence that mass media can substantially impact users' web interests. This fact increases the probability of spurious correlations due to a so-called confounding factor, defined as a "hidden" variable (or set of variables) capable of distorting the true relationship between other apparently correlated (or uncorrelated) variables [29]. In this specific case, media hype can create highly confounding scenarios. For example, a COVID-19 outbreak can generate intense news fanfare, immediately followed by a user's growing web interest in the disease. After 7 days, an increase in COVID-19 cases is registered. Examining the sole couple (user interest, COVID-19 cases), it could seem like the online searches predicted the increase in infections. However, by introducing the "media hype" variable, it is observed that users' web interest is much more correlated with the latter than with COVID-19 cases [21]. For this reason, media coverage is introduced in this analysis as a possible confounding factor capable of distorting the relationship between V and VRQ. In this regard, it is fair to admit that other confounding factors not considered in this paper could alter such a relationship in complex ways. Nonetheless, at present, to the best of the author's knowledge, media influence is the only widely reported confounding factor in the literature regarding Google Trends. Furthermore, the main research hypothesis is well-targeted, thus reducing the likelihood of spurious correlations.

Results

The adoption of the "vaccine reservation" query (VRQ) for our purpose is validated by the very strong correlation with the "covid vaccine" and "vaccine" queries (Multimedia Appendix 1, Figure S1) and the marked increase of its RSV in the period November 2020 to November 2021 compared to the past 4 years (Δ=11,500%; t_{56}=6.8; P*<.001). The keywords related to the desire not to get vaccinated registered an average RSV of 4% compared to "vaccine reservation." VRQ's RSV has significantly exceeded that of searches for specific names such as "pfizer reservation," "astrazeneca reservation," "moderna reservation," and "johnson&johnson reservation" (δ=190%; t_{55}=6.6; P*<.001). Table 1 shows very strong correlations between VRQ and the national vaccination (V) trends (min r^2=0.460; P*<.001, lag 0 weeks; max r^2=0.903; P*<.001; lag 6 weeks). Significant correlations were also highlighted between VRQ's RSV and the VRH of the newspaper "La Repubblica" (Multimedia Appendix 1, Table S1) and between VRH and V (Multimedia Appendix 1, Table S2). However, in these cases, the explained variations were markedly lower (max acceptable r^2=0.237, P<.001, P*=.005, lag –3 weeks; max acceptable r^2=0.286, P<.001, P*=.002, lag 8 weeks). The differences between the Spearman coefficients were highly significant (z=6.16, P*<.001; z=5.86, P*<.001).

Table 1. Spearman cross-correlations (R) between the "vaccine reservation" query (VRQ) and vaccination administrations in Italy from November 2020 and November 2021. The highest correlation is obtained by shifting the VRQ 6 weeks ahead.

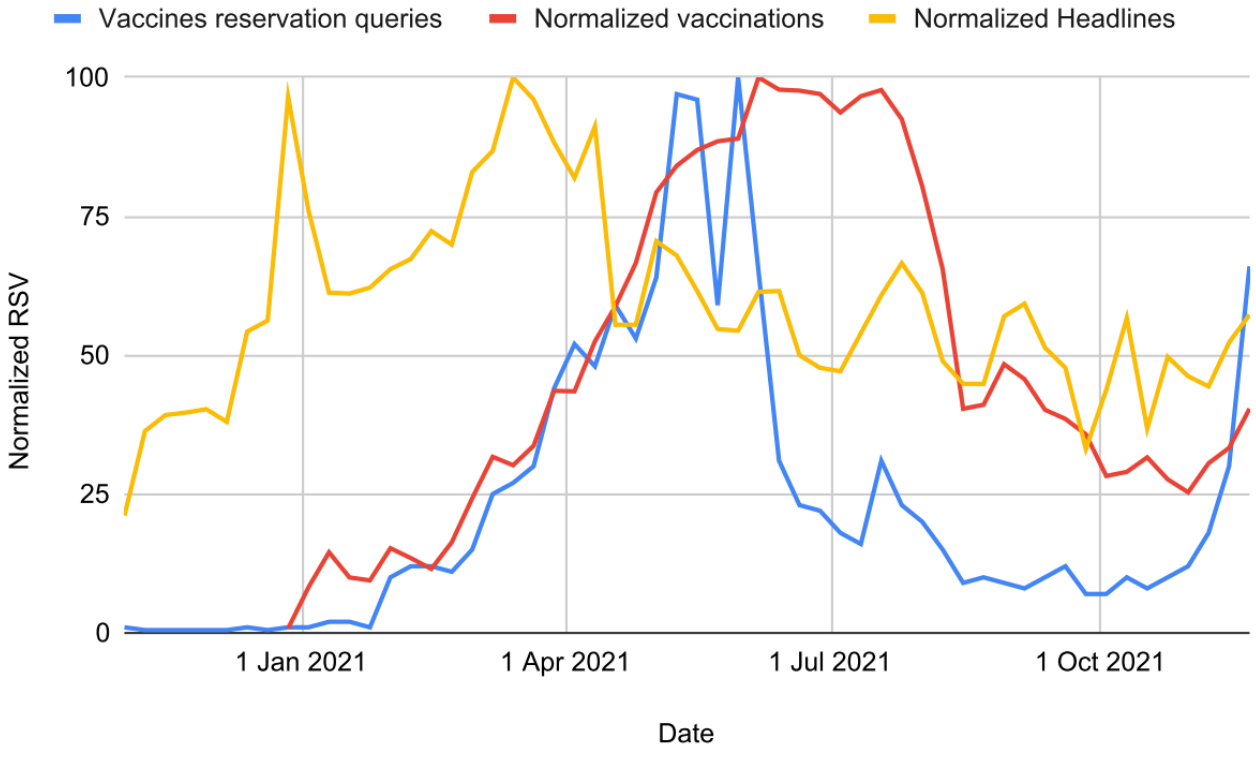
Lag week	*R* (VRQ vs V[a]; 95% CI)	*P* value	*P** value	N
–1	0.536 (0.297-0.711)	<.001	.002	47
0	0.678 (0.481-0.803)	<.001	<.001	48
1	0.777 (0.633-0.869)	<.001	<.001	48
2	0.833 (0.720-0.903)	<.001	<.001	48
3	0.887 (0.806-0.935)	<.001	<.001	48
4	0.927 (0.874-0.958)	<.001	<.001	48
5	0.946 (0.906-0.969)	<.001	<.001	48
6[b]	0.950 (0.912-0.971)	<.001	<.001	48
7	0.946 (0.905-0.969)	<.001	<.001	48

[a]V: vaccinations.

[b]The highest correlation is obtained by shifting the VRQ 6 weeks ahead.

The comparison of the trends is shown in Figure 1. All regional RSV trends have been similar to the national one (Multimedia Appendix 1, Figure S2) and were compatible with vaccination trends at the regional level [30]. Finally, the following regression model was built using appropriately translated time series based on the optimum lag previously identified (only values inside the acceptability range were considered): $Sqrt(V) = A + B \times Log(VRH) + C \times Log(VRQ)$, with A=–0.988 (SE 1.930; P=.61, P*>.99), B=2.67 (SE 1.16; P=.03, P*=.29), C=2.84 (SE 0.22; P*<.001). We observe that VRQ significance was greater than VRH. The following assumptions were considered verified: residual normality (Shapiro-Wilk P=.38), homoscedasticity (White test P=.77), and no multicollinearity (variance inflation factor [VIF]=1.46). Even considering an unlikely causal lag range of ±12 weeks, VRQ is the most significant variable to predict vaccinations: $Log(V) = A + B \times Log(VRH) + C \times Log(VRQ)$, with A=0.381 (SE 0.285; P=.19, P*>.99), B=0.487 (SE 0.180; P=.01, P*=.12), and C=0.353 (SE 0.041; P*<.001). Furthermore, despite that B>C, the 95% CIs are largely overlapping (overlap 0.308). The following assumptions were considered verified: residual normality (Shapiro-Wilk P=.86), homoscedasticity (White test P=.23), and no multicollinearity (VIF=2.45).

Figure 1. Comparison between the vaccine-related headlines of the newspaper "La Repubblica," national vaccinations, and national queries on vaccination reservations from November 2020 to November 2021. RSV: relative search volume.



Discussion

Principal Findings

This study shows a marked and significant cross-correlation between web queries on vaccine reservations and actual vaccinations against COVID-19 in Italy. Based on the lower cross-correlations between vaccine-related news and vaccine web searches, the mass media may have only partially influenced web searches related to vaccine booking. Nevertheless, even assuming a positive impact of the mass media on these queries, this does not compromise the adoption of Google Trends as a predictive tool for vaccinations: indeed, the mass media could push users to search for online information on vaccines and then book their administration. Furthermore, COVID-19 vaccine reservation is easily obtainable through a user-friendly online procedure proposed by the regional health organizations (eg, [31]). This fact helps explain the strong correlation between web searches and vaccinations. Therefore, it is likely that the cross-correlations found between vaccine-related queries and vaccinations are not spurious. Alongside this, it is necessary to consider that the Italian mass media have even risked compromising the effectiveness of the vaccination campaign against COVID-19 by providing infodemic news on rare side effects [32]. Hence, it is plausible that, given the high number of vaccinations achieved at the national level, more authoritative sources have also been consulted by users. The capacity to provide accurate predictions on vaccination trends several weeks in advance is an extremely relevant epidemiological tool for developing future containment strategies [33]. These findings show that Google Trends can be exploited for this purpose if used properly. The search for simple well-targeted keywords on Google Trends is more likely to return the actual scenario of web interest on a certain topic. Specifically, it is essential not to use too complex or specific names, which tend to be ignored by users, and to try to express a precise action (in this case, the vaccine reservation).

Among the limitations of this paper, it is fair to emphasize that no definitive causal evidence has been provided, and unknown confounders may have skewed the results in unpredictable ways. Moreover, the variability of time lags between online booking and vaccine administration was not considered in this study. Finally, although well targeted, there are no guarantees that all the keywords relating to the desire not to be vaccinated have been selected. In this regard, given the broad antivaccination movement, many users may not have expressed an online interest in not getting vaccinated.

Conclusions

This research provides preliminary evidence in favor of using Google Trends as a surveillance and prediction tool for vaccine adherence against COVID-19 in Italy. Further research is needed to establish appropriate use and limits of Google Trends for vaccination tracking. However, these findings prove that the search for suitable keywords is a fundamental step to reduce confounding factors. Additionally, targeting hypotheses helps diminish the likelihood of spurious correlations. It is recommended that Google Trends be leveraged as a complementary infoveillance tool by government agencies to monitor and predict vaccine adherence in this and future crises by following the methods proposed in this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary figures and tables.
[DOCX File , 391 KB - xmed_v3i2e35356_app1.docx]

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Abbreviations

RSV: relative search volume
VIF: variance inflation factor
VRH: vaccine-related headlines
VRQ: vaccine reservation query

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Original Paper

The Influence of SARS-CoV-2 Variants on National Case-Fatality Rates: Correlation and Validation Study

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Abstract

Background: In 2021, new variants of the SARS-CoV-2 virus appeared with increased transmissibility and virulence as compared with the original wild variant. The first variants of concern (VoCs), Alpha (B1.1.7) and Gamma (P.1), first appeared in the United Kingdom and Brazil, respectively. The Delta (B.1.617.2) variant, seen in India in October 2020, dominated COVID-19 infections across all regions through the second half of 2021.

Objective: This research explores the degree to which SARS-CoV-2 VoCs generate waves of fluctuations in case-fatality rates (CFRs) across countries in several regions, increase the risk of mortality to persons with certain comorbidities, and decrease the risk of mortality as the percentage of fully vaccinated populations increases.

Methods: This analysis introduces a measure of the temporal dynamics of COVID-19 infections in the form of a proxy CFR (pCFR), which can be compared among countries. It uses economic and demographic data reported by the World Bank and International Monetary Fund, plus publicly available epidemiological and medical statistics reported to the relevant national and international public health authorities. From these ecological data, pandemic average and daily COVID-19 CFRs and their correlations with potential cofactors were computed for 2021, a year dominated by the spread of World Health Organization–designated VoCs. The study does not investigate disease pathology; rather, it compares the daily case rates and pCFRs to reveal underlying contributing factors that vary from country to country and region to region.

Results: The in-depth global regression analysis of cofactors found that the strongest single correlation with COVID-19 fatality was 0.36 (SD 0.02) with $P<.001$ for chronic kidney disease. No other single physiological cofactors display positive correlations

exceeding 0.26 (SD 0.26), with *P*=.008 (asthma) and *P*=.01 (coronary disease). The study confirms that the pCFR is a valuable metric for tracking waves of infection due to different VoCs within countries.

Conclusions: The influence of social, economic, and medical cofactors on the CFR due to VoCs remains qualitatively similar, albeit strengthened, to the levels found for the wild strain. The strong regional variations of the influence of all cofactors observed for the wild strain persists in infections for all VoCs with very strong correlation coefficients seen in the Middle East for asthma (0.76), coronary heart disease (0.60), lung disease (0.70), and chronic kidney disease (0.52). Strong regional variations emphasize the influence on COVID-19 mortality due to regional differences in national economics, patterns of health care policies, and variations in cultural practices and environment. The pCFR-based analysis reveals clear patterns of the spread of VoCs across regions, but there is little evidence for the spread of the Lambda and Mu (B.1.621) variants of interest outside of South America.

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KEYWORDS

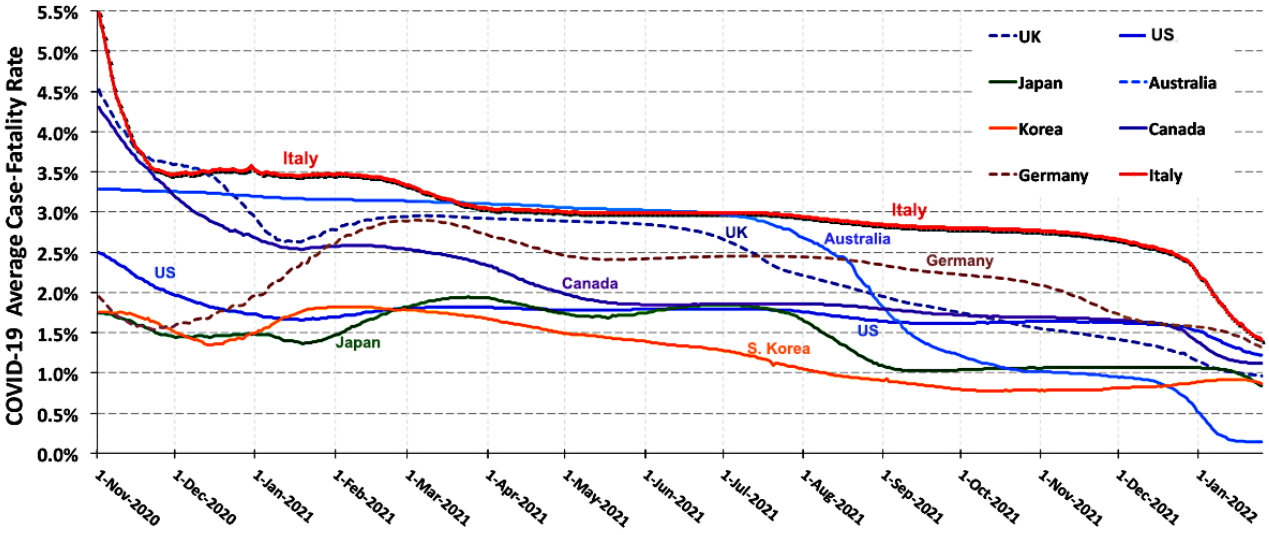
SARS-CoV-2; COVID-19; variants of concern; case-fatality rates; virulence; vaccine effectiveness; correlation study

Introduction

Background

The period from November 2020 to the end of 2021 is characterized by the rapid spread of several "variants of concern" (VoCs) of the SARS-CoV-2 virus [1-3] across most highly populated nations with both increased levels of transmissibility and virulence. In January 2021, the Alpha (B.1.1.7) variant [4] began its spread from the United Kingdom across Europe. The Gamma (P.1) variant in Brazil [5], first seen in mid-November 2020, began to dominate infections in South America during 2021. During mid-2021, the Delta (B.1.617.2) variant [6,7], first seen in India, became the dominant source of COVID-19 in North America, Asia, and Europe. Figure 1 shows the pandemic's average case-fatality rate (CFR) for the period from November 1, 2020, through January 2022, when multiple VoCs, in addition to Alpha (B.1.1.7), were widespread.

Figure 1. The pandemic's average case-fatality rate for the period during which other variants of concern became widespread.



The rationale for this investigation is to explore the degree to which new VoCs have increased the susceptibility for severe consequences to COVID-19 for persons with common comorbidities and to examine how national vaccination policies may have affected the severity of health outcomes of variant-induced infections. With respect to the influence of comorbidities on COVID-19 outcomes, other researchers have pointed out the shortcomings of the usual warnings by the US Centers for Disease Control and Prevention (CDC) [8,9].

A recent study of four unique endotypes of patients hospitalized with COVID-19 infections found that high-level comorbidities did not associate with poor outcome endotypes [10,11]. Previously, a study on the proximate and underlying causes of death as determined by the autopsy of 26 hospitalized patients found that death was "directly related to COVID-19 in the majority of patients." Pre-existing health conditions had only contributory implications, and death was not an immediate result of those comorbidities [12]. From the outset of the pandemic, patient age has been a frequently cited cofactor contributing to the severity of COVID-19. Although Alpert et al [13] described a clinical definition for immune age, its application here would require an extensive set of patient data not available for a country-by-country study of national populations.

An earlier study by Barletta [14] examined correlations of COVID-19 fatalities due to the wild strain in 2020, with 15 medical cofactors and eight socioeconomic cofactors (listed in Multimedia Appendix 1). The statistical bases of that study were national statistics of SARS-CoV-2 with respect to the original strain of the virus through December 2020. Since that time, the number of reported cases of COVID-19 has increased

from 82.9 million to 288.3 million as of December 31, 2021. Over the same period, the number of deaths increased from 1.81 million to 5.44 million. During 2021, more than 4.56 billion people received at least one dose of an anti–COVID-19 vaccine, and more than 3.82 billion are considered fully vaccinated. COVID-19–related data for all countries was taken from Our World in Data (OWID) [15].

Specific Objectives

The principal objectives in this study are to establish a valid proxy national CFR and to assess its daily fluctuations, to investigate on a global and regional basis the correlation between average national pCFRs and potential cofactors/comorbidities, and to describe by region the correlation between proxy national CFRs of country pairs.

Methods

Temporal Dynamics

The analysis of this study starts with an examination of the temporal behavior of the pandemic's average CFR as shown in Figure 1. Previously Ghani et al [16] suggested a time-sensitive metric for novel infectious diseases in the context of severe acute respiratory syndrome, explicitly considering recoveries from reported cases. However, that study did not account for the time delay between the first report of infection and the date of the subsequent outcome; however, that consideration is unimportant for a metric averaged over the duration of a lengthy persistent pandemic such as that produced by SARS-CoV-2. The curve for Italy exemplifies how high values of the average CFR in early 2020 reduced the sensitivity of this metric as convincing evidence of waves of increased virulence of the VoCs that spread in 2021. Figure 1 displays a long period during which the CFR in the United Kingdom increased, probably due to the B.1.1.7 variant, and then fell as Britain's vigorous testing, vaccination, and infection characterization programs took hold. Similarly, the increase in the German CFR in early 2021 is likely driven by the B.1.1.7 variant; however, laboratory data characterizing the variant of the infections in Germany were not available to substantiate that hypothesis. The fluctuations in the CFR in Figure 1 for Australia, Japan, Korea, and the United States are not readily explainable from the pandemic averaged data.

Although the pandemic averaged data are suggestive, they are far from dispositive. Further analysis requires introducing a proxy measure of the CFR, more sensitive to temporal variations in the virulence of the dominant variant but far less sensitive to systematic irregularities in the timing of government reports of fatalities ascribed to COVID-19.

Fourier analysis of the time series of daily reports of new COVID-19 infections displays an unambiguous isolated peak in the frequency spectrum at 1 per week. This manifest systematic irregularity in the reported data (with far fewer cases and deaths on weekends) plus the inherent statistical noise in the data both justify introducing a proxy for the daily CFR. Using an appropriate proxy rate, one can then explore whether the daily CFR in several countries shows evidence of more (or less) virulent variants taking hold or whether robust programs of COVID-19 testing plus vaccination, including boosters, decrease the mortality rate of the disease.

Study Design

To explore correlations and temporal variations of the influences of VoCs, this study introduces a credible proxy for daily CFRs, which will be sensitive to the extent of the spread of a variant throughout a country. The definition of a suitable proxy CFR (pCFR) and the subsequent analysis and validation of its temporal distribution on a country-by-country basis are presented in the Results section. To evaluate changes in the susceptibility to cofactors, this study follows the methodology of Barletta [14], in which the input data are based on national epidemiological statistics for COVID-19 and potential cofactors as reported to the relevant national and international authorities and tabulated by OWID [15] and the US CDC [8].

Data Sources and Setting

For consistency with the previous analysis [14], this study analyzes the same sample of 99 countries as listed in Table A.1 of Multimedia Appendix 1. These countries from the Americas, Asia, Europe, and the Middle East had been selected as representative of those having the most reported COVID-19 infections during mid-2020; their population is 5.5 billion persons. At present, the countries omitted represent less than 3% of the world's reported COVID-19 cases. Although using sex-disaggregated data would have been preferable, a suitable self-consistent data set, disaggregated by sex and ethnicity, has not been reported or is not publicly available for many of the countries included in the analysis. The grouping of countries by region serves as a quasi-proxy for ethnicity data. The focus on the time series of the pCFR and daily infections allows one to observe and, if necessary, adjust for seasonal variations.

Susceptibility With Respect to Comorbidities

A further question is whether national populations infected with the VoCs display different susceptibility with respect to comorbidities and economic cofactors than they did to the wild variant of the virus. To answer this question, one can analyze correlations of potential contributing cofactors during the period from January 1 through December 2021 over the same set of countries studied previously by Barletta [14].

The potential cofactors that are evaluated with respect to their correlation with fatalities in COVID-19 infection are grouped into three main categories:

1. Physiological characteristics: age and BMI
2. Cofactors: obesity, hypertension, inflammatory heart disease, coronary disease, asthmas, lung disease, lung cancer, susceptibility to influenza-induced pneumonia, chronic kidney disease, leukemia, COVID-19 testing, and reported COVID-19 cases per million persons
3. Socioeconomic and political factors: adjusted gross domestic product (GDP), national health care expenditures, World Health Organization (WHO) health care index, malnutrition mortality, hospital beds per 1000 persons, percentage of population fully vaccinated, number of persons per household, percentage population in urban centers, and percentage of population in slums

Data related to COVID-19 infections are those tabulated daily in OWID [15]. The relevant data regarding comorbidities, as reported to the WHO, can be found in World Health Rankings [17].

Analysis Methodology

The statistical data analysis used in this paper proceeds in the following order:

1. Plot the pandemic averaged CFR against all individual potential cofactors on a region-by-region basis to explore potential relationships between the CFR and potential cofactors (examples are shown in Multimedia Appendix 1, Section C)
2. If plots of the CFR against potential cofactors display no strong evidence of nonlinear effects when fit with trial trend lines, compute the linear correlation of the pandemic averaged CFR and potential cofactors using the Pearson "product moment correlation" (specific examples with linear fits per region appear in Multimedia Appendix 1, Figures C.1, C.2., and C.4b)
3. Compute the linear correlations between the average CFR for 2021 and all potential cofactors for country pairs both globally and region by region using the data analysis package of Excel version 16.43 (Microsoft Corporation)
4. Absent evidence of significant nonlinear effects as determined in step 2, perform a detailed linear regression analysis of all 24 potential cofactors with the set of national pCFR values, using the standard data analysis package of Excel version 16.43
5. To compare results of correlations of national data within regions, consider country pairs for which the spread of a VoC is likely due either to extremely high transmissibility or due to significant travel of persons across national borders
6. To compare experience in several countries, compare and contrast the time series of daily CFRs

Unfortunately, the raw reported data are noisy, as they are subject to uneven reporting of both new cases and deaths attributed to COVID-19 as well as to inherent statistical fluctuations in the daily data. Moreover, computing the daily CFR on day N as defined in [15]:

$$\text{Trial daily CFR (N)} = \langle \text{Deaths (N)} \rangle / \langle \text{Cases (N)} \rangle \quad \textbf{(1)}$$

in which the brackets,⟨ ⟩, denote a 7-day rolling average, yields misleading values for the CFR on day N because the deaths on that day had to be caused by COVID-19 infections that began generally 2 to 3 weeks earlier.

To mitigate these deficiencies in the data, one introduces a plausible proxy, pCFR, for the apparent daily case-fatality ratio. The pCFR is a retrospective diagnostic that compares the deaths on a given day against the average number of new cases during a period from 14 days to 14 + M days prior to that given day. The model overlays those data with a rolling 14-day average of the results to suggest the actual temporal trends in the virulence of SARS-CoV-2 infections. Noting that substantial consequences of infection often appeared within a 7-day period from 14 to 21 days (the range of M) after the reported symptomatic infection, one can define the proxy pCFR by equation 2.

The time series of the trial CFR of equation 1 correlates only moderately well with that of the pCFR. Sample calculations for the United States and the United Kingdom yield correlation coefficients of 0.74 and 0.65, respectively, suggesting that the statistics of SARS-CoV-2 contagion and COVID-19 fatalities do not change rapidly over a 2- to 3-week timescale. To examine the sensitivity of the pCFR to the averaging period of the number of cases that influence the number of deaths on day N, one can change N-21 to N-28 in the denominator of equation 2. The correlation of the resulting two time series ranges from 0.92 to 0.98; hence, the results of the analysis depend only weakly on the period over which the pCFR is computed. To reduce further artificial variations caused by irregularities in reporting, this study uses the smoothed daily deaths computed by OWID [15].

A second trial proxy might be the ratio on day N:

where d represents the rolling average over d days in equation 3. Yet another alternative might be the derivative  . Unfortunately, like most differential measures, both  and are extremely noisy functions that obscure even strong variations in the CFR. An example of  is shown in Multimedia Appendix 1, Section B for the case of the United Kingdom.

Results

Temporal Dynamics

The correlation analysis of the previous study [14] of average CFRs of COVID-19 with potential comorbidities and societal cofactors relied on data reported to governmental authorities from March 2020 through October 2020. During that period, the WHO had not yet designated any VoCs [1], although cases subsequently attributed to the B.1.1.7 (Alpha) and B.1.351 (Beta) strains dated from mid-October 2021 and mid-May 2021, respectively [5]. Consequently, the correlations of Barletta [14] were all attributed to the wild strain of the virus even though some cases—especially those in South Africa—may have been more properly attributable to the B.1.351 variant. By mid-December 2020, the WHO had designated both the B.1.1.7 strain and the B.1.351 strain from South Africa as VoCs.

With many European nations included in the data set of this study, the initial date of November 1, 2020, was set for the analysis of the effect of VoCs on virulence and on transmissibility and spread of the disease, and the influence of cofactors in the presence of new VoCs.

Effects of COVID-19 Vaccines

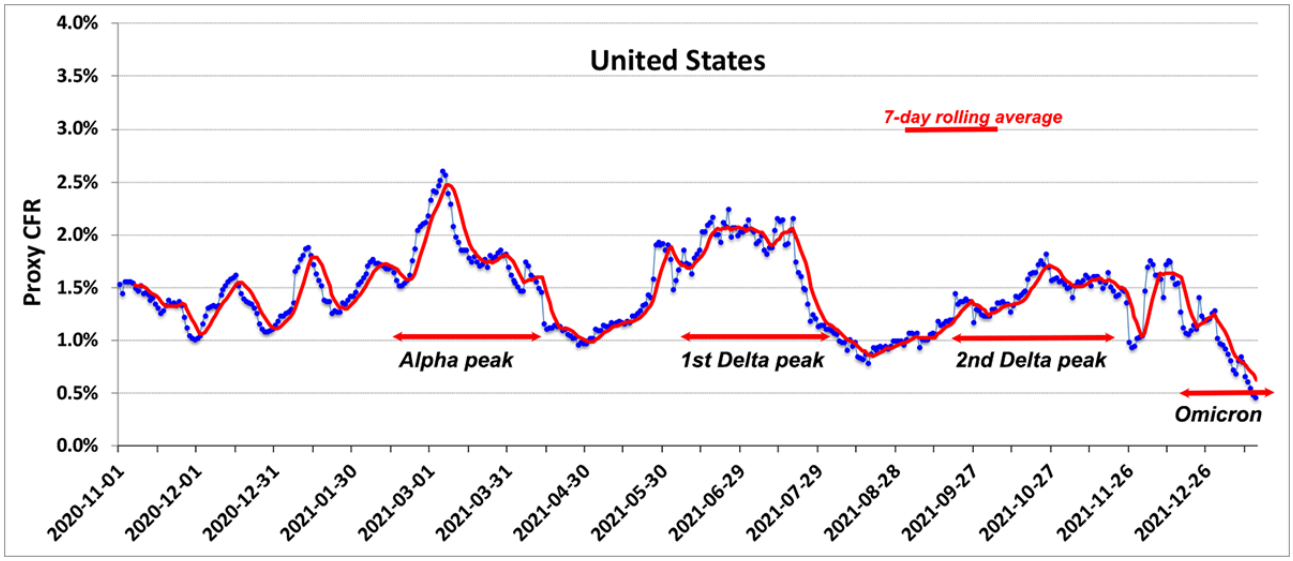
The level of vaccine-induced immunity in respective populations is a potential cofactor in tracking the dynamics of SARS-CoV-2. Doubtless, one may expect the national reports of the number of new COVID-19 infections, the CFRs, and the reproduction rate of the SARS-CoV-2 virus to be influenced by the degree to which a nation's population is fully immunized by vaccines. Therefore, those statistics have been analyzed versus the

percentage of total population fully vaccinated. A table of examples is given in Multimedia Appendix 1, Section C.

A limitation of the pCFR, likely shared by other daily measures of fatality rates, is that it is most subject to large fluctuations when the COVID-19 daily case rate—and therefore the death rate—is small. That situation often happens when the fraction of total population fully vaccinated exceeds 40% to 50%, especially when other prophylactic measures contribute strongly to driving the reproduction rate, R_0, to less than 1. The positive aspect of this sensitivity of the pCFR when case numbers are small is that highly variable trends in the pCFR can spot surges of cases in clusters of unvaccinated persons or in less than vigilant groups.

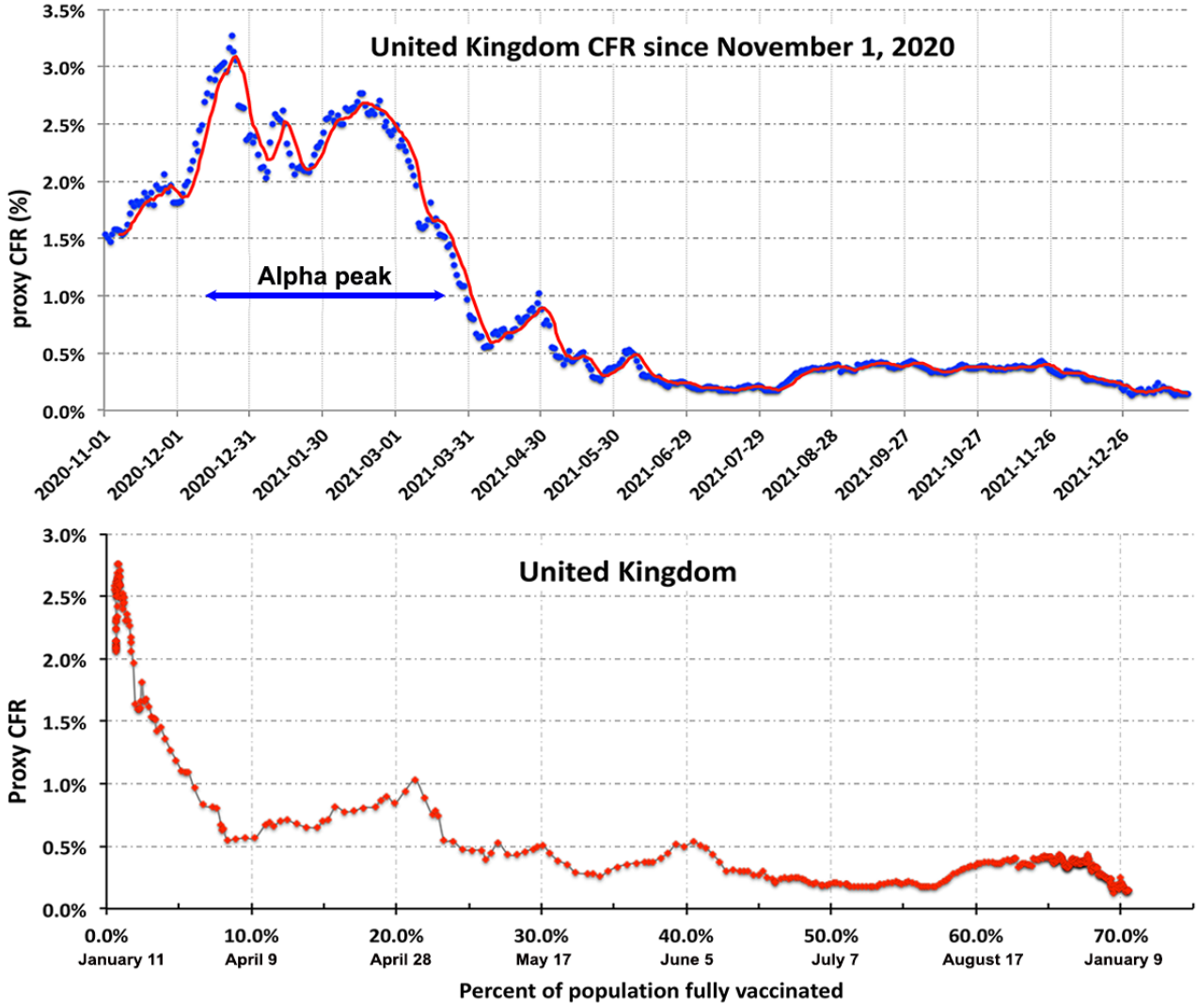
Figure 2, which displays the time sequence of the pCFR for the United States, shows clear evidence that was not readily visible in the pandemic averaged CFR for the differences in rates of mortality in February and March 2021 due to the B.1.1.7 variant that appeared in the United States in January 2021 [4], before less than 0.6% of the population had received vaccinations. The CDC [4] had predicted a peaking of the number of infections due to B.1.1.7 in March 2021; that surge in cases likely accounts for the increase in the pCFR seen in March 2021.

Figure 2. Daily proxy CFR values and waves of infection in the United States. CFR: case-fatality rate.



In contrast, the United Kingdom reported infections from the B.1.1.7 variant in mid-December. The variant spread quickly, raising the pCFR to ~3% before any significant fraction of the UK population could be vaccinated. Figure 3A shows the marked increase in the pCFR in late December and January. By March 2021, roughly 30% of the total UK population had received their first dose of the vaccine, and by the end of April, over 80% of the population ≥59 years of age had received their first dose [18]. The pCFR began to decrease steadily in March 2021.

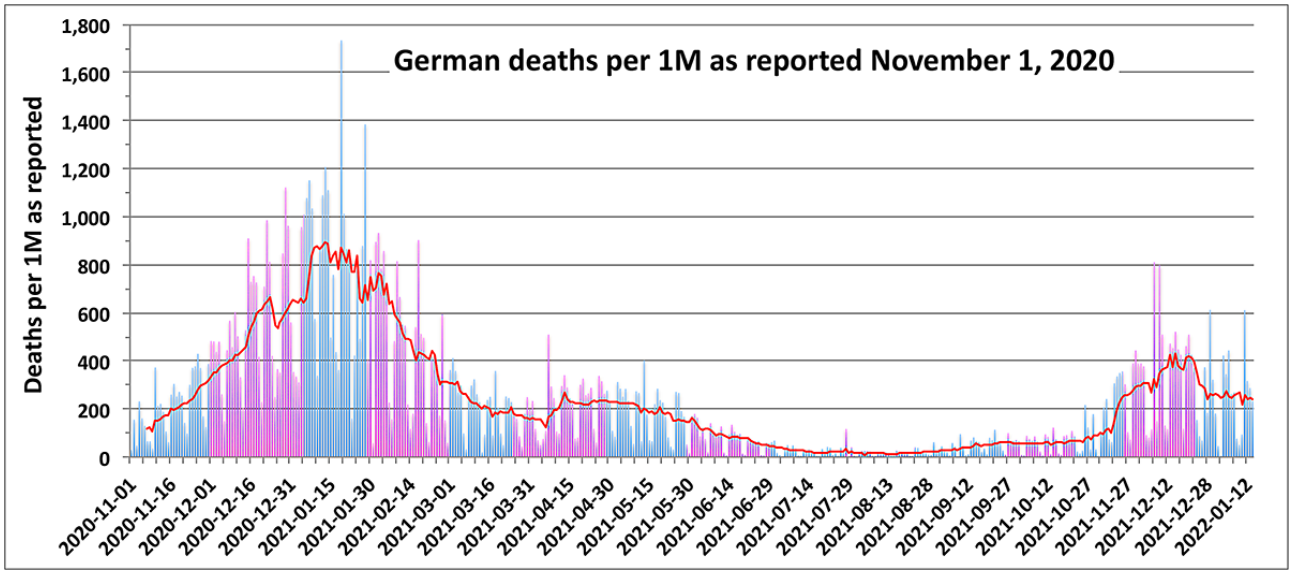
Figure 3. Upper panel: Daily proxy CFR in the United Kingdom since November 2020. Months are in cyan and magenta. The red line is a 7-day rolling average. Lower panel: Proxy CFR for the United Kingdom vs percentage of the population fully vaccinated. CFR: case-fatality rate.



With a vigorous program of both testing (at twice the rate of the United States) for SARS-CoV-2 infection plus full immunization exceeding 68% of the total UK population by November 2021, the pCFR in the United Kingdom has fallen below 0.5%, comparable to other countries in Europe and commensurate with levels sometimes associated with seasonal influenza. The effects of the vaccination program on the pCFR are clear in a plot of the pCFR versus the percentage of the total population fully vaccinated [15] (Figure 3b). The strong prolonged increase in the pCFR during the time of B.1.1.7 dominance is consistent with clinical reports by Twohig et al [7] of increased mortality due to the B.1.1.7 strain. Unfortunately, complete sex-disaggregated and ethnically disaggregated data sets are not available for full comparison with the results of Twohig et al [7].

Figure 4 illustrates the case of Germany—intermediate between that of the United Kingdom and the United States. The slower spread of the B.1.1.7 variant likely explains the increase of the pCFR during January and March that parallels the rise of the pCFR in Britain. This behavior offers further evidence that the B.1.1.7 VoC is more virulent than the original wild strain of SARS-CoV-2. Probably due to the excellent preparations regarding triage protocols taken by the German health care system, in mid-March 2021, the pCFR began to decrease toward its pre–B.1.1.7 level. Yet as testing and vaccinations for COVID-19 in Germany [15] lagged well behind the levels in the United Kingdom [19], reaching 10% full vaccination only in early May 2021, the pCFR increased by the end of May, most likely due to the more virulent B.1.617.2 (Delta) variant. That behavior is similar to that seen in the United States (Figure 2). By the beginning of July, full vaccination in Germany had reached 40%, and the pCFR showed signs of lessening to approximately 3%. The manifest periodicity in the number of daily deaths displayed in Figure 4 is due to the suppressed reporting of COVID-19 statistics on the weekends and justifies the use of smoothed sets of underlying data in computing the pCFR.

Figure 4. Daily deaths as reported for Germany since November 2020. Months are in light and dark bands. The red line is a 7-day rolling average.



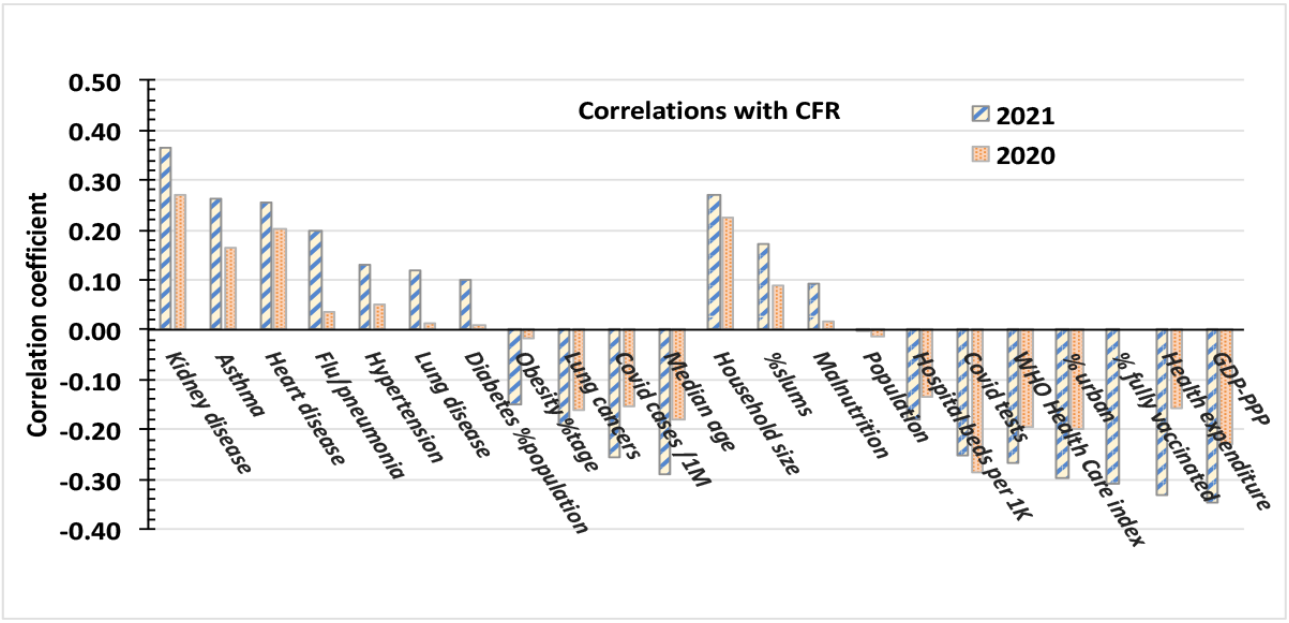
Doubtless, the variations in the national pCFR are also affected by the pervasiveness of national vaccination programs. To elucidate that influence, one can examine the variation in the pCFR versus the percentage of the total population who have been fully vaccinated (not including boosters). As booster programs become prevalent, plots of the case rate and pCFR versus percentage of boosted populations can also be revealing. An example related to the B.1.1.529 variant is offered in Multimedia Appendix 1, Section D.

Effects of Comorbidities

An objection to relying on the initial analysis of the previous subsection is that the pandemic averaged case-fatality ratios remain dominated by the very high mortalities at the outset of the pandemic before appropriate and adequate isolation of the infected and modalities of treatment were understood. To mitigate that objection, one focuses only on the period of January 2021 through November 2021 that has been dominated by surges of VoCs that were described at the time of the WHO's designation to have higher transmissibility and perhaps higher virulence than the original wild strain of SARS-CoV-2. In addition to accounting for the variations in the virulence and transmissibility of the new VoCs, one should also ask whether those variants exhibit significantly different sensitivity to physiological, environmental, and economic cofactors than were previously reported by Barletta [14].

The SARS-CoV-2 statistics for 2021, correlated with the disease data of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Council [20] yield Figure 5. The striped bars account for the correlations only during the variant-dominated period of 2021. The speckled bars display the correlations of the pandemic averaged CFR throughout the pandemic dominated by the wild strain through December 30, 2020. With one exception, one sees no great differences between the variant-dominated and the pandemic-averaged values of 2020 beyond the general strengthening of previously observed trends. The tripling of the correlation between the average CFR with the total number of COVID-19 deaths per capita is likely due to deaths in unvaccinated populations caused by the B.1.617.2 (Delta) variant, which by September 2021 accounted for 80% of infections in the United States, according to the US CDC [21].

Figure 5. Linear correlations with the pandemic average CFRs in 2021, a variant-dominated period (striped), compared with values of the pandemic's averaged CFRs for 2020 (speckled). CFR: case-fatality rate; GDP-PPP: gross domestic product based on purchasing power parity; WHO: World Health Organization.



Apart from participants who participated in trials of the COVID-19 vaccines, no nation had begun a program of systematic immunization of its population in 2020. Therefore, the correlation value equals 0.0 for the vaccination cofactor in 2020 as shown in Figure 5.

Unlike a typical epidemiological analysis that would use the biological age of patients in a study, in this ecological data set, we must characterize the age distribution of an entire country by a single number. One might choose the median age of its population, the percentage of the population older than 65 years, or the life expectancy. As expected, these three characteristics are highly correlated, with correlation coefficients of 0.88 and 0.80 between the median age and the percentage older than 65 years and the life expectancy, respectively. However one characterizes age in a country, that value reflects social and economic aspects distinct from the physiological age of individual persons.

A detailed multivariate regression analysis of worldwide data including 24 independent variables reveals no constellation of cofactors, including the number of hospital beds per capita, that drives average national CFRs. The best regression model included only chronic kidney disease and the adjusted GDP as the independent variables. The *P* values for these variables were *P*=.01 and *P*=.02, respectively. The result for chronic kidney disease is consistent with findings of the ERA-EDTA Council [20]. That report indicates that, globally, the mortality risk from chronic kidney disease exceeds that from diabetes mellitus and chronic coronary disease, again in agreement with this analysis.

Regional Variations

A potential source of misinterpretation of the global statistics is the considerable variation of the correlations of cofactors from one region to another, as well as from the overall global values. Figure 6 compares the correlations of the pCFR for six commonly cited cofactors for the period dominated by the VoCs active during 2021. A restricted multivariate analysis over only countries in Europe reaches similar results.

Figure 6. Heat map of regional variation of correlations with the case-fatality rate averaged over the period with *P* values for world data from January 2021 to December 2021.

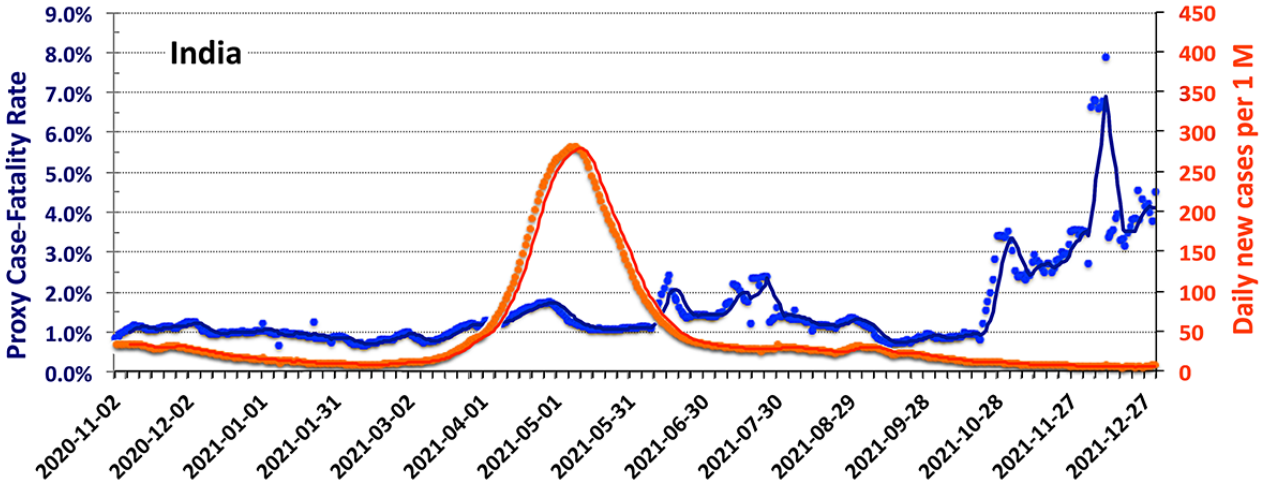
	Chronic kidney disease	Coronary heart disease	Diabetes mellitus	Hypertension	Obesity	Lung disease	Asthma	Malnutrition
World	0.36	0.25	0.10	0.13	-0.15	0.17	0.26	0.09
P values (world)	*P<.001*	*P=.01*	*P=.33*	*P=.21*	*P=.14*	*P=.09*	*P=.01*	*P=.36*
Americas	0.23	-0.12	0.21	-0.17	-0.39	-0.12	-0.26	0.28
Asia	0.40	0.17	0.35	0.59	-0.13	0.11	0.37	0.46
Europe	0.47	0.46	0.53	0.52	0.07	0.06	-0.02	-0.24
Africa	0.27	0.39	-0.04	-0.05	-0.17	0.14	0.22	-0.25
Middle East	0.52	0.60	-0.07	-0.03	-0.45	0.70	0.76	0.72
	0< X <0.15	0.15 <X <0.30	0.30 < X < 0.45	X > 0.45	0 < X <-0.15	-0.1 5 <X< -0.3	-0.3 <X <-0.4	-0.4 <X

The examination of statistics from Israel [22], which instituted an early and vigorous vaccination program early in 2021, could shed light on the role of testing and vaccination to suppress the serious consequences of infections with SARS-CoV-2. The smoothed data from OWID [15]—in Multimedia Appendix 1, Figure B.6—show evidence of an increase in the pCFR during

mid-September 2021 consistent with an initial spread of the B1.617.2 variant in Israel. The spike in mid-May is likely spurious and too statistically insignificant due to the very low case rate to allow firm conclusions. Across all elements of the population of Israel, the overall vaccination rate is only 63%; however, the vaccination rate for persons ≥60 years of age is 80%. The variations in the pCFR from September through December are the result of the waning of the effectiveness of initial vaccinations [23], the rapid program of booster vaccination, and the increased virulence of the B1.617.2 variant.

Examining smoothed data [15] from India in a manner similar to that used to generate Figures 2-4 provides a useful day-by-day comparison among the countries. As was the case in the United States in July 2021, the dominant variant in India is B.1.617.2 (Delta), which started to become common in March 2021 [23]. Although the Indian data have less statistical noise than that from Israel, the smoothed day-by-day statistics of Figure 7 allow for a clearer look at temporal trends than do the raw data. Consistent with the increasing pervasiveness of the B.1.617.2 variant, the pCFR increases significantly from its February low of less than 1%, rising in March and April to 1.5% at the peak of the infection wave and to 2% by June when the surge was waning.

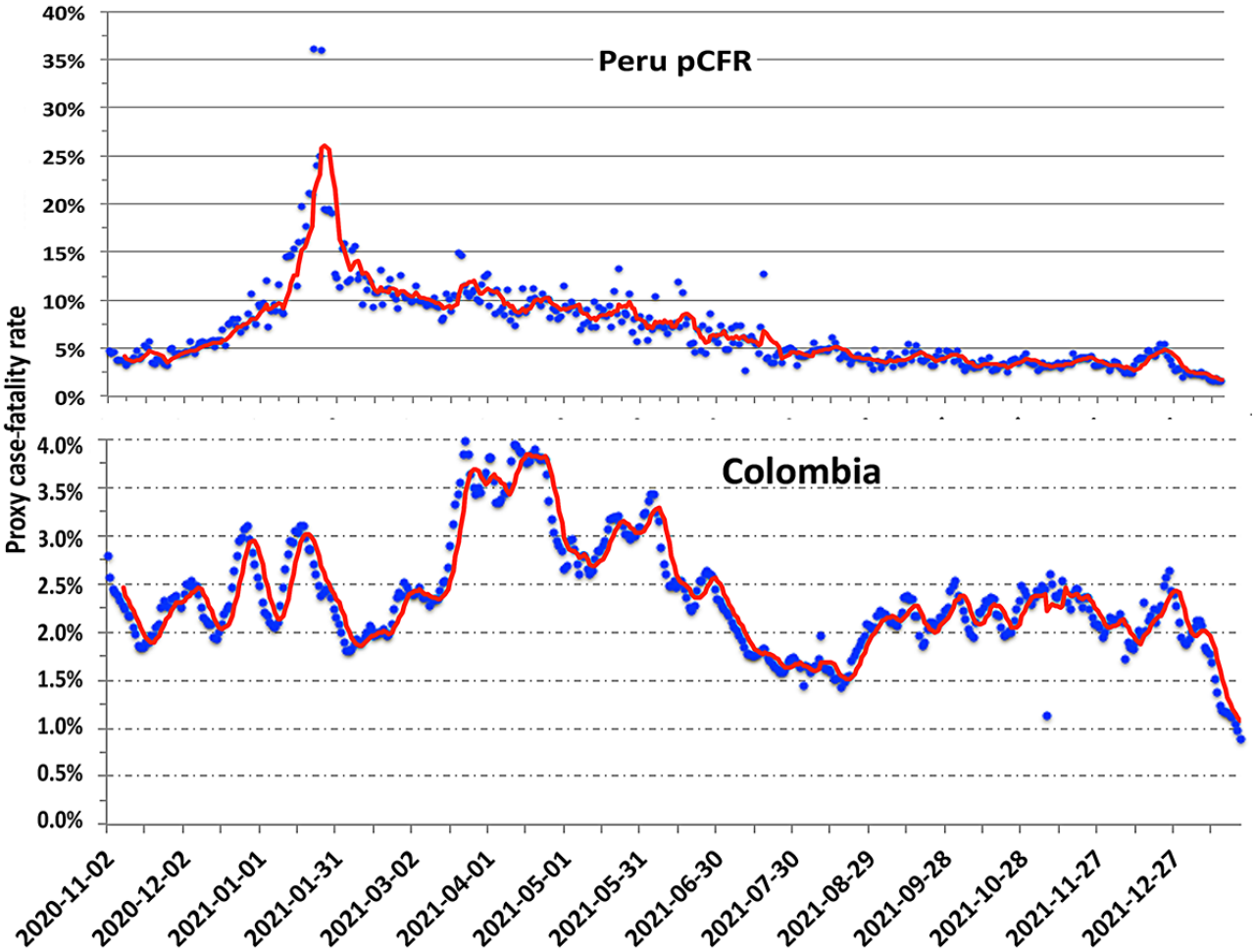
Figure 7. The smoothed values of the proxy case-fatality rate (blue) and daily new cases per 1 million persons (red) in India since November 1, 2020. The dark lines are the 7-day rolling averages.



The results of Figure 7 are unlikely to include any significant effect of India's program of vaccination that uses five different vaccines. By late-November 2021, only 30% of its population had been fully vaccinated [24]. Moreover, all the vaccines evaluated against B.1.617.2 appear to be roughly 10% less effective in controlling the development of COVID-19 in patients with the B.1.617.2 variant [25] than against the wild strain (at the 95% confidence level). The jump in the pCFR, seen in November 2021, occurred while the percentage of fully vaccinated persons was only 32% and the number of daily new cases remained at less than 6.3 per 1 million persons. During that entire period, the reproduction rate of the virus remained at less than 0.95.

The WHO-designated variant of interest, C.37 (Lambda), has been circulating widely in South America, having first been reported in Lima, Peru in December 2020 [26-28]. As shown in Figure 8, Peru saw a strong spike in the pCFR in January and February 2021, reaching 20%. Since that time, the pCFR has decreased gradually to roughly 5%. By July 2021, only slightly more than 10% of the Peruvian population had been fully vaccinated [15]; by November 2021, that number had increased to 49.4%.

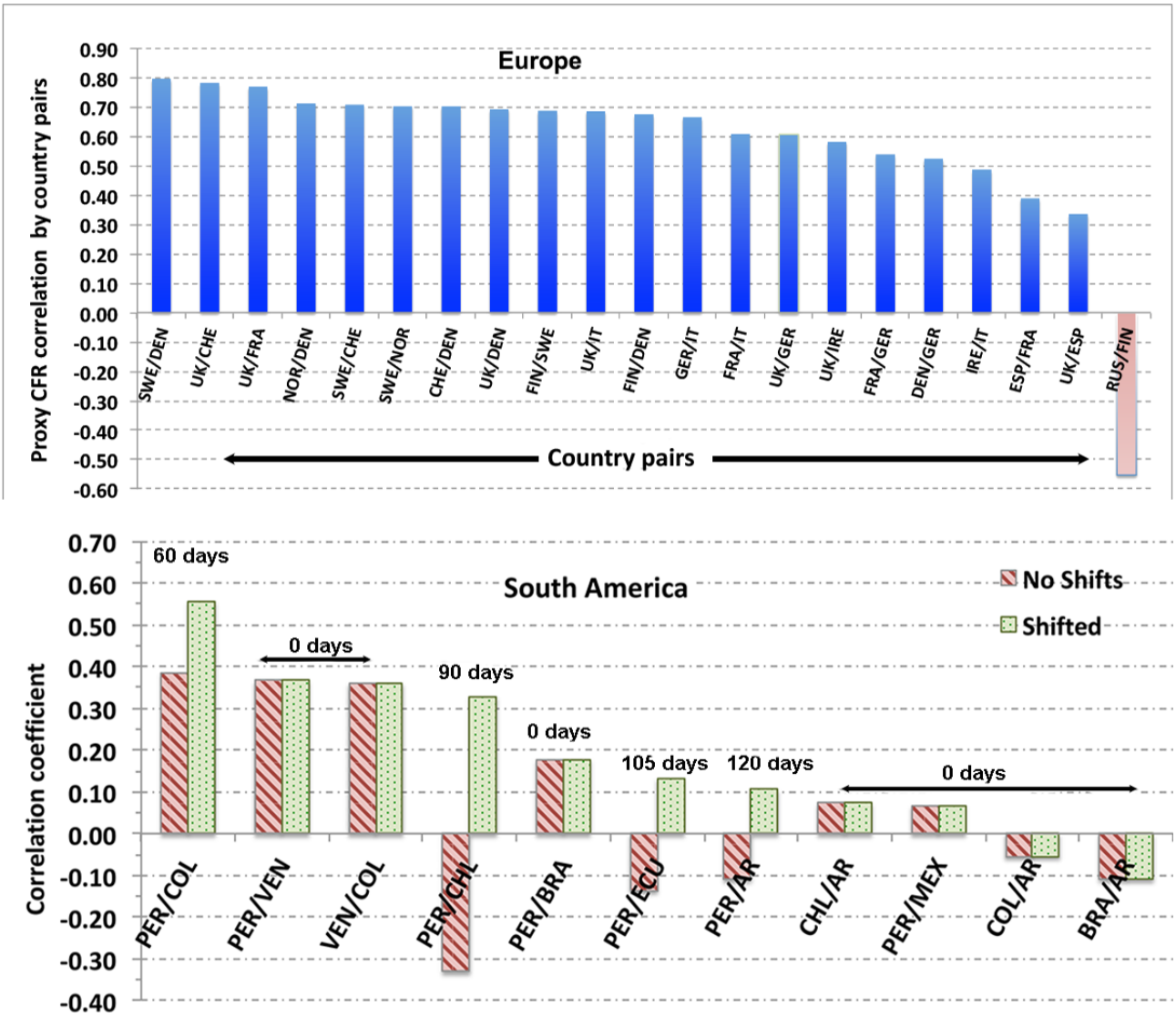
Figure 8. The behavior of the pCFR in Peru (upper plot) and Colombia (lower plot) since November 2020 based on the smoothed data of [15]. The red lines are the 7-day rolling averages. pCFR: proxy case-fatality rate.



The analysis of the C.37 virus by Kimura et al [27] identified a modified structure in the receptor binding domain of the spike protein that accounts for Lambda's higher resistance to vaccine-induced immunity than is the case for the original wild variant. Hence, the initiation of the vaccination program in Peru cannot by itself account for the continuing decline in the pCFR. The South American scene is further complicated by the simultaneous circulation of multiple VoCs, particularly in Brazil, where the P.1 (Gamma) variant appeared in early 2021 [4,5].

The lower panel of Figure 8 provides an example for Colombia. Comparison between plots of the temporal behavior of the pCFR (Figures 3 and 4 and Figures 7-9) can be made qualitative by computing the correlation *r* value for pairs of countries grouped into regions. One such set of calculations is displayed in Figure 9 for Europe and South America. The uncertainty in the correlation values is approximately ±0.05.

Figure 9. Correlations of proxy CFR between pairs of countries in Europe (top panel) and South America (bottom panel). CFR: case-fatality rate.



The upper panel of Figure 9 displays a strong to moderate correlation between countries in the Schengen region for which travel was relatively unhindered during the spread of the B.1.1.7 variant from the United Kingdom. Likewise, the country pairs in the Middle East—Iraq/Turkey, Turkey/Iran, and Iran/Iraq—show strong effects of transnational traffic during the Syrian civil war with correlations in the pCFR of 0.818, 0.711, and 0.634, respectively. Negative correlations in Figure 9 indicate either different courses of infection, treatment modality, vaccination program between the country pairs, or other impediments to the spread of a more infectious strain from one country to the other. An example of such a negative correlation, produced by neglecting the time delay in the spread of SARS-CoV-2 variants between countries is given in Multimedia Appendix 1 Section B, Figure B.7, which compares the time variation of the pCFR in Peru and in Argentina.

The distributions, when both are reckoned from November 2020, show no indication of the Lambda variant spreading from Peru to and through Argentina. One also sees no evidence of the Brazilian Gamma (P.1) variant causing a spike in the pCFR in Argentina (days 150-180 in Figure B.7) when the fraction of Gamma (P.1) cases was highest there. Even evidence of the spread of Lambda to Peru's neighboring countries of Colombia and Venezuela, as reflected in the pCFR, are moderate-low, with *r* values of 0.38 and 0.37, respectively. In fact, the values for Chile and Argentina are negative, –0.33 and –0.11, respectively. However, shifting the Peruvian distribution later in time (ie, day 1 for Peru corresponds to Day 1 + X_{delay}) to account for the time of the variant to propagate from one country to another increases the correlation coefficients significantly.

The striped bar in the PER/COL pairing in Figure 9 shows that shifting the Peruvian profile 60 days later in time, introduces a much larger similarity with the Colombian profile of the pCFR with the *r* value of 0.56 (speckled bar). Moreover, the correlation in the distribution of new cases shifts to 0.68. For Argentina, the correlation in the pCFR increases to 0.11 for a 120-day shift, while the correlation of the distribution of new cases increases to 0.86.

Such a large value of X_{delay} is consistent with the Delta variant being first reported in Argentina in August 2021 [29]. The differences in the pCFR in new cases in Argentina could be caused by differences in effective treatment in the two countries or by differences in the predominant variants of SARS-CoV-2.

Notably, Peru displays no evidence of a peak in the pCFR due to the B.1.617.2 in August when the fraction of Delta cases peaked [30].

The light purple bar in the PER/COL pairing in Figure 9 shows that shifting the Peruvian profile 60 days later in time introduces a much larger similarity with the Colombian profile. Additionally, the correlation of new cases shifts to 0.68. One may interpret these results as indicating the amount of time needed for the Lambda variant to spread widely into Colombia, where its prevalence is now high [31]. Further obscuring the degree to which the Lambda variant has spread out of Peru has been the competition in Peru between the Lambda variant and the Gamma variant. That competition has been examined by Vargas-Herrera et al [30].

For North America, one observes only a moderate correlation in the pCFR (0.57) between the United States and Canada. That low value may be explained by differences in the US and Canadian health care systems and by the fact that the border between the countries was closed since March 2020 through most of 2021.

Effects of COVID-19 Vaccines

As COVID-19 vaccines have been broadly reported by Barda et al [32] to be effective in reducing the severity of infections that nevertheless occur, one must account for a vaccine effect when using a metric based on CFRs. This study uses plots of the pCFR versus the percentage of population fully vaccinated and versus the percentage of population receiving a booster shot to discern waves of infection due to different variants. Examples relevant to the B.1.1.529 VoC are given in Multimedia Appendix 1 (Figure D.1, D.2, and D.3) that display the simultaneous spike in infection accompanied by a strong reduction in the pCFR. In comparing countries with different vaccination profiles, time series measured in days from November 2020 were used.

Discussion

Summary of Findings

Finding for Objective 1

The proxy for the daily CFR, pCFR, as defined by equation 1 and computed over a smoothed distribution of the deaths attributed to COVID-19 infections, provides a useful metric to track the national dynamics of the spread of SARS-CoV-2 VoCs overlaid with the implementation of that country's vaccination program. The variations in risk of mortality, especially near the first appearance of new VoCs, is clearly seen in the time series of values of the pCFR.

The example of the United Kingdom is instructive in this regard. A clear increase in the fatality rate due to the increased virulence of the B.1.1.7 variant is followed by the sharp decrease in the daily CFR to about 0.25% thanks to the United Kingdom's aggressive program of vaccination [18] as confirmed by the clinical study of Challen et al [33]. That low rate persisted despite the spread of the Delta variant throughout the United Kingdom. A similar increase in mortality due to B.1.1.7 was later observed in the pCFR data for the United States as displayed in Figure 2.

Finding for Objective 2

Using the pCFR, one finds that the influence of both economic and medical cofactors on the rate of fatalities due to infections caused by WHO-designated VoCs remains similar albeit somewhat strengthened with respect to the levels found for the wild strain of SARS-CoV-2. Based on a detailed global regression analysis, the strongest observed single correlation globally is 0.36 (SD 0.02), with $P<.001$ for chronic kidney disease for January through November 2021. No other physiological cofactors displayed positive linear global correlations, exceeding 0.26 for asthma with $P=.008$ and coronary heart disease with $P=.01$.

Finding for Objective 3

Strong regional variations of the influence of all categories of cofactors observed for the wild strain persist in the infections due to all VoCs. That variation emphasizes the effect on COVID-19 mortality due to regional differences in national economics, in patterns of national health policies, and possible variations in cultural and environmental factors. Moreover, the regional variations that appear in Figure 6 can explain some of the conflicting observations of risk factors found especially in the literature published or e-published in 2020.

Limitations

A limitation of using the pCFR metric is that large fluctuations in the pCFR can occur when the daily caseload is low. Whether these fluctuations are driven by transmission among small clusters of individuals with similar medical conditions or in small communities without adequate medical facilities cannot be discerned without detailed patient data. Nationally aggregated public health data are not sufficient.

For most countries studied, the pCFR successfully tracks waves of reinfections as well as the introduction and propagation of new VoCs (Figure 2, Figure 5, Figure 7, and Figure 8). The timing of strong increases in the daily pCFR in the United States and Germany from June through late July 2021, peaking at 2.0% and 4.5%, respectively, correspond to the rapid spread of the B1.167.2 variant and support the characterization of Delta as being both more virulent and more contagious than the original wild strain. Despite the moderate success of its vaccination program, the pCFR in the United States continued to increase in August 2021. In contrast, the pCFR in Germany decreased by early August to a value of roughly 1%. By October 2021, the pCFR began to increase in both countries due to a resurgent B1.167.2 wave.

The prevalence of multiple coexisting conditions also varies from region to region, partially explaining the regional variations seen in Figure 6. If a generally accepted measure of the readiness of the immunity system to fight infection were available, as was proposed by Han [34], one might obtain a clearer definition of COVID-19 mortality risk factors. However, producing a large database of Han's [34] metric would require genetic sequencing of large representative samples of individuals in a broad range of countries.

Comparison With Prior Studies

The results for objective 2 are consistent with the findings of the ERA-EDTA Council [21] although inconsistent with the finding of the July 2020 literature review and meta-analysis of Singh et al [35] and Bajgain et al [36] that found diabetes and cardiovascular diseases as the most common cofactors. That is not to say that other cofactors may not be seen in many patients who die from COVID-19; the correlation coefficients for patients with coronary heart disease and diabetes mellitus are high enough that persons with those conditions should take extra prophylactic precautions against infections.

Following the method of Ranard et al [11] for a data set limited to November 2020 through November 2021, this study finds minimal quantitative differences with the conclusion of Ranard et al [11] that the most commonly cited comorbidities do not per se substantially increase the risk of serious consequences of SARS-CoV-2 infections. However, one cannot ignore that many persons with such conditions frequently have multiple cofactors and have either an inherent or medication-depressed level [37] of immune function that can worsen the effects of a COVID-19 infection.

Consistent with Solis-Moreira [32], the time series of the pCFR show only weak evidence for significant spread of the Lambda and Mu variants of interest outside of South America, although some cases have been seen in Europe and North America. However, careful examination of the correlation of the pCFR distributions shows delays consistent with the times that Lambda appeared in countries not having a common border with Peru or Colombia.

While the epidemiological data are still too early to draw conclusions with respect to the highly contagious Omicron (B.1.1.529) variant, its worldwide spread provides a testing ground for many of the ideas presented herein. The early spread of the variant is described in Multimedia Appendix 1, Section D. Already, limited statistics support the hypothesis that this VoC is more transmissible and significantly less virulent than the B1.167.2 variant. The degree to which booster vaccinations and strict prophylactic measures can suppress both severity and extent of this VOC requires further detailed analysis. Whether new mutations derived from Omicron (B.1.1.529) retain such properties in addition to vaccine evasion is a topic for future research.

Conclusions

This research explores the degree to which SARS-CoV-2 VoCs generate waves of fluctuations in CFRs, increase the risks of mortality to persons with certain comorbidities, and respond to public health initiatives with decrease risks of mortality as the percentage of fully vaccinated populations increases. The pCFR that was introduced to address these issues is a valid proxy for national rates of the level of virulence of the VoCs. Waves of infection due to VoCs and their spread are generally, but not always, manifest in daily variations of the pCFR. An exception is the behavior of the pCFR (Figure 3) for B1.167.2 infections in the United Kingdom; however, in most cases, the temporal variations of the pCFR show strong correlations in propagation of VoCs. For example, the temporal distribution of the pCFR in Germany (Figure 4) shows distinct peaks coinciding with the spread of B1.1.7 and B1.167.2 throughout the Schengen zone.

This study tested the hypothesis that apparent increases in the virulence of VoCs might be due to increased susceptibility to severe infection in persons with certain comorbidities. The comparison of Figure 5 does not substantiate that hypothesis.

Robust programs of vaccination can alter dynamics of VoCs by lowering the pCFR averaged over monthlong periods as shown by the experience of the United Kingdom. However, complete suppression of the pCFR to uniform low levels is not always seen; such an example for Italy appears in Multimedia Appendix 1, Figure D.1. Plotting the pCFR, case rate, and reproduction number, R_o, against the percentage of total population fully vaccinated allows one to account for the effect of vaccinations; however, large variations in the pCFR and R_o can persist in countries with vaccination rates >60% (Multimedia Appendix 1, Table D.1 and Figure D.2). As the efficacy of vaccines wanes after several months [38], one should also plot metrics with respect to the percentage of the populations receiving booster shots.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary tables and figures.
[DOCX File , 2444 KB - xmed_v3i2e32935_app1.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CFR: case-fatality rate
ERA-EDTA: European Renal Association–European Dialysis and Transplant Association
GDP: gross domestic product
OWID: Our World in Data
pCFR: proxy case-fatality rate
VoC: variant of concern
WHO: World Health Organization

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Original Paper

Mask Use to Curtail Influenza in a Post–COVID-19 World: Modeling Study

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Abstract

Background: Face mask mandates have been instrumental in the reduction of transmission of airborne COVID-19. Thus, the question arises whether comparatively mild measures should be kept in place after the pandemic to reduce other airborne diseases such as influenza.

Objective: In this study, we aim to simulate the quantitative impact of face masks on the rate of influenza illnesses in the United States.

Methods: Using the Centers for Disease Control and Prevention data from 2010 to 2019, we used a series of differential equations to simulate past influenza seasons, assuming that people wore face masks. This was achieved by introducing a variable to account for the efficacy and prevalence of masks and then analyzing its impact on influenza transmission rate in a susceptible-exposed-infected-recovered model fit to the actual past seasons. We then compared influenza rates in this hypothetical scenario with the actual rates over the seasons.

Results: Our results show that several combinations of mask efficacy and prevalence can substantially reduce the burden of seasonal influenza. Across all the years modeled, a mask prevalence of 0.2 (20%) and assumed moderate inward and outward mask efficacy of 0.45 (45%) reduced influenza infections by >90%.

Conclusions: A minority of individuals wearing masks substantially reduced the number of influenza infections across seasons. Considering the efficacy rates of masks and the relatively insignificant monetary cost, we highlight that it may be a viable alternative or complement to influenza vaccinations.

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KEYWORDS

mask; protection; COVID-19; influenza; transmission; intervention; infectious disease; respiratory; simulation; model; prevalence; efficacy

Introduction

In March 2020, the World Health Organization officially declared COVID-19 a global pandemic, as it extended beyond borders and reached various parts of the world [1]. The spread of the virus has halted several activities and has placed uncertainty on future events. Scientists and researchers have recommended safety measures such as social distancing, wearing of masks, and quarantines to reduce infection rates or "flatten the curve" [2]. Fortunately, the mechanism of airborne infections has been well studied. In a social environment, oral fluid droplets filled with viral particles can travel from person to person [3]. Several studies indicate that the spread of such droplets can be reduced by facial coverings such as face masks [4]. As such, many governments have issued face mask mandates in public places in efforts to stop the spread of disease. In the advent of this new reality, recent analysis of respiratory specimens from 2018 to 2020 in Hong Kong indicate that rates of other respiratory pathogens such as respiratory syncytial virus and influenza are decreasing with increased mask-wearing [5]. This is not unique to Hong Kong; data from the United States, Australia, Chile, and South Africa also show significantly reduced rates of influenza following the widespread adoption of nonpharmaceutical interventions such as masks [6].

Noting the success achieved by this nonpharmaceutical measure, we ask if similar but less stringent measures should be kept in place after the COVID-19 pandemic to deal with influenza, which is another pertinent airborne disease.

To gain an in-depth and quantitative understanding of face masks' impact on the reduction in influenza activity, we simulate how past influenza seasons 2010/2011 to 2018/2019 would have played out had people worn masks. The simulations were developed using deterministic compartmental models with the incorporation of variables to account for the impact of masks. Using publicly available influenza infection data for the past seasons from the Centers for Disease Control and Prevention (CDC), the influenzas transmission rates model for each season (2010/2011 to 2018/2019) was calibrated. We then simulated the seasons factoring in different scenarios of mask prevalence as well as inward-outward filtration efficacy of masks.

Methods

Susceptible-Exposed-Infected-Recovered Model and Parameters

Susceptible-exposed-infected-recovered (SEIR) models are a standard disease modeling technique in epidemiology. The population is compartmentalized into various groups: susceptible, exposed, infected, and recovered. Susceptible is the population susceptible to the disease. The exposed population are infected but have not been detected by testing. Infected is the population who have been confirmed to be infected and can transmit the disease. Recovered is the population who are recovered. To develop the SEIR model, the relationship between these groups is then mathematically characterized by differential equations. In our model, we used a basic SEIR model with a time-dependent transmission rate that is described by the following equations (Table 1):

Table 1. Variables used in equations.

Variable	Parameter
S	Susceptible
E	Exposed
I	Infected
R	Recovered
β	Probability of disease transmission per contact times the number of contacts per unit time
δ	Rate of progression from exposed to infectious or inverse of the incubation period
γ	Rate of progression from infected to recovered or the inverse of the generation time
N	Total population (S + E + I + R)

Since the flu fatality rates are insignificant in relation to the total population [7], deaths from the flu and unrelated births and deaths were disregarded.

The transmission rate β(t) is described as the number of contacts an infected individual has per timestep, multiplied by the probability of disease transmission in a contact. Thus, as only  of the population can be infected, every infected individual infects β(t)  individuals per timestep.

In regard to influenza, all parameters of the SEIR model except the time-dependent transmission rate (β(t)) are publicly available

via CDC data [8]. The CDC collects and compiles influenza activity year round in the United States. This is accomplished via the National Respiratory and Enteric Virus Surveillance System and the US World Health Organization Collaborating Laboratories System. This program consists of about 100 public health and 300 clinical laboratories throughout all 50 states, Puerto Rico, and the District of Colombia. All public health and clinical laboratories report the total number of tested specimen and the positive influenza tests. Since the influenza disease burden is based on testing and hospital reports, it is susceptible to underreporting. For example, there are cases where people with the flu may not report to the CDC or go see a health care provider. Therefore, to correct for this underreporting, the CDC uses a multiplier method with a routine population-based surveillance program to extrapolate a data set more representative of actual case rates [8].

We estimated β(t) by fitting the model to the scaled past infection data.

To account for mask use, a simplified version of the model used by Eikenberry et al [9] was adopted.

$m_{pre} \in [0, 1]$ is the mask prevalence, taken as the proportion of contacts in which an individual wears a mask. We assume that infection status does not affect mask-wearing behavior.

$m_{eff}I \in [0, 1]$ is the efficacy of mask use by the infected individual (ie, the reduction of the chance of infection when only the infected individual wears a mask).

$m_{eff}S \in [0, 1]$ is the efficacy of mask use by the susceptible individual (ie, the reduction of the chance of infection when only the susceptible individual wears a mask).

Consequently, we assumed that the reduction of the chance of infection when both individuals in a contact wear a mask is $1 - (1 - m_{eff}I) \cdot (1 - m_{eff}S)$. For example, if the outward efficacy is 0.7 and the inward efficacy is 0.9, then the infection only happens in 3% of contacts where both individuals wear a mask. We combined the parameters to define the *mask impact* $m \in [0, 1]$, the proportion of contacts in which masks prevent an infection given the three parameters previously listed—that is, the sum of the proportions of contacts prevented if both individuals wear masks, only the infectious individual wears a mask, only the susceptible individual wears a mask, or no one wears a mask, leading to the following formula that sums these four cases up:

To incorporate *m* (the proportion of contacts prevented through mask use) into the model, note that without masks, every infected individual infects β(t)  individuals per timestep—thus, with masks, this changes to $(1 - m) \cdot \beta(t)$  , and we get the following model:

We will now look at the data used to fit $\beta(t)$ for this model to past flu seasons (without masks; ie, with m=0).

Infection Data

The CDC FluView application [10] provides weekly numbers of positive flu tests (we did not separate between different strains) in public health and clinical laboratories for the seasons 2010/2011 to 2018/2019. As mentioned previously, data from weekly numbers of infected individuals were extrapolated from weekly numbers of positive tests using the CDC's estimated total number of infections per season.

For any season, let P_i be the number of positive flu tests in week i. Let T be the total number of infections for the season. We assume that the number of positive tests is proportional to the actual number of infected I_i, that is, $I_i = \lambda P_i$, for all weeks i, for a fixed (per season) scaling factor $\lambda > 0$. As infections persist on average, the sum of the infected per week over all weeks is (approximately) the total number of infections for the season:

$$i \; I_i = T$$

Therefore, $i \; \lambda P_i = i \; I_i = T$ and the season's scaling factor can be solved with:

For each season, we calculated the scaling factor λ and used it to scale the CDC data.

Beta Estimation From Infection Data

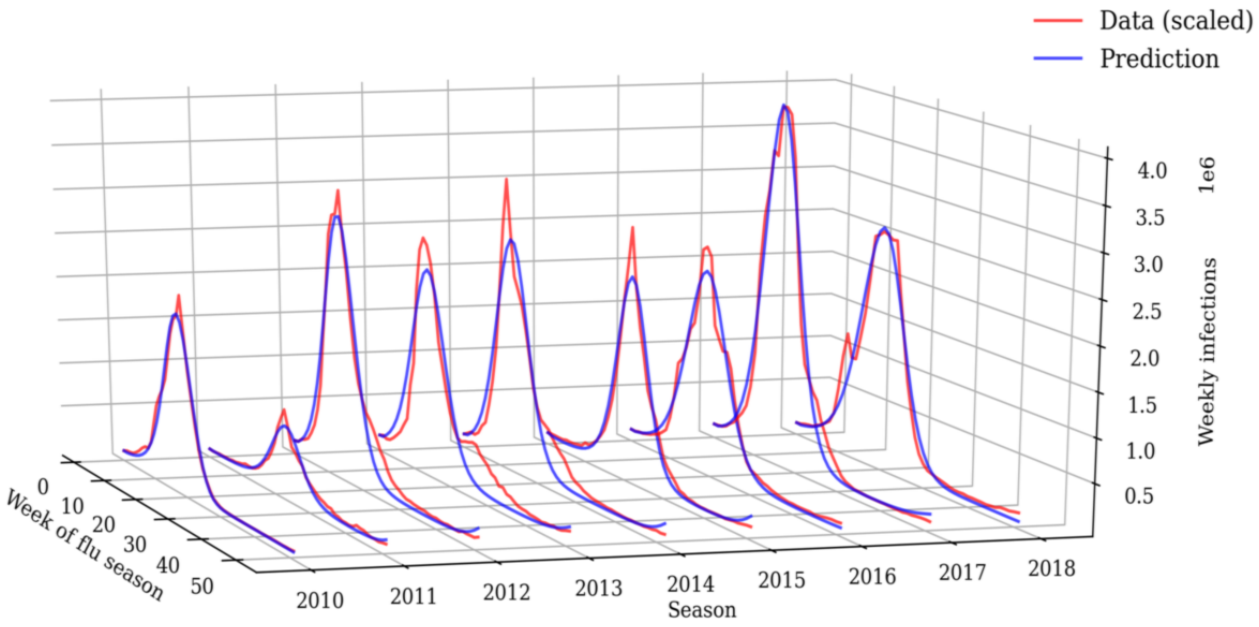
To estimate the time-dependent transmission rate, we fit a seasonal function of the form:

to the scaled data for each season, similar to the approaches by Towers and Feng [11] and Towers et al [12].

Timesteps t are in weeks. The incubation period and generation time are adapted from Mummert and Otunuga [13], yielding $\gamma = 1.0$ (infections last 1 week) and  (incubation period of 2 days).

Least squares fitting using the LMFIT Python library [14] yielded good fits on all seasons (Figure 1).

Figure 1. Results of the transmission rate fitting to data of past flu seasons. Actual infection data and prediction for influenza seasons 2010/2011 to 2018.

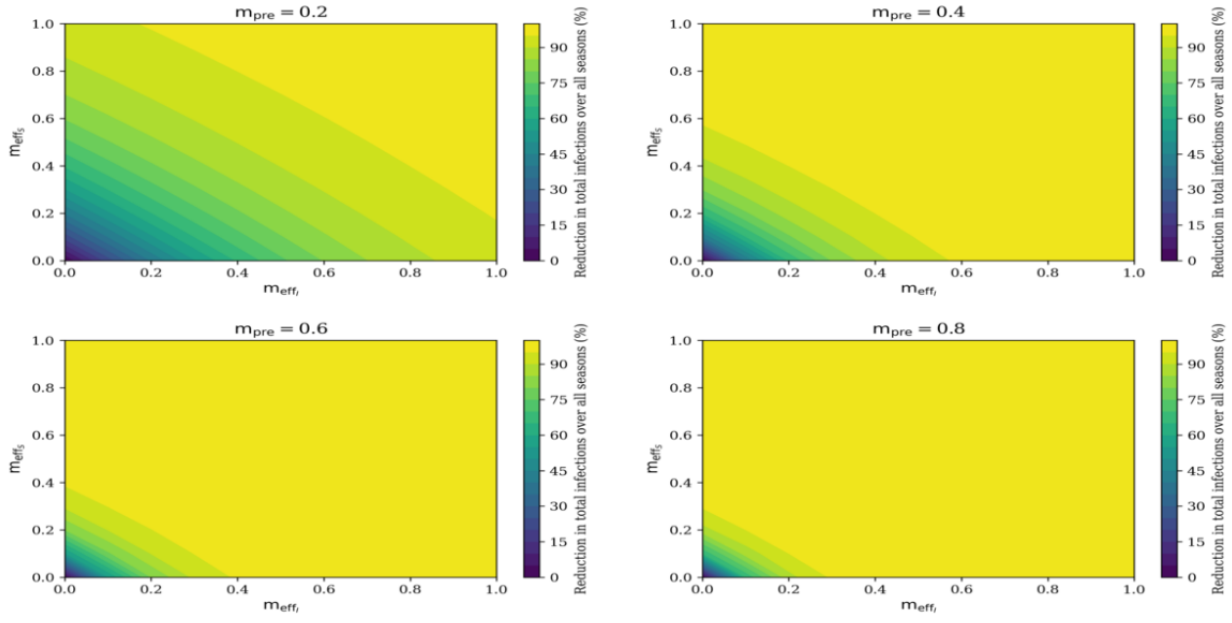


Results

We simulated the past influenza seasons with the estimated transmission rate $\beta(t)$ and compare the outcome with and without masks. As evidenced by MacIntyre and Chughtai [15] and Brienen et al [16], mask efficacy is highly uncertain. Therefore, different combinations of mask prevalence and outward and inward efficacy were implemented (Figure 2).

From May to December 2020, mask use during the COVID-19 pandemic in the United States ranged from 50% to 70% [17]. Data from Pan et al [18] indicated that common fabrics such as a thin cotton bandana (two-ply) has a mask efficacy between 0.3 to 0.5 (30%-50%). We believe it is unlikely that mask prevalence will be as high after the COVID-19 pandemic without a mask mandate. Bearing this in mind, we look at two scenarios we deemed the most relevant: the *mask mandate* scenario with a mask prevalence of 0.5 (50%) and outward and inward efficacies of 0.35 (35%), and the *masks suggested* scenario with a prevalence of 0.2 (20%) and outward and inward efficacies of 0.45 (45%).

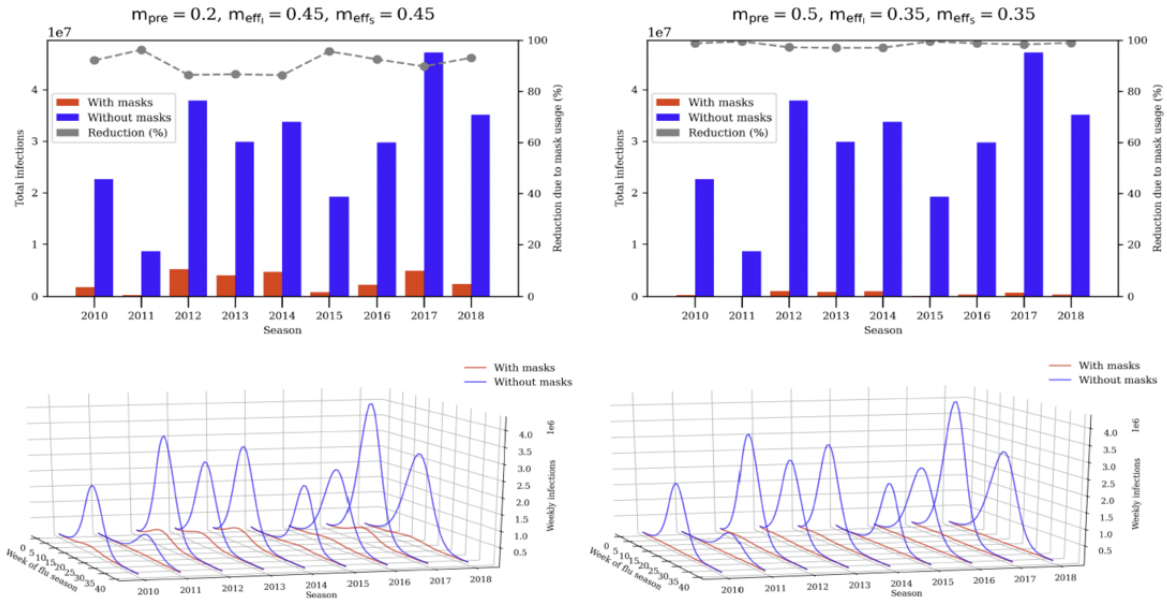
Figure 2. Reduction of total infections over all seasons pertaining to total infected mask wearing population and (meffi), and total susceptible mask wearing population (meffs) at mask prevalence levels (mpre) = 0.2 (20%), 0.4 (40%), 0.6 (60%) and 0.8 (80%).



Discussion

Our simulations showed that the "mask suggested scenario," with relatively low mask prevalence of around 0.2 (20%) and assumed moderate inward and outward efficacy of 0.45 (45%), would have substantially reduced influenza infections by >90% over several past seasons. The "mask mandate scenario," with 0.5 (50%) mask prevalence combined with an efficacy of 0.35 (35%), led to >95% reduction in influenza illnesses across seasons (Figure 3).

Figure 3. Simulated weekly infections for mask suggested scenarios (left) and mask mandate scenarios (right).



The findings show that when mask prevalence is high, for example, over 0.6 (60%), low mask efficacies (caused by masks worn too long, that are loose-fitting, etc) are sufficient to fully contain the flu. With that, it appears that a minority of disciplined mask wearers is sufficient to prevent most infection.

Currently, vaccinations are the prominent way to protect against influenza, having been available on a large scale since 1945 [13]. However, vaccination rates in the United States are not high enough to provide herd immunity [14]. In fact, flu vaccinations averted around 15% to 20% of influenza illnesses over the seasons from 2011/2012 to 2018/2019 [19]. Suggested data from this paper indicate that mask mandates in collaboration with vaccinations may be a more formidable tool against curbing influenza. Unlike masks, vaccines have to be newly manufactured each season with significant R&D investments. Nevertheless, vaccines only have to be administered once per year while face masks would need to be worn continuously. The continuous use of face masks in public spaces may be seen as more burdensome by the general population.

The economic burden of seasonal influenza in the United States is about US $6.3 to US $25.3 billion [20]. Assuming the economic cost scales linearly with the number of infections, a scenario in which at least 95% of infections are reduced (which includes both the *mask mandate* and *masks suggested* scenarios) saves US $6 to US $24 billion per season at negligible cost. Similar to public opinion regarding potential health hazards such as smoking and driving without seatbelts shifting over time and legislation being introduced, we can imagine the COVID-19 pandemic changing public (and expert) opinion toward everyday mask use. Although, large parts of the population might be tired of wearing masks after the COVID-19 pandemic. Public opinion shifts, but at least a minority of individuals may wear masks. Our simulations show that this would substantially reduce the burden of seasonal influenza at little monetary cost.

The limitations of our approach include no stratification by age or contact scenario, significant uncertainties in mask use and efficacy, and disregard of other nonpharmaceutical interventions.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
SEIR: susceptible-exposed-infected-recovered

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Original Paper

COVID-19 Return to Sport: NFL Injury Prevalence Analysis

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Abstract

Background: Sport injuries have been common among athletes across the globe for decades and have the potential to disrupt athletic careers, performance, and psyche. Many health professionals and organizations have undertaken injury mitigation strategies to prevent sport injuries through protective equipment, training protocols, and a host of other evidence-based practices. Many of these specialized training methods were disrupted due to protocols to mitigate the spread of COVID-19. This research examines the effects of the COVID-19 pandemic in relation to the prevalence of athletic injuries in the National Football League (NFL).

Objective: During the COVID-19 pandemic, NFL teams and athletes across all levels of sport were reported to have reduced training in preparation for their seasons due to protocols to mitigate the spread of COVID-19. This study compares the prevalence of injury during the 2018, 2019, and 2020 NFL seasons, with the aim to determine the potential causes of the differences in injury prevalence.

Methods: Official injury reports from each team were counted during the 17-week regular season of each year (2018, 2019, and 2020). The data were analyzed using an unpaired t test to compare the injury prevalence between each of the three seasons.

Results: The 2018 season produced a total of 1561 injuries and a mean of 48.8 injuries per team. The 2019 season produced a total of 1897 injuries and a mean of 59.3 injuries per team, while the 2020 season produced a total of 2484 injuries and a mean of 77.6 injuries per team. An unpaired t test was performed using the data to compare the mean number of injuries per team during each of the seasons. Comparison of the 2020 season against the 2019 season showed a statistically significant difference (P<.001); comparison of the 2020 season to the 2018 season found a statistically significant difference (P<.001); and comparison between the 2019 and the 2018 seasons found a statistically significant difference (P=.03).

Conclusions: Although the 2019 and 2018 seasons showed a statistically significant difference (P=.03), this difference is not as large when we compare the 2020 seasons versus the 2019 (P<.001) and 2018 (P<.001) seasons. The astronomical increase in injury prevalence during the 2020 season over the previous years raises the possibility that there was a reduced physiological adaptation to stress, due to the limited amount of training as a result of the closure of practice facilities in order to slow the spread of COVID-19.

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KEYWORDS

COVID-19; sport; injury; prevalence; cause; data; statistics; pain; training; practice; physiology; adaptation

Introduction

The National Football League (NFL) is a professional American football league composed of 32 teams. The NFL is composed of high-level, elite athletes who are able to train rigorously and consistently at state-of-the-art facilities, with the assistance of some of the best trainers and medical professionals in the world. As the COVID-19 pandemic spread across the world, many professional, collegiate, and amateur sports were brought to a halt [1]. The majority of athletes across all levels of competition across the United States and the rest of the world were unable to compete in organized sports or in-person training activities due to health precautions of COVID-19 [1,2]. In addition, NFL team facilities were closed from March 25, 2020, to May 19, 2020, in order to help mitigate the spread of COVID-19 [3]. Research has reported reductions in training frequency and availability for athletes across the United States during the COVID-19 shutdown period between March and June of 2020 [1]. During home confinement due to the COVID-19 shutdown, athletes likely experienced detraining, which is the loss of previous training-induced physiological adaptations caused by a lack of sufficient training stimulus [4]. It has been shown that detraining has deleterious effects at the level of the muscle. One study showed that just 8 weeks of detraining results in decreased muscle mass, muscle strength, and overall muscle power [5]. It is also postulated that these effects in skeletal muscle could significantly increase the risk of injuries, especially within contact sports [5]. Overall, detraining has been proven to negatively impact an athlete's physical performance [6]. The last time NFL players saw restricted access to training facilities was when the NFL underwent a lockout in 2011 for 14 weeks. As the 2011 NFL lockout ended and training camp began, there was a marked increase in Achilles tendon ruptures during training camp and preseason [7]. Preseason injuries could not be tracked during the 2020 NFL season, as these games were canceled in order to help reduce the spread of COVID-19.

American football is a contact sport, with at least some level of contact occurring on every play. Given that American football is a contact sport, it comes with nonmodifiable risks of injury [8]. In order to reduce the risk of injury, athletes prepare their bodies through vigorous training and strict dietary control so that they can stay healthy for as long as possible. Though no amount of training can completely exclude an athlete from getting injured, physiologic bone remodeling after high-intensity workouts offer some amount of protection from the extreme impact forces placed on the players' bodies during competition [9]. The Wolff law states that bones will adapt to the degree of mechanical loading, such that an increase in loading will cause the architecture of the internal and external bone layers to become stronger [9,10]. Conversely, a decrease in loading will cause a decrease in bone strength [9,10]. The duration, magnitude, and rate of force applied to the bone dictate the way in which the integrity of the bone is subsequently altered [9,10].

Resistance exercise is a method of conditioning in which an individual works against resistive loads such as free weights, resistance bands, or body weight in order to increase sport performance or overall health and strength [11]. Resistance exercise has been shown to create a significant acute hormonal response, which is important for tissue growth and remodeling [12]. Anabolic hormones have been shown to elevate 15 to 30 minutes after resistance exercise, providing an adequate stimulus [12]. These anabolic hormones are known to be crucial for skeletal muscle resistance training adaptations [13]. Exercise adaptations lead to physiological changes in muscles and tendons that can be advantageous to improving athletic performance, such as hyperplasia or hypertrophy [14,15]. Resistance training has also demonstrated changes in body composition, neuroendocrine function, and cardiovascular response to stress [16].

In this study, we aimed to determine if there is a change in injury prevalence during the COVID-19 season (2020). We hypothesize that there will be an increase in overall number of injuries and an increase in the mean number of injuries per team during the COVID-19 season (2020). If true, we further hypothesize that this increase in injuries may be due to reduced physiological adaptations of training due to lack of access to sufficient training facilities and training stimuli, stemming from COVID-19 health precautions.

Methods

Study Design

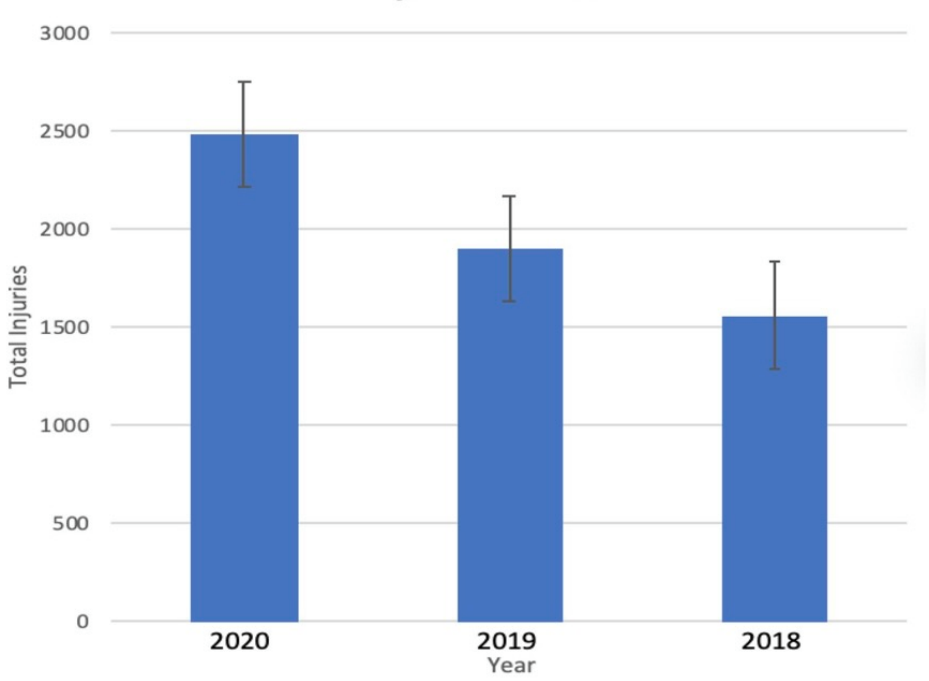
The number of injuries for each team was tallied during the 17-week long NFL regular season using the weekly medical data injury reports that are published publicly by each team. If an official team report was not available through the individual team, deferment was made to the injury report on the official NFL website. Athletes on the injury reports for the same injury for consecutive weeks were only counted once; however, athletes were counted again if they presented with a new injury to a different anatomical region. Illnesses, COVID-19–positive cases, holidays, and nonmedical days off were not included in the total tally. Illnesses were not included in the final tally because they are not within the scope of this research. An injury

has been defined as a physical complaint during a match or training that affects performance; therefore, illnesses should be reported separately from the incidence of physical complaints [17]. Because football is a contact sport, contact injuries were included in the study, as contact is a nonmodifiable risk factor for injury [8]. The total tallies of injuries per team were compared to those of the previous season and statistically analyzed using an unpaired *t* test.

Data Analysis

A data analysis was conducted by comparing the three different seasons. An unpaired *t* test was performed on the data set to compare the mean number of injuries per team per season to each of the three seasons. Figure 1 illustrates total injuries per NFL season.

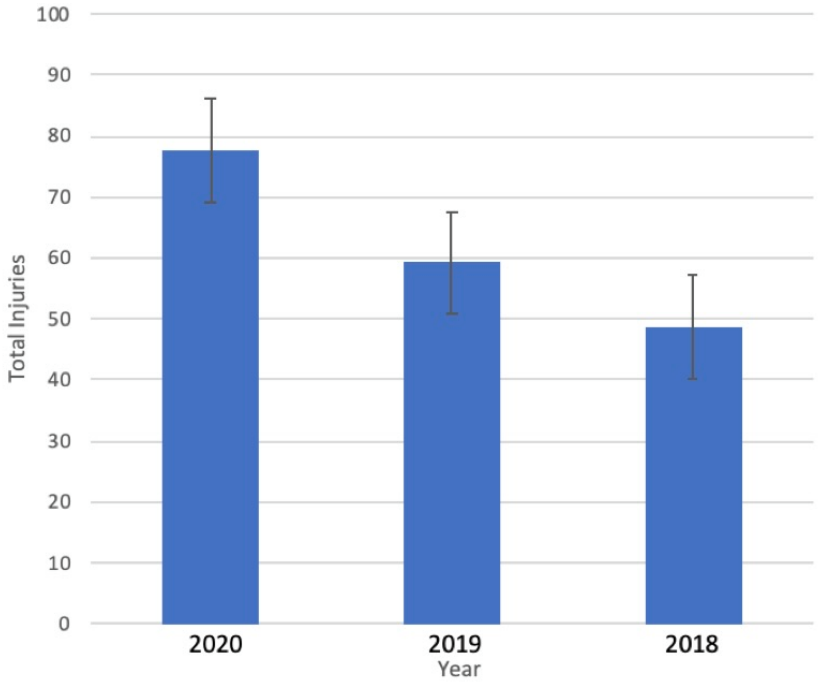
Figure 1. Total injuries per National Football League season.



Results

After tallying the injuries, the 2020 season produced a total of 2484 injuries with a mean number of 77.6 injuries per team. The 2019 season produced a total of 1897 injuries with a mean number of 59.3 injuries per team. The 2018 season produced 1561 injuries with a mean number of 48.8 injuries per team. An unpaired *t* test was performed to compare the mean number of injuries per team of each season. Comparison of the 2020 season against the 2019 season showed a statistically significant difference ($P<.001$). Comparison of the 2020 season to the 2018 season also showed a statistically significant difference ($P<.001$). Comparison between the 2019 and the 2018 seasons showed a statistically significant difference ($P=.03$) as well. Figure 2 shows mean injuries per team per NFL season.

Figure 2. Mean injuries per team per National Football League season.



Discussion

The results of this study demonstrated an increased number of overall injuries in the 2019 season and 2020 season when compared to the 2018 season. The results of the study also demonstrated an increased mean number of injuries per team during the 2019 season (P=.03) and the 2020 season (P<.001) when compared to the 2018 season. The 2020 season also demonstrated a statistically significant (P<.001) increase in the mean number of injuries per team when compared to the 2019 season. There could be several possible factors that play into the injury prevalence between the three NFL seasons. However, we believe that a decrease in physiological adaptation, due to reduced access to training facilities during the COVID-19 pandemic, contributed to the difference in injury prevalence during the 2020 NFL season when compared to the 2018 and 2019 seasons.

We acknowledge that there may be limitations to the study in that it may not have accounted for other injuries, such as injuries sustained during the preseason of the 2018 and 2019 seasons, injured reserve players, and unreported injuries. We also admit that there is a limitation due to an inability to calculate the exact hours of training per season. This calculation would be significantly hindered, as we used a public data set and do not have access to the individuals' training regimens within the data set. Furthermore, even if training hours could be gathered, there would be a potential for significant recall bias in any survey that attempted to calculate these hours, as the data go several years into the past. While we admit this is a limitation, we have created the best possible scenario by showing there was closure of the NFL training facilities between March 25, 2020, and May 19, 2020 [3], and demonstrating decreased training during the COVID-19 lockdown period in the United States among the majority of athletes and across all levels of sport [1].

Training is important for athletes as it can induce advantageous physiological adaptations to bone, muscles, and tendons when provided with an adequate stimulus [9-15]. Training positively impacts athletic performance, while detraining has shown to negatively affect athletic performance [5,6]. With all of the information regarding facility closures, reduced training during the COVID-19 pandemic, and the effects of training and detraining on athletes, we can confidently conclude that decreased physiological adaptations secondary to a reduction in training contributed to the increase in overall injuries and mean number of injuries during the 2020 NFL season. Further support of this conclusion is provided by the past NFL shutdown in 2011, which showed an increase in Achilles tendon ruptures among players during the preseason [7].

The demonstration of increased injury prevalence during the 2020 NFL season could be impactful to athletic programs around the world and allow organizations to focus on strategies to mitigate injuries in the future. This information may also be useful for understanding sport preparation and rehabilitation protocols. There should be more work carried out, at both the professional and amateur levels, to determine the training intensity necessary for physiological adaptation to occur that will reduce injuries. There must also be further follow-up to see if there was also a rise in injuries at the collegiate and amateur levels of sport.

Potential follow-up studies could include analyzing the prevalence of injuries for individual teams with severe COVID-19 outbreaks, examining the relationship between geographic COVID-19 hotspots and number of athletic injuries, and examining injury prevalence at the collegiate and amateur levels of sport. We invite other researchers to continue researching the number of injuries in athletes before and after the COVID-19 lockdown measures.

Conflicts of Interest

None declared.

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Abbreviations

NFL: National Football League

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Original Paper

Patterns of Physical Activity Among University Students and Their Perceptions About the Curricular Content Concerned With Health: Cross-sectional Study

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Abstract

Background: University students are at risk of losing their focus on maintaining healthy levels of physical activity because of their engagements with curricular and cocurricular activities. In India, the physical activity levels of the adult population have been reported to be declining in the recent years. However, studies focusing on university students pertaining to their physical activity are lacking in the Indian context. Moreover, a question that has not been properly addressed is the following: “do the curricula in higher education promote physical activity?”

Objective: Our paper aims at describing the physical activity levels of the students in a large public-funded central university located in northern India. The study also aims at capturing the student perceptions about the emphasis they receive on leading a physically active lifestyle during their routine curricular activities.

Methods: This is a cross-sectional descriptive study and uses International Physical Activity Questionnaire—Long Form to record physical activity among 4586 students. Stratified sampling method was used to enroll the students from each stream (faculty). Out of 30,667 students, about 15% were included from each faculty. The study was conducted between 2016 and 2019. To capture the student perceptions, we used a newly developed 5-item scale.

Results: From a total of 4586 participants in the study, 2828 (61.7%) were male and 1758 (38.3%) were female students. The mean age of our sample was 22.34 (SD 3.12) years. Our results indicate that about 14.5% (n=666) of all students in the study fall under the “Inactive” category. Furthermore, the perception about the curricular content pertaining to physical activity varied widely between the students of different streams.

Conclusions: Our sample reported a better physical activity pattern in comparison to the reported overall physical activity levels of the adult population of India. Our results also suggest that health-related topics are inadequately represented in many of the streams of higher education in the university.

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KEYWORDS

physical activity; university students; university; exercise; students; inactive; curricula; healthy lifestyle; higher education

Introduction

Background

Patterns of physical activity are undergoing significant change in the recent years among individuals of all age groups across the globe [1-5]. Literature suggests that these changes are mostly influenced by factors such as changing lifestyles, gender differences, economic status, sociocultural influences, educational levels, occupational factors, and other determinants [6,7]. Many workers in the field have reported a declining trend in physical activity profile among children, young adults, and adults across different societies including India [8-11]. An increased engagement with virtual games, cell phones, television, computers, and social media are possibly some of the important contributing factors to this trend among youth. Increased use of vehicular mode of transportation and reduced involvement in outdoor activities also contribute to this outcome [12-15]. Further, the incidence of health conditions such as being overweight, obesity, coronary artery disease, hypertension, diabetes mellitus, and depression are known to have increased among young adults, and a suboptimal physical activity has been recognized to be an important factor associated with these conditions [16-23]. According to the World Health Organization (WHO), more than a quarter of the world's adult population are insufficiently active, and around 1 in 3 women and 1 in 4 men do not do enough physical activity to stay healthy [24]. WHO recommends various levels of physical activity for people belonging to different age groups [24].

Trends in Physical Activity

It would be pertinent to understand the trends in physical activity that have been reported in India and elsewhere. In a study conducted by the Indian Council of Medical Research, physical activity patterns in adults across India were studied. The research reported that out of the 14,227 individuals studied, 54.4% (n=7740) were inactive, 31.9% (n=4538) were active, and 13.7% (n=1949) were highly active [9]. This trend is a matter of concern as the percentage of inactive population appears to be very significant.

There are several studies to show that the decreasing physical activity levels among youth are a matter of concern in many countries. Physical activity patterns among university students have received some attention in the recent years across the globe [25-29]. A study on European university students from 13 countries investigated the trends of smoking, diet, physical exercise, and attitudes toward health. The study compared these trends between the results of 2 surveys carried out in 1990 and 2000 and suggests that differences in health behaviors, beliefs, and risk awareness were disappointing [25]. In another study, 259 medical students in the age group of 18-22 years were interviewed using the International Physical Activity Questionnaire (IPAQ) in Bangalore. The study reported that 41.3% showed high levels of physical activity, 43.2% showed moderate, and 15.4 % of students showed low level of physical activity respectively [26]. Another study was conducted among 100 students in the Health Science faculty at a private university in Lebanon. The investigators report that most of the students did not consume a healthy diet and that they don't exercise as much as they like to [27]. A study among 334 students at the Alexandru Ioan Cuza University from Iasi, Romania conducted using the International Physical Activity Questionnaire—Long Form (IPAQ-L) reported that the lifestyle and physical activity levels were reasonably good, and the overall average metabolic equivalent (MET) minutes per week were 5343.92 (SD 2314.02) [28]. A study among 297 undergraduate students from 20 to 22 years of age from the University of Maribor reported that 79.8% of students were insufficiently physically active according to the WHO recommendations [29]. In another study, weekly physical activity scores of the students from sports departments and non–sport departments were compared among 300 university students in Turkey. The results revealed that the students from sports departments performed better than others in terms of weekly total physical activity [30].

However, there are no large and systematically performed studies available to show if the overall physical activity levels are comparable with the recommended ones among students at Indian universities. This question becomes important considering the fact that universities are the places where health awareness is supposed to be inculcated among the youth, and these students are at the risk of losing focus on physical activity because of the burden of curricular activities.

Similarly, studies exploring the curricular content and student perceptions about the motivation and information they receive during their routine curricular activities with reference to leading a physically active lifestyle are scarce. However, a few studies have shed light on the perceptions of student population toward health-related information in the curriculum. Nevertheless, these perceptions among students vary from one setting to another [31-34]. Such studies are not available in an Indian context. This question becomes important keeping in mind the diverse nature of the Indian education system and curricula.

The increasing involvement of the student population with mobile phones, computers, social media, and virtual games has had a negative impact on physically active lifestyles. This has also had an impact on mental health status among the youth. Increased use of mobile devices also has been said to be responsible for increasing sleep-related and circadian

rhythm–related disorders. The addictive nature of these platforms is a worrisome aspect [35-37].

Hence, we planned this study to understand the physical activity trends among the students at Banaras Hindu University (BHU) and to capture their perceptions regarding the curricular content related to physical activity. BHU is a public central university located in Varanasi, Uttar Pradesh, established in 1916. It is one of the largest residential universities in Asia. BHU is organized into 6 institutes and 14 faculties (streams) and 144 departments. The total student enrollment at the university is around 30,000, and this number represents almost all states of India along with a few foreign countries.

Since the university is a public-funded one, the fee structure of the university is highly affordable, and all the admissions are based on successfully securing ranks through different all-India level screening tests held every year. For all graduate, postgraduate, and doctoral programs, there is a lot of competition for the same reason. Hence, it can be presumed that the distribution of the student population represents the society in terms of socioeconomic status because only meritorious students get to study in this university. As the university is positioned as a major learning center in the eastern part of India, the student population mostly represents this part of the country.

Objectives of the Study

The primary objective of the study was to understand the proportion of students at Banaras Hindu University (BHU) who fall under different categories of physical activity (ie, physically inactive, active, and highly active). While analyzing the trends, we also considered the different programs under which these students are registered (undergraduate, postgraduate, or doctoral). The study also aimed at comparing the physical activity profiles of students from different faculties of BHU. Throughout the study, we aimed to understand the differences in the physical activity profiles with respect to age and gender. Another objective of the study was to map views and opinions of the students regarding the information and motivation they receive in their respective faculties and departments as a part of their routine curricular activities to keep themselves physically active.

Methods

Study Design and Sampling

This is a cross-sectional survey study wherein a stratified sampling technique was employed. Individual stream (eg, Humanities, Science, Social Sciences, Medicine, and Ayurveda) was considered as one stratum. We collected the details of the total number of students registered in each of the 16 streams from the offices of the respective deans. It was decided to include about 15% of all the students from each stream considering the time and other limitations. This meant approximately 4600 students, which was thought to be sufficient to draw meaningful conclusions. In this study, though we collected the data from 4733 students, we report the physical activity patterns of 4586 students as we had to delete certain entries during data processing.

Tools Used in the Study

To record the physical activity profiles of the students, we used the IPAQ-L [38,39]. This tool has been developed by IPAQ group and is widely used in large surveys. This tool employs an indirect method of measuring physical activity based on the recall of one's activities over the past 1 week. The purpose of this tool is to provide a common instrument that can be used to obtain internationally comparable data on health-related physical activity. Further, a newly developed 5-item questionnaire was used to record the opinions and views of the student population. This tool was designed to capture the perceptions of the students regarding the encouragement they receive in their respective faculties and departments to keep themselves physically active.

Translation and Revalidation of IPAQ-L

The IPAQ-L is available in different languages (English, French, German, Greek, etc) but not in Hindi. Since Hindi is the common language of communication in this part of India, the questionnaire was translated from English to Hindi by a language expert. The questionnaire was then back-translated to English by another language expert and was verified for its accuracy by another team of experts in the department. Suitable corrections were made before the tool was finalized and administered. No item was deleted or added. Both the Hindi and English versions of the tool were used in the study to collect data based on student preference after verifying the accuracy.

Development of a New Tool to Capture the Views and Opinions of the Student Population

Since the IPAQ-L is quite lengthy, the tool to capture student perceptions about curricular content dealing with health had to be very short. After discussing with the team of experts in the department, a short 5-item questionnaire was developed, which was administered to all participants in the study. These 5 items were retained from the original questionnaire, which had 10 items, after receiving feedback from an expert group. This too was administered both in Hindi and English per students' preference. The statements (items) included in this questionnaire were as follows:

1. The curriculum of my course or courses addresses the topics related to "importance of day-to-day physical activity in maintaining health."
2. My faculty or department promotes physical activity or sports activities among the students in an organized manner regularly.
3. I consider the sports facilities (playgrounds, sports equipment, and sports training) available in my faculty for the students to be adequate in general.
4. I keep monitoring my body weight regularly, and I am aware of the health consequences of being overweight and obesity.
5. I consider that general health–related aspects (such as diet, nutrition, and sports) are sufficiently addressed in my curriculum.

The options given for each of the questions were in the form of a 5-point Likert scale (1=Strongly Agree, 2=Agree, 3= Undecided, 4=Disagree, and 5=Strongly Disagree).

Reliability of the New Tool

The 5-item scale was first administered to 100 students from the Institute of Agricultural Sciences for the purpose of validation. The Cronbach coefficient alpha for the scale was .725, which falls under the category of acceptable range [40]. Hence, the scale was considered as reliable.

Ethics Approval

Ethical clearance was obtained by Institutional Ethics Committee (Reference 2014-15/EC/1323) before starting the study.

Data Collection and Data Entry

Investigators collected the data regarding the total number of students registered from different faculties of BHU by writing to the deans. Since the information contained only numbers and not the list of students, it was decided that the required number of classes be randomly selected, and all students of those classes (batches) be administered with the tool. The first author of this paper visited different departments and received permission from concerned heads of the departments to collect the data in leisure hours from different classes. The specific classes were selected by computer-generated random sequence method. A written consent was obtained from each of the participants. Though we collected the hard copies of the filled-in questionnaires from the volunteers, to ensure precision and uniformity, we prepared an online form to enter the data. Finally, the data were downloaded in the form of a spreadsheet. The data were collected between 2016 and 2019. IPAQ-L and the 5-item questionnaire were filled simultaneously by all volunteers.

Data Analysis

The data analysis to evaluate physical activity patterns was carried out according to the data processing rules of the IPAQ-L. The major steps involved in this process were data cleaning, excluding the outliers based on the maximum values allowed; this ensured receiving minimum values for the duration of the reported activity; truncation of data; calculating MET minutes per week scores for walking, moderate-intensity; and vigorous-intensity activities; as well as calculating the Total Physical Activity Scores. All these steps were followed per the guidelines of the IPAQ-L. The final step was to classify the entire sample into categorical data in terms of (1) low (inactive), (2) moderate (active), and (3) high (highly active) levels of physical activity.

The classification of physical activity into three levels is based on the following criteria [39,40]:

Low Activity

No activity is reported, or some activity is reported but not enough to meet categories 2 or 3.

Moderate Activity

Any of the following 3 criteria applies: (1) 3 or more days of vigorous-intensity activity of at least 20 minutes per day; (2) 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day; or (3) 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum of at least 600 MET minutes per week.

High Activity

Any one of the following two criteria: (1) vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET minutes per week; or (2) 7 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities accumulating at least 3000 MET minutes per week.

Results

Sample Characteristics

The total student strength of BHU was 30,667, and upon calculation, 15% of this population is 4600. We collected a sample of 4733. However, after excluding the outliers and erratic entries as per the IPAQ-L criteria, the sample that was analyzed included 4586 students.

Table 1 shows the distribution of participants as per their programs of study, gender, and age group. The total number of male and female students included in the study was 2828 (61.7%) and 1758 (38.3%), respectively. Mean age of the sample in the study was 22.34 (SD 3.12) years (male students: 22.37, SD 3.13 years; female students: 22.29, SD 3.12 years). Out of 4586 students, 3048 (66.4%) were from undergraduate programs, 1406 (30.7%) were from postgraduate programs, and 132 (2.9%) were from doctoral level programs.

Table 1. Distribution of volunteers as per age group, gender, and program of study.

Age group (years) and gender	Program of study			Total	
	PhD, n (%)	Postgraduate, n (%)	Undergraduate, n (%)	Based on gender, n	In each age group, n
16-20					1445
Female	N/A[a]	7 (1.2)	553 (98.8)	560	
Male	N/A	20 (2.3)	865 (97.7)	885	
21-25					2539
Female	5 (0.5)	434 (44)	547 (55.5)	986	
Male	14 (0.9)	633 (40.8)	906 (58.3)	1553	
26-30					503
Female	17 (9.7)	107 (60.8)	52 (29.5)	176	
Male	52 (15.9)	163 (49.8)	112 (34.3)	327	
31-35					82
Female	11(36.7)	16 (53.3)	3 (10)	30	
Male	21 (40.4)	22 (42.3)	9 (17.3)	52	
36 and above					17
Female	4 (66.7)	2 (33.3)	0 (0)	6	
Male	8 (72.7)	2 (18.2)	1 (9.1)	11	
Total					4586
Female	37	840	1155	1758	
Male	95	566	1893	2828	

[a]N/A: not applicable.

Physical Activity Levels

Table 2 displays the overall distribution of subjects into low (inactive), moderate (active), and high (highly active) levels of physical activity. In our sample, we noted that about 666 students (14.5% of all students) fell under the low category of physical activity (407 [14.4%] male and 259 [14.7%] female students), whereas an almost equal proportion (ie, 651 students [14.2% of all students]: 269 [15.3%] female and 382 [13.5%] male students) fell under moderate physical activity category. Further, about 3269 students (71.3% of all: 2039 [72.1%] male and 1230 [70%] female) fell under high level of physical activity. The difference between physical activity levels for male and female students was statistically not significant (χ^2_2=3.237, *P*=0.2). Further, the difference was also not significant between male and female participants for any program of study. Table 2 also shows the distribution of volunteers into high, moderate, and low levels of physical activity based on their programs of study and gender. Among the 132 PhD scholars, 28 (21.2%) fall under the low category, 12 (9.1%) under moderate, and 92 (69.7%) under high category. Among all 1406 postgraduate students, 215 (15.3%) fall under the low, 199 (14.2%) under the moderate, and 992 (70.5%) fall under the high category. Among the 3048 undergraduate students, 423 (13.9%) fall under the low category, 440 (14.4%) under the moderate category, and 2185 (71.7%) fall under the high category. The difference between physical activity of students of various programs was not statistically significant (χ^2_2=8.282, *P*=.08).

Table 3 depicts the distribution of volunteers into high, moderate, and low categories based on age group. As the table suggests, the number of students in the “highly active” category is highest among lower age groups, and the number of students in the “inactive” category is highest among higher age groups. The difference between physical activity of students of different age groups was statistically significant (χ^2_2=35.387, *P*<.001). This indicates that as the age increases, the likelihood of indulging in physical activity decreases.

Table 2. Distribution of volunteers into high, moderate, and low levels of physical activity based on programs of study and gender.

Program of study and gender	Category				Comparison between gender and category
	Highly active (high), n (%)	Active (moderate), n (%)	Inactive (low), n (%)	Total, n	
PhD					χ^2=1.760, *df*=2, *P*=.42
Female	23 (62.2)	5 (13.5)	9 (24.3)	37	
Male	69 (72.6)	7 (7.4)	19 (20)	95	
Total	92 (69.7)	12 (9.1)	28 (21.2)	132	
Postgraduate					χ^2=5.404, *df*=2, *P*=.07
Female	380 (67.2)	88 (15.5)	98 (17.3)	566	
Male	612(72.9)	111 (13.2)	117 (13.9)	840	
Total	992 (70.5)	199 (14.2)	215 (15.3)	1406	
Undergraduate					χ^2=1.522, *df*=2, *P*=.47
Female	827 (71.6)	176 (15.2)	152 (13.2)	1155	
Male	1358 (71.8)	264 (13.9)	271 (14.3)	1893	
Total	2185 (71.7)	440 (14.4)	423 (13.9)	3048	
Total					χ^2=3.237, *df*=2, *P*=.2
Male	2039 (72.1)	382 (13.5)	407 (14.4)	2828	
Female	1230 (70)	269(15.3)	259 (14.7)	1758	
Grand total	3269 (71.3)	651 (14.2)	666 (14.5)	4586	

Table 3. Distribution of volunteers into high, moderate, and low categories based on age group; overall comparison of physical activity levels among different age groups: χ2=35.387, df=2, *P*<.001.

Age group (years) and gender	Category				Comparison between male and female
	Highly active (high), n (%)	Active (moderate), n (%)	Inactive (low), n (%)	Total, n	
16-20				1445	χ^2=.327, *df*=2, *P*=.52
Male	659 (74.5)	126 (14.2)	100 (11.3)		
Female	402 (71.7)	86 (15.4)	72 (12.9)		
21-25				2539	χ^2=2.988, *df*=2, *P*=.22
Male	1123 (72.3)	208 (13.4)	222 (14.3)		
Female	686 (69.6)	155 (15.7)	145 (14.7)		
26-30				503	χ^2=0.976, *df*=2, *P*=.61
Male	218 (66.7)	42 (12.8)	67 (20.5)		
Female	124 (70.5)	18 (10.2)	34 (19.3)		
31-35				82	χ^2=3.663, *df*=2, *P*=.16
Male	29 (55.8)	6 (11.5)	17 (32.7)		
Female	16 (53.3)	8 (26.7)	6 (20)		
36 and above				17	χ^2=6.783, *df*=2, *P*=.03
Male	10 (90.9)	0 (0)	1 (9.1)		
Female	2 (33.4)	2 (33.3)	2 (33.3)		

Total Physical Activity MET Distribution

Table 4 depicts the distribution of MET minutes per week under different categories in the form of total walking, total moderate activity, total vigorous activity, and total physical activity MET minutes per week. The mean total physical activity MET minutes per week for male students was 4678.5 (SD 3037.01), and for female students was 4321.4 (SD 2874.09). Overall mean total physical activity MET minutes per week was 4541.6 (SD 2980.35). The difference between the MET minutes per week among male and female students was statistically significant for all categories of physical activity domains reported as suggested by *P* values. It means that the total MET minutes per week were less among female students in comparison to their male counterparts in each domain.

Table 4. Distribution of METa minutes per week under different domains.

MET	Gender			Mann Whitney test *P* value
	Female (N=1758), mean (SD)	Male (N=2828), mean (SD)	Total (N=4586), mean (SD)	
Total walking MET	2107.2 (1334.39)	2201.2 (1380.27)	2165.2 (1363.49)	.02
Total moderate MET	1387.47 (1198.08)	1498.81 (1258.63)	1456.13 (1236.81)	.004
Total vigorous MET	826.76 (1665.84)	978.46 (1760.39)	920.31 (1726.15)	<.001
Total physical activity MET	4321.4 (2874.09)	4678.5 (3037.01)	4541.6 (2980.35)	<.001

[a]MET: metabolic equivalent.

Faculties With Least Active Students

As Table 5 suggests, among all the faculties, the Faculty of Ayurveda had a maximum number of least active students (ie, n=33, 41.3%). The following faculties were next in the rank: Education 18 (26.5%), Law 49 (24.6%), Medicine 43 (18.6%), Performing Arts 32 (16.9%), Environmental Science 3 (16.7%), Management 10 (15.9%), Science 127 (14.4%), Arts 140 (13.5%), Social Sciences 59 (12.6%), Agriculture 37 (12.3%), Commerce 37 (12.2%), Women's College 54 (12.3%), Visual arts 13 (10.9%), Sanskrit Studies 10 (6.7%), and Dental Sciences 1 (2.9%). The difference between physical activity levels in different streams was statistically significant as suggested by *P* values.

Table 5. Distribution of volunteers into high, moderate, and low categories based on their faculty affiliation (χ2=126.2, df=30, *P*<.001).

Faculty	Category			
	Highly active (high), n (%)	Active (moderate), n (%)	Inactive (low), n (%)	Total, n
Agriculture	226 (75.1)	38 (12.6)	37 (12.3)	301
Arts	739 (70.9)	163 (15.6)	140 (13.5)	1042
Ayurveda	33 (41.2)	14 (17.5)	33 (41.3)	80
Commerce	236 (77.6)	31 (10.2)	37 (12.2)	304
Dental Sciences	26 (76.5)	7 (20.6)	1 (2.9)	34
Education	38 (55.9)	12 (17.6)	18 (26.5)	68
Environmental Sciences	15 (83.3)	0 (0)	3 (16.7)	18
Law	133 (66.8)	17 (8.6)	49 (24.6)	199
Women's College	333 (75.3)	55 (12.4)	54 (12.3)	442
Management	42 (66.6)	11 (17.5)	10 (15.9)	63
Medicine	142 (61.5)	46 (19.9)	43 (18.6)	231
Performing Arts	127 (67.2)	30 (15.9)	32 (16.9)	189
Sanskrit Studies	120 (81.1)	18 (12.2)	10 (6.7)	148
Science	626 (71.1)	128 (14.5)	127 (14.4)	881
Social Sciences	347 (74.3)	61 (13.1)	59 (12.6)	467
Visual Arts	86 (72.3)	20 (16.8)	13 (10.9)	119
Total	3269 (71.3)	651 (14.2)	666 (14.5)	4586

Domains of Physical Activity Reported

Our sample reported activities for transportation using bicycle (n=2255, 49.18%), walking (n=4190, 91.37%), vigorous housework outside home (n=1196 26.10%), moderate housework outside home (n=2635, 57.46%), moderate housework inside home (n=3208, 69.97%), vigorous leisure physical activity (n=1879, 40.97%), moderate leisure physical

activity (n=1993, 43.46%), and leisure time walking (n=3456, 75.36%).

Views and Opinions of the Students

Multimedia Appendix 1 shows the responses of the students to each option to the 5-item questionnaire based on gender. The statistically significant difference was observed in the responses for item numbers 1, 3, and 4 among male and female students, whereas no statistically significant response was found for item numbers 2 and 5. Multimedia Appendix 1 shows the number and percentage responses of the students to each option to the 5-item questionnaire based on gender.

Multimedia Appendix 2 shows the responses of students to 5-item questionnaire based on the programs in which they are registered. A statistically significant difference between the responses based on the courses registered (undergraduate, postgraduate, or PhD) is observed for all 5 items.

Multimedia Appendix 3 shows the mean scores for each item in each faculty. A mean score of less than 3 for any item was considered to be indicating a positive perception about the curricular activities leading to an encouraging environment that fosters a physically active and healthy lifestyle. A mean score of more than 3 for any item was considered as indicating dissatisfaction toward the curriculum of the faculty with respect to leading a physically active lifestyle. From Multimedia Appendix 3, it becomes clear that the faculties of Agriculture Sciences, Arts, Ayurveda, Dental Sciences, Medicine, Performing Arts, and Science were those where the mean scores for any of the questions did not exceed 3 or more. Hence, it can be presumed that the students in these faculties receive some kind of motivation that leads to a physically active lifestyle as a part of their curricular activities.

Discussion

Physical Activity Profiles Compared With Other Studies

This is one of the first studies from India that looks at physical activity levels in a focused way among a large number of university students. According to the Indian Council of Medical Research study (2014), the total percentage of inactive adults was 54.4% in India [9]. The percentage of highly active adults was 13.7%. However, the mean age group of this study sample was around 40 years. Since our study sample belongs to a mean age of around 22 years, a true comparison of the results is not possible. However, our results are much more encouraging than the ones reported in this study. It appears from our results that younger adults are more likely to indulge in physical activity than the older people. Since our sample had a mean age of 22 years, it is likely that our sample is more physically active.

A study based on the pooled data from 358 population-based surveys from across 168 countries, including 1.9 million participants reported that the global age-standardized prevalence of insufficient physical activity was 27.5% in 2016, with a difference between sexes of more than 8 percentage points [2]. In comparison to this, our sample gives a better picture. We report only about 14.5% of inactive student population. However, our study sample is smaller, younger, and more homogenous than such studies with bigger data. Hence, the results of our study are to be viewed in this context.

Another study conducted among university students in Romania included a total of 333 students, with an age average of 21.05 (SD 1.98) years [28]. According to the results of this study, mean total physical activity MET minutes per week are almost comparable with those of our study, especially among female students. However, the average total physical activity MET minutes per week among males was better in their study than in ours. This again confirms the idea that the younger age group of adult population is more inclined toward indulging in physical activity.

Another study determined the physical activity performed by undergraduate students from 20 to 22 years of age, including its frequency and intensity [29]. The sample consisted of 297 students from the University of Maribor. Their results indicate that 79.8% of students were inactive; hence, our situation in BHU appears to be much better where 71% of students are highly active. These differences need further evaluation keeping the contextual differences in view.

In yet another study, the investigators investigated the physical activity and quality of life of sports department students and other department students attending university [30]. A total of 300 university students participated in this study. In comparison with the genders, the total average physical activity score of men was found to be 4938.86 (SD 3919.33) MET minutes per week, while that of women was found to be 2592.44 (SD 2276.82) MET minutes per week. In comparison to these results, female students in our study appear to be much more physically active.

According to the results of a study consisting of 200 study subjects, 59% were having a sedentary lifestyle, 27% were moderately active, and 14% had vigorously active lifestyle. The study was conducted among the patients attending health training centers in Nagpur, and participants' age ranged from 40 to more than 70 years [5]. This study reported a significantly increasing trend for sedentary lifestyle with age, a finding that is consistent with our results as well, although the age range of the subjects in our study was different. This further confirms the age-related differences in the physical activity levels.

A study conducted in urban and rural Vellore city, Tamil Nadu, assessed the prevalence and factors associated with insufficient physical activity among adults aged 30-64 years [11]. The prevalence of insufficient physical activity was in 63.3% in the urban area and 40.6% in the rural area. Though our results cannot be meaningfully compared with this study (as the sample characters are different), we report a better physical activity profile. The differences are likely to be because of differences in the mean age of the samples studied.

Student Perceptions

Our study suggests that the student perceptions vary significantly from one stream of study to another indicating that the curricular activities of all streams do not encourage physically active lifestyle equally. The curricular activities of Agriculture Sciences, Arts, Ayurveda, Dental Sciences, Medicine,

Performing Arts, and Science appear to be encouraging physical activity in one form or the other. This heterogenous perception indicates that there is a need for having a relook at all curricula to see if sufficient emphasis is placed in health-related aspects.

The growing health care burden of India is mainly due to the increasing prevalence of lifestyle-related diseases such as hypertension, obesity, diabetes, depression, and metabolic syndrome. Increasing use of sugars, fats, and other high-calorie fast foods among youth is compounding the situation. Most of these diseases are preventable if right intervention in terms of dietary pattern and regular physical activities are incorporated at the right age. An increasing use of smartphones, as well as increasing indulgence in virtual games and social media are said to be causing multiple sleep-related and cognition-related disorders [12-23].

There have been several studies where the student perceptions about various aspects pertaining to their physical activities have been evaluated. Different approaches of inculcating the habit of leading a physically active lifestyle among the student community have also been suggested [41-50]. However, the situation in India is complex owing to the presence of a variety of regulations and norms of developing curricula in higher education institutions. Similarly, there are different types of universities including deemed universities, private universities, state universities, and central universities [51]. The education policies thus far have mostly emphasized the importance of physical education in schools.

Our study suggests that various curricula of higher education have several lapses when it comes to health-related topics. Universities need to take up the initiative in making the students aware of the correct ways of leading a healthy lifestyle. Irrespective of the stream of education, keeping oneself physically and psychologically fit is essential to leading a healthy life. Our results seem to suggest that health education must become a part of all streams of higher education irrespective of the stream.

Limitations and Other Aspects to Consider While Interpreting Our Results

Limitations and some other aspects pertaining to our findings will be enumerated in this section.

1. Since this study employs an indirect method of recording the physical activity levels based on 7-day recall, there are chances that respondents might tend to overestimate their physical activity levels.
2. The data were collected from 2016 to 2019, and the seasonal changes in the activity might have been gone unnoticed.
3. Indian Universities follow 6-day weeks, Sundays being the only holidays. This might be a reason for the higher level of weekly physical activity in the context of our study population.
4. Since BHU is a large residential university in terms of the area of the campus (4 square kilometers), a large proportion of the students reside in hostels and do not use vehicular mode of transportation for daily commute within the university. This might be another reason for a higher level of physical activity reported in general.
5. Many playgrounds are located within the campus of this university, and in the early morning and evening hours, one can see a good number of students using these playgrounds for playing sports and games. The engagement with games could be another reason why a higher level of physical activity is reported in this study. This could also be attributed to collective motivation in engagement of sports and games.
6. BHU is located in a state that is not in the forefront when it comes to economic development in comparison to many other states. WHO has observed that physical inactivity goes on increasing as the regions or countries develop economically [24]. This could be another reason for our sample having shown a relatively higher level of physical activity.

Conclusion

In our sample, we report that about 14.5% of all students fall under the “inactive” category (14.4% among all male and 14.7% among all female students), about 71.3% of all students (72.1% among all male and 70% among all female students) fall under the “highly active” category, and about 14.2% of all students (13.5% of all male and 15.3% of female students) fall under the “active” category. In our study, we found that physical activity levels go on decreasing as the age increases (ie, students with the lowest physical activity rates belong to higher age groups, and highly active students belong to lower age groups). Our study also suggests that physical education and other aspects of health are inadequately and heterogeneously represented in university curricula. These topics are required to be incorporated into regular curricula in all streams of higher education in Indian universities.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Number and percentage responses of the students to each option to the 5-item questionnaire based on gender.

[DOCX File , 18 KB - xmed_v3i2e31521_app1.docx]

Multimedia Appendix 2
The number and percentage responses of students to 5-item questionnaire based on the programs in which they are registered .
[DOCX File , 20 KB - xmed_v3i2e31521_app2.docx]

Multimedia Appendix 3
Mean scores for each of the 5 items in the 5-item questionnaire for different faculties.
[DOCX File , 16 KB - xmed_v3i2e31521_app3.docx]

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Abbreviations

BHU: Banaras Hindu University
IPAQ: International Physical Activity Questionnaire
IPAQ-L: International Physical Activity Questionnaire—Long Form
MET: metabolic equivalent
WHO: World Health Organization

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