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Peer-Review Report

Peer Review of “In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study”

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Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.08.05.20169219v1

Companion article: https://preprints.jmir.org/preprint/24645

Companion article: https://med.jmirx.org/2021/3/e30790/

Companion article: https://med.jmirx.org/2021/3/e24645/

(JMIRx Med 2021;2(3):e30763) doi:10.2196/30763

KEYWORDS

modified early warning score; MEWS; AVPU scale; Korle-Bu Teaching Hospital; KBTH; Ghana; critical care; vital signs; global health

This is a peer-review report submitted for the paper “In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study.”

Round 1

General Comments

This paper [1] presents a comparison of the limited modified early warning score (LMEWS) versus the standard MEWS in their ability to predict in-hospital mortality in Ghana. The authors demonstrate that LMEWS is a good predictor of in-hospital mortality, especially in lower-resource health care settings.

The study is well executed and well written, but I am not sure whether it aligns with the scope of *JMIRx Med*—this is a purely clinical study relevant to a public health or anesthesiology journal.

Specific Comments

Major Comments

My main comments are about the methodology of the article:

1. There is no explanation on how the study size was arrived at.
2. It is not clearly described whether there any missing data and how they were handled.
3. It is not clear whether there was an attempt at a blind assessment of the predictors.
4. A flow chart of the patients in the study is absent, including the time of follow-up with patients.
5. The ethics considerations were not sufficiently addressed. What kind of approval was obtained for the retrospective secondary use of data? Minors (patients were aged 13 years and older) were also included so the question of assent is also relevant here.

Round 2

General Comments

This paper [1] presents an interesting observation on the predictive ability of the modified early warning score on in-hospital mortality among critically ill patients.

The revised manuscript addresses some of the concerns, but I am not sure that all of them are satisfactorily answered.

Specific Comments

Major Comments

1. All reviewers expressed concerns about the sample size, and it is still not clear whether the sample size was calculated before the study. The response was that the sample size was calculated to be 82 participants, but it is not clear whether this was for the whole study (all 4 groups in the flow chart representing the flow of participants) or for individual groups. Also, there was a disbalance between the size of the 4 groups (81 with a nonsignificant MEWS and 31 with a significant MEWS, and 79 with a nonsignificant LMEWS and 33 with a significant LMEWS).
2. The question about missing data was addressed, and there was only a single case of missing data.

3. The blinding of the assessor was not performed. Although the authors argue that it was not necessary, it is an important methodological tool to address biases in analyses.
4. I am not satisfied with the response regarding the ethics approval of the study. It is not clear whether the patients or their parents consented to the inclusion of data collected during medical procedures in a research study.

Conflicts of Interest

None declared.

Reference

1. Abbey EJ, Mammen JSR, Soghoian SE, Cadorette M, Ariyo P. In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study. JMIRx Med 2021 Jul 8;2(3):e24645 [FREE Full text] [doi: 10.2196/24645]

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Peer-Review Report

Peer Review of "In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study"

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Related Articles:

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Companion article: https://med.jmirx.org/2021/3/e24645/

(JMIRx Med 2021;2(3):e30785) doi:10.2196/30785

KEYWORDS

modified early warning score; MEWS; AVPU scale; Korle-Bu Teaching Hospital; KBTH; Ghana; critical care; vital signs; global health

This is a peer-review report submitted for the paper "In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study."

Round 1

General Comments

This study [1] is about a measure of illness severity that can potentially promote the early detection of clinical deterioration in critically ill patients. More specifically, the study investigated in-hospital mortality and the predictive ability of a modified early warning score (MEWS) in Ghana. By employing receiver operating characteristic (ROC) curves and other statistical techniques, the authors validated a limited MEWS (LMEWS). Finding a promising measure of instances of clinical deterioration is valuable for the timely and proper management of acute deterioration events in clinical settings. Though this paper seems to have made contributions to the medical field, there are some issues worthy of consideration.

Specific Comments

Major Comments

1. One of the main concerns about this study is that the sample size is relatively small (N=112) for a national referral hospital in Ghana. Authors should provide more evidence on whether the sample and size were representative of the target population. Relatedly, since the authors state that they recruited practically all medical inpatients hospitalized for a period of more than 2 years (January 2017 to March 2019), it would be good to provide the total recorded number of in-hospital patients for that period.
2. In making the case for the validity of LMEWS, the authors have relied heavily on the afferent arm of clinical deterioration in critically ill patients, while not accounting for the efferent arm of medical response. The afferent arm identifies patients at risk of clinical deterioration and activates the efferent arm if necessary. The efferent arm examines the patients and intervenes in the treatment. The functioning of the efferent arm in the study settings ought to have been discussed in drawing up the conclusion and recommendation of the LMEWS.

Conflicts of Interest

None declared.

Reference

1. Abbey EJ, Mammen JSR, Soghoian SE, Cadorette M, Ariyo P. In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study. JMIRx Med 2021 Jul 8;2(3):e24645 [FREE Full text] [doi: 10.2196/24645]

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Peer-Review Report

Peer Review of "In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study"

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School of Medicine, University of Missouri, Columbia, MO, United States

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.08.05.20169219v1

Companion article: https://preprints.jmir.org/preprint/24645

Companion article: https://med.jmirx.org/2021/3/e30790/

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(JMIRx Med 2021;2(3):e30787) doi:10.2196/30787

KEYWORDS

modified early warning score; MEWS; AVPU scale; Korle-Bu Teaching Hospital; KBTH; Ghana; critical care; vital signs; global health

This is a peer-review report submitted for the paper "In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study"

Round 1

General Comments

This paper [1] describes a study of the modified early warning score (MEWS) and the limited MEWS (LMEWS) instruments for predicting mortality in a tertiary hospital in Ghana.

Specific Comments

Major Comments

1. The two objectives were not described precisely nor were they carefully tied to the methodology. For example, the first objective refers to both "prediction" and "detection" of "deterioration." It is not clear whether the methodology measures prediction or detection, and it is not clear how deterioration is defined. Mortality is prominent in the results, so this paper might be using mortality as a synonym of deterioration, but that is not clear. In addition, both objectives refer to MEWS, but the results give equal attention to MEWS and LMEWS; it is not clear whether LMEWS is a synonym for the "physiologic measures currently monitored" in the second objective statement; otherwise, LMEWS should be added to both objective statements along with MEWS. In either case, "physiologic measures currently monitored" should be carefully and clearly defined before being used in a statement of objectives.
2. Several statistical measures and tests were reported without being described or explained. I am familiar with some of them, such as the C-statistic, but a reader who is not would need some context for the numbers 0.838 and 0.833—something along the lines of, "where 1.000 means perfect accuracy and 0.500 means perfectly random associations (or 'the flip of a coin')." I am not able to suggest explanations for the Pearson chi-square value or the Hosmer-Lemeshow goodness-of-fit test, or the *P* value of the Hosmer-Lemeshow goodness-of-fit test because I am not familiar with this particular measure. Unfortunately, the reporting of the results did not explain the measure at all.
3. The order of MEWS and LMEWS results is completely inconsistent; please always report LMEWS before MEWS or always report MEWS before LMEWS.

Minor Comments

1. The grammar and punctuation should be edited throughout; for example, the second sentence of the *Abstract* contains an extraneous semicolon, and the third sentence of the *Abstract* contains an extraneous comma.

Conflicts of Interest

None declared.

Reference

1. Abbey EJ, Mammen JSR, Soghoian SE, Cadorette M, Ariyo P. In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study. JMIRx Med 2021 Jul 8;2(3):e24645 [FREE Full text] [doi: 10.2196/24645]

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Peer-Review Report

Peer Review of "The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis"

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/27485

Companion article: https://med.jmirx.org/2021/3/e31329/

Companion article: https://med.jmirx.org/2021/3/e27485/

(JMIRx Med 2021;2(3):e31416) doi:10.2196/31416

KEYWORDS

COVID-19; health information; informational support; online health; online health communities; online platform; pandemic; social support

This is a peer-review report submitted for the paper "The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis".

Round 1 Review

General Comments

My comments are as follows:

1. The authors [1] did not review relevant existing works carefully. A number of studies on online health communities (OHCs) have been conducted already. You should compare your results with these relevant works.

2. Although you have mentioned that one coder is a limitation, it is an evitable limitation and needs to be overcome, or how can you ensure the accuracy of the results? I suggest that the authors recode the posts and responses by two coders (at least) who are familiar with this field.

3. What are the criteria by which you determine the name of the coding and the definition of the coding?

Conflicts of Interest

None declared.

Reference

1. Jong W, Liang OS, Yang CC. The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis. JMIRx Med 2021 Jul 22;2(3):e27485 [FREE Full text] [doi: 10.2196/27485]

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Peer-Review Report

Peer Review of "The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis"

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/27485

Companion article: https://med.jmirx.org/2021/3/e31329/

Companion article: https://med.jmirx.org/2021/3/e27485/

(JMIRx Med 2021;2(3):e31423) doi:10.2196/31423

KEYWORDS

COVID-19; health information; informational support; online health; online health communities; online platform; pandemic; social support

This is a peer-review report submitted for the paper "The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis".

Round 1 Review

General Comments

This paper [1] describes an interesting and very important study on the contents of an online health community (OHC) on COVID-19. The authors conducted a content analysis of the community posts in an online health information platform and provide recommendations for public health responses during this, and future, pandemics. I believe this is very important work.

I provide some feedback that would potentially strengthen the paper and improve its readability for the journal audience.

Specific Comments

Major Comments

1. There are some issues with the references: the order needs to be revised, eg, the first reference is number 8.

2. In the fourth paragraph of the introduction (starting with "Although social support…"), there are no references to which definitions of social support or information needs or information seeking are used by the authors. In fact, there appears to be some overlap between these three concepts in this paragraph, while they are actually three distinct concepts in the literature. I would suggest the authors familiarize themselves with some of the seminal work on information-seeking behavior by Wilson and Bates and on social support by Tardy and Barrera:

Barrera, M. Distinctions between social support concepts, measures, and models. Am J Community Psychol 1986; 14(4):413-445.

Bates, M. Toward an integrated model of information seeking and searching. 2002 Presented at: Fourth International Conference on Information Needs, Seeking and Use in Different Contexts; September 11, 2002; Lisbon, Portugal p. 1-15.

Tardy, CH. Social support measurement. Am J Community Psychol 1985; 13(2):187-202.

Wilson, T. Models in information behaviour research. J Doc 1999; 55(3):249-270. [doi:10.1108/EUM0000000007145]

3. The section titled *Prior Work* was difficult to read; it lacks organization and coherence. I was unsure what points the authors were making since it seemed to be just a summary of the existing literature without any synthesis of the findings. Perhaps this section can be divided into two subsections: "Social support in OHCs" and "Information needs during the pandemic," or something similar. The authors can identify the clear knowledge gaps at the end that their study is addressing.

4. In the *Methods* section, can the authors provide some detail on who did the coding and how the codebooks in Tables 1 and 2 were developed? It is only in the *Limitations* section that we discover it was one coder; were other researchers perhaps involved in the development of the codebook, was it tested and revised, was the coding checked, etc?

5. In the *Results* section, the authors state "Those who were in a position to offer information had a significantly higher percentage of responding more than once (P < 0.001)." Can

they provide more explanation on how they defined “being in a position to offer information” and how the information was derived from the posts or user profiles?

6. Were there any incidences of emotional support in the posts? Their presence (or lack thereof) would be an interesting point to add if possible.

7. In the *Discussion* section, it may be interesting to contrast these findings with those reported in other studies in different contexts.

Minor Comments

8. The whole paper might benefit from professional editorial revision. In the first paragraph of the Introduction, for example, I would suggest revising “trauma in the” to “trauma among healthcare workers” and revising “becomes” to “become increasingly important”.

9. On page 5, “namely sliding-ONMF and rolling-ONMF” is used with no explanation.

10. In the *Methods* section, a short summary of MedHelp would perhaps be helpful for the journal’s international readers.

11. Do the authors perhaps mean “Types of information seeking topics” for Table 1?

12. Perhaps the authors can reference the method they used for analysis (qualitative content analysis)?

Round 2 Review

General Comments

The authors have addressed all the previous comments made, and the paper is much more coherent and relevant. I especially appreciate the additional section on prior work and the detail added to the methods section for clarity.

The manuscript may still require some professional editing; there are some minor grammatical errors that could be addressed.

Conflicts of Interest

None declared.

Reference

1. Jong W, Liang OS, Yang CC. The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis. JMIRx Med 2021 Jul 22;2(3):e27485 [FREE Full text] [doi: 10.2196/27485]

Abbreviations

OHC: online health community

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Peer-Review Report

Peer Review of "Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study"

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Ministry of Public Health and Population, Sana'a, Yemen

Related Articles:

Companion article: https://preprints.jmir.org/preprint/28255

Companion article: https://med.jmirx.org/2021/3/e31512/

Companion article: https://med.jmirx.org/2021/3/e28255/

(JMIRx Med 2021;2(3):e31513) doi:10.2196/31513

KEYWORDS

cutaneous leishmaniasis; outbreak; Iraq; risk factors; risk; disease; infectious disease; disease prevention; prevention

This is a peer-review report submitted for the paper "Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study."

Round 1 Review

General Comments

This paper [1] is very useful, as cutaneous leishmaniasis is a neglected infectious disease in the Eastern Mediterranean region.

Specific Comments

Major Comments

1. What is the accurate definition of the controls, mentioned as family members? If they are family members, could there be risk factors in most of the housing characteristics that they share, such as animals in the house, electricity, and distance from animals?

Minor Comments

2. In the *Background* section, I suggest putting the epidemiology globally, followed by the Eastern Mediterranean region, then Iraq (was interrupted).

3. I have a comment on mentioning the risk factors in the *Background* section.

4. In the *Results* section, "usage of fogging and bed nets" is repeated twice in two paragraphs.

5. In the *Methods* section, the ratio of cases:controls should be mentioned.

6. Some of the references need to be revised.

Conflicts of Interest

None declared.

Reference

1. Lehlewa AM, Khaleel HA, Lami F, Hasan SAF, Malick HA, Mohammed RH, et al. Impact of modifiable risk factors on the occurrence of cutaneous leishmaniasis in Diyala, Iraq: case-control study. JMIRx Med 2021 Jul;2(3):e28255 [FREE Full text] [doi: 10.2196/28255]

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Peer-Review Report

Peer Review of "Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study"

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/28255

Companion article: https://med.jmirx.org/2021/3/e31512/

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KEYWORDS

cutaneous leishmaniasis; outbreak; Iraq; risk factors; risk; disease; infectious disease; disease prevention; prevention

This is a peer-review report submitted for the paper "Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study."

Round 1 Review

General Comments

This paper [1] is about a leishmania outbreak, which is a very important public health problem in developing countries.

Specific Comments

Major Comments

1. References need to be rewritten as per the IJMR guide.

2. There are grammar issues.

Minor Comments

3. In the Abstract and the *Discussion* section, I suggest you merge the recommendations with the conclusion, and the same in the Discussion…try to make the recommendations bullets in the Discussion.

4. Please don't use "we" in the beginning of the *Methodology* section.

Round 2 Review

General Comments

This paper about a leishmania outbreak in Iraq [1] is talking about a very important health problem in this region and other developing countries.

Specific Comments

Minor Comments

1. Please change the title of the *Background* section to "Introduction."

2. All tables are not organized, so please delete empty rows and use bold style for table titles.

3. I suggest that you group the references instead of writing each reference separately, eg, (1-4), not (1) then (2) then....

4. Proofreading is highly recommended.

Conflicts of Interest

None declared.

Reference

1. Lehlewa AM, Khaleel HA, Lami F, Hasan SAF, Malick HA, Mohammed RH, et al. Impact of modifiable risk factors on the occurrence of cutaneous leishmaniasis in Diyala, Iraq: case-control study. JMIRx Med 2021 Jul;2(3):e28255 [FREE Full text] [doi: 10.2196/28255]

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Peer-Review Report

Peer Review of “Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study”

Abdulkareem Ali Hussein Nassar[1], MPH

TEPHINET – The Task Force for Global Health, Decatur, GA, United States

Related Articles:

Companion article: https://preprints.jmir.org/preprint/28255

Companion article: https://med.jmirx.org/2021/3/e31512/

Companion article: https://med.jmirx.org/2021/3/e28255/

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KEYWORDS

cutaneous leishmaniasis; outbreak; Iraq; risk factors; risk; disease; infectious disease; disease prevention; prevention

This is a peer-review report submitted for the paper “Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study.”

Round 1 Review

General Comments

This paper [1] is suitable for publication by this journal. The importance of this study is that it aims to identify possible risk factors and the impact of removing these factors on reducing the number of cutaneous leishmaniasis cases in Diyala, Iraq, in 2018. It provides evidence-based information to be used for prevention and control measures.

Specific Comments

Although this paper has a large sample size, it is not clear how the sample size is calculated.

Major Comments

There is no major comment.

Minor Comments

This paper needs some minor revisions.

Abstract

1. Results section: the word “persons” in the sentence “Data from 844 persons (cases=432, 51.2%) persons were analyzed.” is repeated. Therefore, it should be deleted.

2. Results section: I suggest the authors include quantitative results in the Abstract (odds ratios with confidence intervals, etc).

3. I suggest the authors merge the Recommendations under the *Conclusion* section.

Introduction

4. The authors explained the abbreviation (CL) for cutaneous leishmaniasis at the beginning of the introduction but sometimes did not use it in the main text.

Methods

5. “Further details on why we selected these two districts and how the study was conducted were published elsewhere.” The authors should delete this sentence and explain why the two districts were selected and how the study was conducted in the *Methods* section of this manuscript. Also, delete reference 17.

6. “A total of 866 persons were interviewed within the 717 families visited, 451 cases (292 from Al-Mansuriya District and 159 from Al-Muqdadiya District) and 415 controls (182 Al-Mansuriya District and 233 from Al-Muqdadiya District). However, we excluded 22 persons from the sample due to incomplete information. The final sample size used was 844 persons (cases=432, controls=412).” Although the sample size is large, there is no statistical method to estimate the sample size.

Results

7. “Data from 844 persons (cases=432, 51.2%) persons were analyzed.” As mentioned before, the authors must delete the repeated word “persons.”

8. The authors must mention the table in the correct position in the text.

9. Table 1: the number of cases and controls for the “use bed net” and “sleeping habits” variables aren’t similar to the sample size. The authors need to review the numbers and calculate the percentages. Moreover, the authors must explain the total

number of cases and controls for the variable "distance of animals from house" in a footnote of instead in the table.

10. Table 2: the attributable fraction for fogging is wrong (10.2 and 28.2). Please change it; the correct fraction is (52.6 and 55.5).

Discussion:

11. The authors need more references to compare these findings with previous literature reports.

Conflicts of Interest

None declared.

Reference

1. Lehlewa AM, Khaleel HA, Lami F, Hasan SAF, Malick HA, Mohammed RH, et al. Impact of modifiable risk factors on the occurrence of cutaneous leishmaniasis in Diyala, Iraq: case-control study. JMIRx Med 2021 Jul;2(3):e28255 [FREE Full text] [doi: 10.2196/28255]

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Peer-Review Report

Peer Review of "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study"

Wayne Buente[1], BS, MS, PhD

University of Hawaii at Manoa, Honolulu, HI, United States

Related Articles:

Companion article: . https://arxiv.org/abs/2103.10979

Companion article: https://preprints.jmir.org/preprint/29570

Companion article: https://med.jmirx.org/2021/3/e32266/

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KEYWORDS

social media; opinion; COVID-19; case study; polarization; communication; Twitter; echo chamber

This is a peer-review report submitted for the paper "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study."

Round 1 Review

General Comments

This paper [1] addresses the issue of political polarization on social media during the COVID-19 pandemic. The study analyzes Twitter data, applying word content and social network analysis. The paper demonstrates the partisan polarity of users and influencers and the presence of echo chambers.

The paper focuses on the political polarization of Twitter users and makes an effective case for their presence and activities. However, the paper could provide a stronger connection to COVID-19 and public health implications. My thoughts are to have a section on COVID-19 and Twitter in the literature review. There have been infodemiology studies that might be useful to reference. It would be helpful to better situate the issue of political polarization of social media users and how it contributes to COVID-19. Why does it matter that political polarization and echo chambers exist for COVID-19 public health concerns? Similarly, there is no real connection to COVID-19 and public health implications in the Discussion section. How can the impressive findings of partisan Twitter users and echo chambers relate to COVID-19 health implications? I would like to see some connections made here to what we know about COVID-19 health and Twitter users.

Another concern is the highly technical methods of the study for Twitter data collection and analysis. I am familiar with Twitter scraping methods/analysis and social network analysis. However, the methodological techniques discussed are new to me. I would like to see better clarification on how these methods work.

Specific Comments

Major Comments

1. The research questions (RQs) are fine for the study. There should be some connection between these 2 RQs and how they represent a "case study of COVID-19."
2. On page 2, under "Related Work," I would like to see an explanation of word embedding, network embedding, and transformers. I realize these are representation learning techniques to improve topic classification. It would be very helpful to have a basic explanation of what these techniques are doing that would be suitable for someone not in the computer science field. Even providing real-world examples would be helpful here. Since embedding and transformers are key parts of the methodology section, these techniques could use better explanation.
3. In the Methods section, I understand utilizing content analysis of profile words and retweet interactions to classify polarization of Twitter users in the data set. However, the specific techniques of average word embedding and transformers were hard to follow. I think it would be helpful to have a more layman's definition of sentence embedding, transformers, and how they work in this data set. Perhaps a sample walkthrough of how a set of Twitter users is classified would be really beneficial in my opinion.
4. Under section 5.1, there is an analysis of bot scores (Figure 2B). Yet previously it was mentioned that the top 10% of users with a bot score were removed. So, is it still helpful to do this analysis? Can we still state that the presence of bots is being controlled in the Twitter data set?

5. Under section 5.2, the following is stated: "Figure 3 reveals the proportion of users in each decile of polarity score that are influential. We show that, consistent with all of the influence measures above, partisan users are more likely to be found influential." Looking at Figure 3, only A and E really demonstrate this statement. Figure 3B, C, and D seem much more proportional (mild U shape).
6. In section 5.1, the classifications discovered are very interesting. These visualizations on partisanship and information dissemination are really nicely done. This finding is certainly a strength of the study. I also appreciate the visualizations for the polarization of influencers in section 5.2. It is helpful to see how partisanship contributes to information and influence in this Twitter data set.
7. I particularly like the Figure 6 visualization since it is the most intuitive of the visualizations.
8. I would like to see the COVID-19 health implications of these findings on the political polarization of Twitter users in the discussion section.

Minor Comments

1. On the first page, there is a reference to "AUC" without definition. Please define the acronym here.
2. In the "Transformers" paragraph, there is a reference to "NLP" without definition. Please define the acronym here.
3. In Figure 3, the caption states, "(B) top 10% in the number of followers," but the graph heading shows the top 5%. I suspect the Figure 3 caption is incorrect.
4. Random Walk Controversy is an interesting data technique. I have never encountered it before.

Round 2 Review

General Comments

I appreciate the authors' explanations for the reviewer comments. On reading the revised paper and the author feedback, I understand that this paper cannot address the COVID-19 tweet content since it appears that it is addressed in another work. As a study on the aspects of information and polarization in social media during COVID-19, I find the work to be much improved and enjoyed being able to review it.

Conflicts of Interest

None declared.

Reference

1. Jiang J, Ren X, Ferrara E. Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study. JMIRx Med 2021 Aug;2(3):e29570 [FREE Full text] [doi: 10.2196/29570]

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Buente W
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Peer-Review Report

Peer Review of "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study"

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Related Articles:

Companion article: . https://arxiv.org/abs/2103.10979

Companion article: https://preprints.jmir.org/preprint/29570

Companion article: https://med.jmirx.org/2021/3/e32266/

Companion article: https://med.jmirx.org/2021/3/e29570/

(JMIRx Med 2021;2(3):e32268) doi:10.2196/32268

KEYWORDS

social media; opinion; COVID-19; case study; polarization; communication; Twitter; echo chamber

This is a peer-review report submitted for the paper "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study."

Round 1 Review

General Comments

This paper [1] studies the polarization of COVID-19 discourse on Twitter using natural language processing (the Retweet-BERT method).

The authors are interested in whether partisan users interact mostly with like-minded partisans and how polarized influential users are. They estimate the partisan nature of users/accounts by who a user retweets—with the assumption that users will follow people who they agree with. The concern here is that in estimating ideology from retweets and then looking at echo chambers, aren't the authors building endogeneity into the measures? The networks one belongs to and follows are certainly a measure of something, but it is not clear that this is separate from the information environment or potential echo chamber. Can the authors theoretically separate the network one belongs to from the sharing of information if retweeting is the basis for the ideology of the respondent? The methods of finding ground truth using hashtags and media retweets seem more appropriate than the method that the authors propose given the theoretical similarity between a user's network and what they tweet or share.

It would also be helpful to have additional theoretical justification for the decision to bin the polarity scores due to the left-skewed nature of the left-leaning seed users. Are the findings robust for thinking about the online space compared to a benchmark of partisanship from national surveys rather than compared to only people online? In other words, what seems like "polarity" online might be extreme or might be only a subset of the entire ideological space in the United States, and it is not clear whether the authors are interested in only Twitter users or want to say something about how people online generally share political information.

The article says that it is about COVID-19 information but there is very little discussion of the content of that information and why or how the authors might expect COVID-19 information to be shared differently than other information. Is this a demonstration of this tool in a particular time period or is there something about COVID-19 information that would make it more likely to be shared? The evidence that right-leaning users retweet right-leaning accounts is not necessarily an issue for polarization or for public health unless the accounts have different information from public health experts or misinformation. Can the authors speak to that?

Conflicts of Interest

None declared.

Reference

1. Jiang J, Ren X, Ferrara E. Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study. JMIRx Med 2021 Aug;2(3):e29570 [FREE Full text] [doi: 10.2196/29570]

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Peer-Review Report

Peer Review of “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.01.05.21249239v1

Companion article: https://preprints.jmir.org/preprint/27017

Companion article: https://med.jmirx.org/2021/3/e31568/

Companion article: https://med.jmirx.org/2021/3/e27017/

(JMIRx Med 2021;2(3):e31547) doi:10.2196/31547

This is a peer-review report submitted for the paper “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

Round 1 Review

General Comments

This study [1] is trying to develop a new method to identify attributed and unattributed potential adverse events (AEs) using the unstructured text of electronic health records (EHRs).

1. After reading the manuscript, I feel the title does not match the study contents. First, the title seems to repeat a fact that is already self-evident.
2. The core of the so-called Shakespeare method is still the latent Dirichlet allocation (LDA) method; I cannot see that any novel methods have been developed.
3. There is no related literature review, as many studies have used LDA methods in EHR data. To really find any AE in unstructured text, natural language processing (NLP) is indispensable.
4. What is the difference between the so-called “Shakespeare method” and LDA topic modeling?
5. What are the three parts in the following statement:
   The Shakespeare method has three parts:
   - Convert each document into a vector of n-gram frequencies.
   - Create two groups of vectors: target and comparison.
   - Trim the n-gram vectors in the target group to those that are significant for the target group.
   - Apply topic analysis to the trimmed target group vectors.
   - Interpret the original documents with topic scores of interest.
6. The description of the method is hard to understand. As stated, “Crucially, events can be described in text but not necessarily attributed to being medical care AEs [14,25,41]; we wanted to develop an unstructured method that would identify them.” What is this unstructured method?

Round 2 Review

General Comments

This revision provided more details of the Shakespeare method. However, it seems the authors do not quite understand the alternative method: NLP. This may lead to mistaken conclusions. The questions below need reconsideration.

Specific Comments

Major Comments

1. It is claimed that “Many methods for finding AEs in text rely on predefining possible AEs before searching for prespecified words and phrases or manual labeling (standardization) by investigators.” The dictionary method in the NLP tool could extract most terms, for example, included in the Unified Medical Language System, which can be limited to a “disorder” semantic group as a potential transfusion AE (PTAE) group.
2. The PTAE terms identified through the Shakespeare method actually are a mixture of reasons for transfusion, consequences of the reasons for transfusion, or alternate reasons for PTAEs. The Shakespeare method is not able to identify specific AEs with a causal relationship with transfusion. Then, what is the difference between this method and the NLP dictionary method?
3. It is advisable to include potential use scenarios of the method (eg, will more manual reviews be needed for the results?).

Conflicts of Interest

None declared.

Reference

1. Bright RA, Dowdy K, Rankin SK, Blok SV, Palmer LAM, Bright SJ. Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method. JMIRx Med 2021 Aug 11;2(3):e27017 [FREE Full text] [doi: 10.2196/27017]

Abbreviations

AE: adverse event
EHR: electronic health record
LDA: latent Dirichlet allocation
NLP: natural language processing
PTAE: potential transfusion adverse event

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Peer-Review Report

Peer Review of “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

Anonymous

Related Articles:

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Companion article: https://med.jmirx.org/2021/3/e31568/

Companion article: https://med.jmirx.org/2021/3/e27017/

(JMIRx Med 2021;2(3):e31548) doi:10.2196/31548

This is a peer-review report submitted for the paper “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

Round 1 Review

General Comments

This paper [1] described the “Shakespeare method,” which was designed to discover associations between adverse events (AEs) caused by blood transfusion from unstructured electronic health record (EHR) notes. The authors applied this method on the MIMIC-III data set and seemed to be able to find transfusion AEs (TAEs) and potential TAEs (PTAEs) that were unknown when those EHR notes were developed.

Specific Comments

Major Comments

1. Is there any plan to release all the code/scripts used in this study? The method seems to be complex involving multiple steps; it will be very difficult to reproduce the results if the code is not available.
2. The manuscript should include more details on how the transfusion and comparison groups were created.
3. The author mentioned that the latent Dirichlet allocation (LDA) method they used in topic modeling requires the number of topics to be selected a priori. In this study, they set it to 45. Some questions:
   - How robust is the “Shakespeare method” with respect to this value? If a different value is chosen, will the method find similar topics? Similar notes for manual document review? Similar TAEs/PTAEs?
   - How would you determine this value if the method is applied to detect AEs for other treatments?
   - A brief introduction to the LDA method should be included in the manuscript.
4. In the *Results* section, the authors mentioned “Despite the inclusion of 1 to 5 grams in the vectorization, the terms that we extracted during classification were unigrams.” That seems to be quite a coincidence; is there any explanation? If only unigrams are used in the bag-of-word representation, will the results be different? Does it mean only unigrams are needed in the future application of this method?
5. If possible, applying the method in other data sets or for other types of treatment will help to understand how generalizable the method is.
6. On page 4, section *The Shakespeare Method*: “Trim the n-gram vectors in the target group to those that are significant for the target group.” How is the trimming performed? How important is it for the final result?

Minor Comments

1. In the *Abstract* section, the authors wrote “We chose the case of transfusion adverse events (TAEs) and potential TAEs (PTAEs) because real dates were obscured in the study data, and new TAE types were becoming recognized during the study data period.” The causal relationship here is a little confusing.
2. On page 3, the authors wrote, “The Shakespeare method has three parts,” but the following bullet-point list has 5 items.
3. On page 8: “The Shakespeare method would likely generalize to other her notes and possibly other types of medical texts.” An additional “her” is inserted.

Round 2 Review

The revision addressed my previous concerns. I have no further comments.

Conflicts of Interest

None declared.

Reference

1. Bright RA, Dowdy K, Rankin SK, Blok SV, Palmer LAM, Bright SJ. Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method. JMIRx Med 2021 Aug 11;2(3):e27017 [FREE Full text] [doi: 10.2196/27017]

Abbreviations

AE: adverse event
EHR: electronic health record
LDA: latent Dirichlet allocation
PTAE: potential transfusion adverse event
TAE: transfusion adverse event

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Peer-Review Report

Peer Review of “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

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Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.01.05.21249239v1

Companion article: https://preprints.jmir.org/preprint/27017

Companion article: https://med.jmirx.org/2021/3/e31568/

Companion article: https://med.jmirx.org/2021/3/e27017/

(JMIRx Med 2021;2(3):e31550) doi:10.2196/31550

This is a peer-review report submitted for the paper “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

Round 1 Review

General Comments

This concise manuscript [1] reports an exploratory study that seeks to detect adverse events from the words within electronic health records. By conducting a computational linguistic analysis, the authors aimed to identify patterns of words that can be used to classify such events. The methodology is novel and has potential use cases that could benefit the automation and scalability of applications in the future.

I have some minor comments for the authors to consider:

1. At the end of the *Introduction* section, it would benefit the reader if the authors could provide some justification for why the Shakespeare method might be useful, rather than simply stating “We hoped.”
2. The methods are well described and the results are straightforward.
3. In the *Discussion* section, there are some missing details that should be added. In particular, it would be useful for researchers seeking to follow up on this work to know what lessons were learned during the course of conducting this research. This could take the form of a short limitations paragraph, and importantly, some recommendations to guide future research. Relatedly, some additional details concerning how this work could inform real-world applications would also be welcome.

Conflicts of Interest

None declared.

Reference

1. Bright RA, Dowdy K, Rankin SK, Blok SV, Palmer LAM, Bright SJ. Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method. JMIRx Med 2021 Aug 11;2(3):e27017 [FREE Full text] [doi: 10.2196/27017]

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Peer-Review Report

Peer Review of “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

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Center for Data and Decision Sciences, Chongqing University of Posts and Telecommunications, Chongqing, China

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.01.05.21249239v1

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Companion article: https://med.jmirx.org/2021/3/e27017/

(JMIRx Med 2021;2(3):e31551) doi:10.2196/31551

This is a peer-review report submitted for the paper “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

Round 1 Review

General Comments

This paper [1] investigated the new and increasing rates of adverse events (AEs) in unstructured text in electronic health records (EHRs). The topic is interesting. The authors used the Shakespeare method to identify attributed and unattributed potential AEs with EHRs. This method would be a useful supplement to AE reporting and surveillance. Although I believe that the topic of the study is very relevant, I have some concerns related to the theoretical background of the study. Specific major and minor comments are listed below.

Specific Comments

Major Comments

1. What is the accuracy of the new method, the Shakespeare method, for identifying attributed and unattributed potential AEs? The previous study showed the process of this method in the literature [2]. This paper did not mention the accuracy of the new method.

Minor Comments

1. Too many keywords. I would suggest that the authors reduce some of the keywords.
2. In the “Conclusions” subsection, I would suggest the paragraphs be reorganized to improve them.

Conflicts of Interest

None declared.

References

1. Bright RA, Dowdy K, Rankin SK, Blok SV, Palmer LAM, Bright SJ. Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method. JMIRx Med 2021 Aug 11;2(3):e27017 [FREE Full text] [doi: 10.2196/27017]
2. Bright RA, Rankin SK, Dowdy K, Blok SV, Bright SJ, Palmer LAM. Potential Blood Transfusion Adverse Events Can be Found in Unstructured Text in Electronic Health Records using the'Shakespeare Method. medRxiv Preprint published on January 6, 2021 [FREE Full text] [doi: 10.1101/2021.01.12.21249674]

Abbreviations

AE: adverse event
EHR: electronic health record

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Peer-Review Report

Peer Review of "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study"

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.03.16.21253767v1

Companion article: https://preprints.jmir.org/preprint/29324

Companion article: https://med.jmirx.org/2021/3/e32459/

Companion article: https://med.jmirx.org/2021/3/e29324/

(JMIRx Med 2021;2(3):e32461) doi:10.2196/32461

KEYWORDS

COVID-19; pandemic; vaccination; vaccine; strategy; vaccination strategy; hospitalization; mortality rates; older adults; mortality

This is a peer-review report submitted for the paper "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study."

Round 1 Review

General Comments

This paper [1] addresses an important subject pertaining to vaccination and COVID-19, which has been a major public health concern across the globe for the past year. However, I have a few concerns and comments about the paper concerning the content of the Introduction, Methods, and Results sections as well as the Discussion.

Specific Comments

Major Comments

1. The title should be revised to reflect the analysis performed by the author. The author should consider changing the title to "COVID-19 Vaccination and the Daily Cases, Hospitalizations, and Death Rates: A Case Study of Tennessee in the United States."
2. I suggest the author provide a brief overview of the COVID-19 pandemic globally and locally in the Introduction.
3. I suggest the author provide a brief description of the study data and how the variables were derived and measured in the Methods section.
4. The author should provide the analytical procedure of the study by describing the statistical methods deployed in the analysis together with the statistical software used. The author did not state whether the analysis is descriptive or inferential and the level of analysis being performed.
5. In the Results section, the author did not provide results for 2020 prior to the onset of vaccination but compared some of the results with December 2020. This will help uncover any changes during the vaccination period.

Minor Comments

1. The author should take a critical look at the write-up and provide a thorough proofreading of the paper to correct the several typos and omissions in the text in order to improve clarity and understandability.
2. The vaccination onset in the Abstract section should be 2020, not 2021.
3. The author should change the "mapping" mentioned in the Discussion section to "charts."
4. Based on the analysis, the author should be careful with the use of "significantly influence" and "impact" throughout the paper.

Round 2 Review

General Comments

The author has effectively addressed all my concerns about this paper. The paper should be accepted for publication.

Conflicts of Interest

None declared.

Reference

1. Roghani A. The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study. JMIRx Med 2021 Aug;2(3):e29324 [FREE Full text] [doi: 10.2196/29324]

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Peer-Review Report

Peer Review of "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study"

Anonymous

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Companion article: https://med.jmirx.org/2021/3/e32459/

Companion article: https://med.jmirx.org/2021/3/e29324/

(JMIRx Med 2021;2(3):e32462) doi:10.2196/32462

KEYWORDS

COVID-19; pandemic; vaccination; vaccine; strategy; vaccination strategy; hospitalization; mortality rates; older adults; mortality

This is a peer-review report submitted for the paper "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study."

Round 1 Review

General Comments

This paper [1] demonstrates that vaccination affects different age groups during the third wave of COVID-19. It shows that vaccination changed transmission rates and resulted in a reduction in hospitalization and death rate.

Specific Comments

This paper has used exciting data during a challenging time to help other regions that are far behind the United States to set their policies and see how prioritizing older people changes statistics. So, I think this paper adds significant points using great data (around 3 months) to contribute to the COVID-19 literature.

Major Comments

1. In the Introduction, it is essential to use other studies to compare different states or countries and other related research. Hence, I suggest including a section that compares other vaccination experiences.
2. I think the Data and Methods section is underdeveloped, so the author should add more information about data collection and statistical analysis.
3. The Discussion section needs more information on policy implications that can help other regions.

Minor Comments

1. Some sentences need to be rewritten, and the text needs to be proofread.

Conflicts of Interest

None declared.

Reference

1. Roghani A. The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study. JMIRx Med 2021 Aug;2(3):e29324 [FREE Full text] [doi: 10.2196/29324]

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Peer-Review Report

Peer Review of "Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis"

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Department of Microbiology and Molecular Genetics, University of Pittsburgh, Pittsburgh, PA, United States

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.01.29.21250643v1

Companion article: https://preprints.jmir.org/preprint/28049

Companion article: https://med.jmirx.org/2021/3/e23393/

Companion article: https://med.jmirx.org/2021/3/e28049/

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KEYWORDS

infectious disease; COVID-19; strain; virus; Romania; transmission; spread; mutation; impact; case study; genome; sequencing; genetics; epidemiology; variant; virology; lineage

This is a peer-review report submitted for the paper "Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis."

Round 1 Review

General Comments

This paper [1] reports the identification and characterization of the SARS-CoV-2 B.1.1.7 variant (the English variant) in North-East Romania and a synopsis of the circulation of this variant in Romania. The manuscript is timely, straightforward, and professionally crafted, and the results are of interest for the characterization of SARS-CoV-2 strains. Such routine surveys are necessary to trace the emergence of new variants of interest and are scarce in Eastern Europe.

Minor Comments

The manuscript needs some revision of English. It is generally well prepared, but there are several instances in which it could benefit from a professional revision.

Conflicts of Interest

None declared.

Reference

1. Lobiuc A, Dimian M, Sturdza O, Filip R, Covasa M. Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis. JMIRx Med 2021 Aug;2(3):e28049 [FREE Full text] [doi: 10.2196/28049]

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Peer Review of "Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis"
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Peer-Review Report

Peer Review of “Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis”

Lei Guo[1], MA, MS

Washington University School of Medicine in St. Louis, St Louis, MO, United States

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.01.29.21250643v1

Companion article: https://preprints.jmir.org/preprint/28049

Companion article: https://med.jmirx.org/2021/3/e23393/

Companion article: https://med.jmirx.org/2021/3/e28049/

(JMIRx Med 2021;2(3):e32299) doi:10.2196/32299

KEYWORDS

infectious disease; COVID-19; strain; virus; Romania; transmission; spread; mutation; impact; case study; genome; sequencing; genetics; epidemiology; variant; virology; lineage

This is a peer-review report submitted for the paper “Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis.”

Round 1 Review

General Comments

First of all, the authors presented an important work about the new UK variant of COVID in Romania [1]. I have the following questions.

Specific Comments

Major Comments

1. In the Methods section, the authors mentioned that “Twenty samples, collected from patients in the cities of Cluj, Craiova and Suceava counties from Romania were selected for analysis, including patients with possible contacts with UK infected individuals.” In the Introduction section, the authors also described the first few possible UK variant cases in Romania.
   Are these 20 cases sequenced by authors related to those cases mentioned in the Introduction? If not, can authors provide some details about the subjects' past travel history? For example, did they stay in UK for more than 2 weeks before they traveled to Romania? And when were these samples collected? The timeline is important to understand how the disease spread and whether they are the first strains of B.1.1.7 in Romania.
2. The authors claimed that “the Romanian strains bearing the particular ORF8 mutations described above clearly originated in the UK, which is also supported by the fact that the patient from Suceava county arrived in Romania from the UK.” I have a similar question about the travel details of the patient as well as the timeline.
3. From a public health standpoint, how did the authors deal with the “news” of the new variant? Was there any communication with local officials or support for contact tracing?
4. In the Discussion section, the authors described that “Many European countries, including Romania, lag in genomic sequencing”. Can the authors provide more details about why Romania lags in genomic sequencing for COVID? For example, cost, equipment, access to labs/institutes. This can help readers and other researchers to understand the issue.

Conflicts of Interest

None declared.

Reference

1. Lobiuc A, Dimian M, Sturdza O, Filip R, Covasa M. Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis. JMIRx Med 2021 Aug;2(3):e28049 [FREE Full text] [doi: 10.2196/28049]

Edited by E Meinert; submitted 21.07.21; this is a non–peer-reviewed article;accepted 21.07.21; published 13.08.21.

Please cite as:
Guo L
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PMID:

Peer-Review Report

Peer Review of "Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study"

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.09.30.20204990v1

Companion article: https://preprints.jmir.org/preprint/28843

Companion article: https://med.jmirx.org/2021/3/e31910/

Companion article: https://med.jmirx.org/2021/3/e28843/

(JMIRx Med 2021;2(3):e31926) doi:10.2196/31926

This is a peer-review report submitted for the paper "Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study".

Round 1 Review

Thank you for your submission [1]. I don't have any suggestions except that a lot has changed since late winter 2020; are you planning to update this manuscript to represent the most recent data? Or alternatively, it may be a good idea to look into the most recent picture and compare it with the findings of the present manuscript.

Reference

1. Barletta WA. Risk factors of SARS-CoV-2 infection: global epidemiological study. JMIRx Med 2021 Aug 18;2(3):e28843 [FREE Full text] [doi: 10.2196/28843]

Edited by E Meinert; submitted 09.07.21; this is a non–peer-reviewed article;accepted 09.07.21; published 26.08.21.

Please cite as:
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JMIRx Med 2021;2(3):e31926
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doi:10.2196/31926
PMID:

Peer-Review Report

Peer Review of “Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study”

Palash Banik[1], MPhil, NCD

Department of Noncommunicable Diseases, Bangladesh University of Health Sciences, Darus Salam, Bangladesh

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.09.30.20204990v1

Companion article: https://preprints.jmir.org/preprint/28843

Companion article: https://med.jmirx.org/2021/3/e31910/

Companion article: https://med.jmirx.org/2021/3/e28843/

(JMIRx Med 2021;2(3):e31927) doi:10.2196/31927

This is a peer-review report submitted for the paper "Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study".

Round 1 Review

General comments

This paper [1] is nicely written by the author, and it is indeed a very important work on SARS-CoV-2 infection. The author presents all the data appropriately and discusses the data rationally. It will be a very interesting and vital reference paper to all those who are working on this topic. I want to see the paper published soon. Best wishes.

Conflicts of Interest

None declared.

Reference

1. Barletta WA. Risk factors of SARS-CoV-2 infection: global epidemiological study. JMIRx Med 2021 Aug 18;2(3):e28843 [FREE Full text] [doi: 10.2196/28843]

Edited by E Meinert; submitted 09.07.21; this is a non–peer-reviewed article;accepted 09.07.21; published 26.08.21.

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Banik P
Peer Review of “Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study”
JMIRx Med 2021;2(3):e31927
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PMID:

Peer-Review Report

Peer Review of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study"

Archisman Roy[1], BSc
Department of Physics, Faculty of Mathematical Science, Institute of Sciences, Banaras Hindu University, Varanasi, India

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.06.30.20143867v2

Companion article: https://preprints.jmir.org/preprint/29062

Companion article: https://med.jmirx.org/2021/3/e31892/

Companion article: https://med.jmirx.org/2021/3/e29062/

(JMIRx Med 2021;2(3):e31895) doi:10.2196/31895

This is a peer-review report submitted for the paper "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study".

Round 1 Review

General Comments

The paper [1] is a well-structured piece of research. The authors divided its content into several parts quite brilliantly. It is beneficial and ancillary to the reviewers for easy understanding and commenting. Coming to the subject matter of it, I felt that the content is extensively deep-rooted. The range and the influential spectrum of the paper are indeed broadly scripted. The distinct segmentation of each author's contribution adds to its vision. To specify the research question beyond drafting the entire write-up and adhering to the focused subject is commendable. The English in use is not so enriched, although the effortless and candid writing makes it suitable for an international journal. In brief, the article is a potentially demanding one. Only a few points can be brought to light for its amelioration. Follow the comments listed below. I am dividing the feedback into major and minor comments. It is requested that you prioritize them.

Major Comments

1. Please compose the Objectives subsection under the Abstract differently from the research question. The issue is the same but write that portion in a distinguishable manner.
2. Please discuss "reintubation" and "extubation" separately under the Introduction section. It is the main requirement for the paper.
3. The Methods section seems to be the weakest part of the paper. Please try rewriting this section. I do not feel attaching any information on "who has approved what" is unimportant (within Methods). Please describe the issue of design. If the "design" pertains to methods, the setup, laboratory requirements, or anything else, mention it.
4. What is your unique contribution to respiratory treatment? I am unable to figure it out.
5. To improve readability, the paper should emphasize:
   - Features
   - Models in use
   - Specific methods (which is already in use but the outputs are dynamic)
   - Tabular forms of data sets
   - Relevant outcomes and accuracy
   - Uncertainty and biasedness
6. Induce a section on the limitations and strengths of the article.
7. Please discuss the implication of the application.
8. The text mentions 6 figures, but I cannot find any of them. Please be careful during submission.
9. The authors have discussed the statistical methods in detail, but there is no mention of their application. Please enclose a good deal of statistical analysis.
10. The description is a bit rigorous and difficult to follow. Use some tabular representations of the data. This will allow for less time-consuming and more effective interpretations of the outcomes and results. I am not talking about the data set, but I am emphasizing the outcomes.

11. The Results, Outcome, and Conclusion sections have been written quite well. Please try to improve the way they are presented though. The mathematical sets are lucid enough to understand the results and their nature. However, there is no derivation or any supportive academic background. It is contradicting to the viability as well as the originality of the paper. So, please ensure you have input all the derivations in the text.
12. The citations mentioned throughout the text are indeed following the literature, so the authors' choice of citations is academically sound.
13. The tables are simple and easy to understand, which is apprehensible.

Minor Comments

1. There are too many typos and grammatical issues.
2. Improve the modeling structure of the entire article.
3. Please conform to the authors' guidelines issued by the publisher.
4. It is expected to have images cited throughout, but the entire text lacks this. Please insert them within the article since it becomes strenuous to follow them otherwise.
5. Please upload supporting data sets in the supplementary materials section.
6. I do not understand what distinguishes "demographics" and the "results" appearing before it.

Round 2 Review

General Comments

There is nothing further to comment on the paper. It has been redrafted with a good deal of care. Every bit of it is clearly illustrated. The title is too descriptive but fine. The abstract is clear enough and understandable. Flow charts, figures, and tables have been intriguingly formatted. I enjoyed reading the paper. As mentioned earlier, the article bears acclaimed content along with suitable citations. The writing style and the English in use are adequate.

Conflicts of Interest

None declared.

Reference

1. Patel M, Chowdhury J, Mills N, Marron R, Gangemi A, Dorey-Stein Z, et al. Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study. JMIRx Med 2021 Aug 18;2(3):e29062 [FREE Full text] [doi: 10.2196/29062] [Medline: 2137297]

Edited by E Meinert; submitted 08.07.21; this is a non–peer-reviewed article;accepted 08.07.21; published 27.08.21.

Please cite as:
Roy A
Peer Review of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study"
JMIRx Med 2021;2(3):e31895
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Peer-Review Report

Peer Review of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study"

Mukul Sehgal, MD, FAAP

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.06.30.20143867v2

Companion article: https://preprints.jmir.org/preprint/29062

Companion article: https://med.jmirx.org/2021/3/e31892/

Companion article: https://med.jmirx.org/2021/3/e29062/

(JMIRx Med 2021;2(3):e31896) doi:10.2196/31896

This is a peer-review report submitted for the paper "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study".

Round 1 Review

General Comments

This paper [1] is an important resource for the use of high-flow nasal cannula in patients with COVID-19 and provides important insights on the current COVID-19 pandemic. Respiratory support for patients with COVID-19 is an important topic for critical patients.

Specific Comments

The paper can be improved in certain areas like methods and design. Also, there is some duplication of the results in the discussion.

Major Comments

1. Inclusion criteria need to be well defined.
2. Initial HFNT (high-flow nasal therapy) settings: there is a discrepancy between the flow mentioned in the Method and Design section (35 L/min) and that mentioned in the Results section (33.5, SD 11.7 L/min of flow). Can you please clarify?
3. The discussion needs to be rewritten. It seems like a duplication of the results, especially the first paragraph.

Minor Comments

1. The dose of methylprednisolone should read "mg/kg."
2. Screening criteria: were the patients identified with high clinical suspicion based on computed tomography COVID-19 negative? If yes, please mention that in the paper.
3. In the sentence, "At initiation of HFNC, a ROX of <5 was predictive of intubation (OR 2.137, *P*=.051)," what was the confidence interval? The *P* value is greater than .05.
4. In the sentence, "Any change in ROX of less than or equal to zero after HFNT initiation over 24 hours was also predictive of intubation," what do you mean by change less than or equal to zero? This sentence is a little confusing.
5. There are multiple references of ROC=0.77 and ROC=0.86; did you mean AUC (area under the ROC curve) or C-statistic?

Conflicts of Interest

None declared.

Reference

1. Patel M, Chowdhury J, Mills N, Marron R, Gangemi A, Dorey-Stein Z, et al. Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study. JMIRx Med 2021 Aug 18;2(3):e29062 [FREE Full text] [doi: 10.2196/29062] [Medline: 2137297]

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Peer-Review Report

Peer Review of "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-sectional Web-Based Study"

Anonymous[1]

NA, NA, ON, Canada

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.02.07.21250695v2

Companion article: https://preprints.jmir.org/preprint/28158

Companion article: https://med.jmirx.org/2021/3/e32954/

Companion article: https://med.jmirx.org/2021/3/e28158/

(JMIRx Med 2021;2(3):e32952) doi:10.2196/32952

This is a peer-review report submitted for the paper "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-sectional Web-Based Study".

Round 1 Review

General comments

This paper [1] is timely given the situation in India. Unfortunately, the manuscript does not include information that can help the readers to contextualize the need to do the study and the rationale to conduct the validation. The discussion is too general to raise awareness concerning the mental health of university students.

Reference

1. Chaudhary AP, Sonar NS, TR J, Banerjee M, Yadav S. Impact of the COVID-19 pandemic on the mental health of college students in India: cross-sectional web-based study. JMIRx Med 2021 Sep 02;2(3):e28158 [FREE Full text] [doi: 10.2196/28158]

Edited by E Meinert; submitted 16.08.21; this is a non–peer-reviewed article;accepted 16.08.21; published 02.09.21.

Please cite as:
Anonymous
Peer Review of "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-sectional Web-Based Study"
JMIRx Med 2021;2(3):e32952
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Peer-Review Report

Peer Review of "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-sectional Web-Based Study"

Anonymous[1]

NA, NA, ON, Canada

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Companion article: https://med.jmirx.org/2021/3/e28158/

(JMIRx Med 2021;2(3):e32953) doi:10.2196/32953

KEYWORDS

This is a peer-review report submitted for the paper "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-Sectional Web-Based Study".

Round 1 Review

General comments

This paper [1] examined how the restrictions caused by COVID-19 impact students' mental health. A total of 324 students completed an online survey to report their fear of COVID-19 and other relevant mental health status. The findings indicate that more than half of the participants had strong fear of COVID-19 and that the fear of COVID-19 was associated with psychological distress of anxiety and depression. In general, the sample size was adequate and the statistical analyses are straightforward. However, the novelty of the present study is not clearly presented.

Specific comments

Major comments

1. As I mentioned in the general comments, the novelty of the present study is not clearly presented. Specifically, ample evidence shows that fear of COVID-19 is associated with psychological distress, and such evidence includes samples from university students. Indeed, Pakpour and his colleagues have done a lot on this topic. Therefore, the authors should justify why there is a need to add their findings to the present literature.
2. There are many grammatical errors in the manuscript, such as "COVID-19 pandemic have created" and "This panic have led to the strong mental impact on them". The authors should have a native English speaker carefully edit the submission to ensure the presentation quality.
3. The authors list "Brief Health Questionnaire" as one of the keywords; however, the present study does not use the Brief Health Questionnaire.
4. Until the *Methods* section, one can identify that the present study focuses on Indians. However, this information is given too late. In addition, the authors should provide some relevant information about COVID-19 in India during the data collection period.
5. The literature review of the present study is thin. As I mentioned earlier, there is ample evidence of the impacts of COVID-19 on mental health. However, the authors did not take references from the current evidence.
6. Additionally, many studies have reported the psychometric properties of the Fear of COVID-19 Scale (FCV-19S). If the authors want to report the concurrent validation of the FCV-19S, they should compare their findings with prior evidence on the psychometric properties of the FCV-19S.

Minor comments

1. Some tables use abbreviations, and the authors should spell out these abbreviations in a footnote.
2. Table 4 should have the correlation values in addition to the *P* values.
3. *P* values should never be 0.000; if the *P* values are really small, use *P*<0.001.
4. I cannot understand what the differences are between Table 4 and Table 5. Moreover, both tables are hard to understand.
5. Some references are not properly listed (eg, M.G H, Sonar NS, Ray B.)

Round 2 Review

General comments

This paper has improved according to the reviewers' and editor's comments. In general, I think that the present form has some merits and is publishable. Although there are no major concerns in the revised version, several minor issues should be addressed in another round of revision.

Specific comments

Minor comments

1. In the Abstract, I think that using * and *** to indicate significance levels is unnecessary because the authors have already provided the actual *P* values.
2. The authors should properly indicate that GAD-7 is the Generalized Anxiety Disorder Scale and PHQ-9 is the Brief Patient Health Questionnaire. The authors did not mention that GAD-7 is the Generalized Anxiety Disorder Scale and PHQ-9 is the Brief Patient Health Questionnaire in the main text. They only indicated this in the footnotes of the tables. Moreover, the authors sometimes used different terms to indicate the two scales (eg, in the Abstract, the authors mention Generalized Anxiety Scale instead of Generalized Anxiety Disorder Scale; sometimes the authors used Brief Patient Health Depression Questionnaire and sometimes Brief Patient Health Questionnaire). This is confusing.
3. The authors should properly indicate that GAD-7 is the Generalized Anxiety Disorder Scale and PHQ-9 is the Brief Patient Health Questionnaire. The authors did not mention that GAD-7 is the Generalized Anxiety Disorder Scale and PHQ-9 is the Brief Patient Health Questionnaire in the main text. They only indicated this in the footnotes of the tables. Moreover, the authors sometimes used different terms to indicate the two scales (eg, in the Abstract, the authors mention Generalized Anxiety Scale instead of Generalized Anxiety Disorder Scale; sometimes the authors used Brief Patient Health Depression Questionnaire and sometimes Brief Patient Health Questionnaire). This is confusing.
4. Reference: Pramukti I, Strong C, Sitthimongkol Y, Setiawan A, Pandin MGR, Yen C, Lin C, Griffiths MD, Ko N. Anxiety and suicidal thoughts during the COVID-19 pandemic: cross-country comparative study among Indonesian, Taiwanese, and Thai university students. *J Med Internet Res* 2020;22(12):e24487.
   - In Table 4, please indicate the reference groups for the categorical independent variables.

Conflicts of Interest

No conflicts declared.

Reference

1. Chaudhary AP, Sonar NS, TR J, Banerjee M, Yadav S. Impact of the COVID-19 pandemic on the mental health of college students in India: cross-sectional web-based study. JMIRx Med 2021 Sep 02;2(3):e28158 [FREE Full text] [doi: 10.2196/28158]

Abbreviations

FCV-19S: Fear of COVID-19 Scale

Edited by E Meinert; submitted 16.08.21; this is a non–peer-reviewed article;accepted 16.08.21; published 02.09.21.

Please cite as:
Anonymous
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JMIRx Med 2021;2(3):e32953
URL: https://med.jmirx.org/2021/3/e32953
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Peer-Review Report

Peer Review of “Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach”

Anonymous

Related Articles:

Companion article: https://www.biorxiv.org/content/10.1101/2020.10.13.337097v1

Companion article: https://preprints.jmir.org/preprint/29844

Companion article: https://med.jmirx.org/2021/3/e33217/

Companion article: https://med.jmirx.org/2021/3/e29844/

(JMIRx Med 2021;2(3):e33214) doi:10.2196/33214

This is a peer-review report submitted for the paper “Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach”.

Round 1 Review

General Comments

Baral and coworkers [1] conducted a screening of L-Asparaginase II (asnB) for selection of asnB with increased asparagine depletion efficiency and decreased unwanted immune response for potentially improved efficacy of acute lymphocytic leukemia treatment in comparison to the commercially available asnBs. In their work, the asparagine hydrolyzation efficiency was assessed by the simulated asparagine binding energy, and the immunogenicity was assessed by the phylogenetic tree distance to the commercial asnB strains via molecular evolutionary genetics analysis. The three best asnBs out of 101 candidates were selected via the screening process. I found the overall work is somewhat of value. However, it can be improved by including some important specifications at each screening step.

Specific Comments

Major Comments

1. The dissertation formatting is not the usual journal article type. Please normalize the introduction and the literature review section into one and make it concise and in a flow, such as (1) introduce the field of the work, its importance, and what has been done; (2) indicate a gap, a research question, or a challenge; and (3) clearly outline the research and its novelty.
2. Please specify the distance matrices used in phylogeny to produce a tree. Is it only sequence-based genetic distance or does it also include measured distance (ie, from immunological studies)? Sequence-based filtering, if lacking immunological factors, may bring in large inaccuracy in your case. If it is not included in the analysis, please suggest some literature references that show sequence-only–based filtering is sufficient to link to immunology. Otherwise, please thoroughly discuss the limitations.
3. At each screening step, please specify, among XX candidates, YY was selected, for ZZ reasons (eg, the distances is greater than AA from *E coli* K12; percent of residues in most favored regions is greater than BB%; the binding energy is greater than CC. This helps with clarifying and keeping track of the optimization.

Minor Comments

1. The tree plot is a bit hard to read. Please make it uniform and enlarge the font size in the same column and make it readable at 100% display. Please use squares rather than circles to highlight the candidates in the tree for better accuracy. Please explain what the numbers plotted on the tree branches are (bootstrap confidence levels?).
2. P15, line 299. Is it at the “top” or at the “bottom” of the tree? The current description does not match with the description in the figure legend.
3. Please include references in section 3.3 and in Table 1 for those identified active cites of asnBs from *E coli* and from other organisms.
4. In Table 2, do not use * as the multiplication sign (×). (Please also do not simply use the letter x for a correction.) In addition, please use a separate column for the references.

Round 2 Review

General Comments

All my comments have been addressed.

Reference

1. Baral A, Gorkhali R, Basnet B, Koirala S, Bhattarai HS. Selection of the optimal L-asparaginase II against acute lymphoblastic leukemia: an in silico approach. JMIRx Med 2021 Sep 7;2(3):e29844 [FREE Full text] [doi: 10.2196/29844]

Edited by E Meinert; submitted 27.08.21; this is a non–peer-reviewed article;accepted 27.08.21; published 08.09.21.

Please cite as:
Anonymous
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Peer-Review Report

Peer Review of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach"

Navneetha Hardikar[1], BSc

Department of Biology, Queen's University, Kingston, ON, Canada

Related Articles:

Companion article: https://www.biorxiv.org/content/10.1101/2020.10.13.337097v1

Companion article: https://preprints.jmir.org/preprint/29844

Companion article: https://med.jmirx.org/2021/3/e33217/

Companion article: https://med.jmirx.org/2021/3/e29844/

(JMIRx Med 2021;2(3):e33215) doi:10.2196/33215

This is a peer-review report submitted for the paper "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach".

Round 1 Review

General Comments

This paper [1] aimed to investigate whether asnB from *E Coli* and *Erwinia* is the best asparaginase for the therapeutic treatment of acute lymphoblastic leukemia by using asnB sequence of *E Coli* to search for homologous proteins in other bacteria and archaea phyla. The authors mention that asnB with the lowest Michaelis Menten constant (Km) and the lowest immunogenicity is to be considered the most suitable enzyme. A phylogenetic tree was created, after which homology modeling was conducted, followed by docking to identify the binding energies to determine the relationship between binding energy and Km. The technical aspects of the paper are adequately conveyed, and the in silico method is appropriate to answer the question. However, I have a few comments that need to be clarified.

Specific Comments

Major Comments

1. Perhaps, explain what blastp does to provide more insight.
2. It would be beneficial to include a figure that displays the sequence alignment of the query sequence along with the similarity percentage.
3. The discussion is well-written, although could benefit from including other relevant studies/prior works to support your results.
4. Conclusion is relatively weak. Please consider revising it and sufficiently summarizing the Methods and Results.

Minor Comments

1. Section 2.2: Please define DOPE and SOAP before abbreviating.
2. Discussion: It is mentioned that only 6 of 10 species could have a Km value assigned to a certain sequence, please mention these 6 species.
3. Discussion: The sentence "Thus it can be predicted that an enzyme with better kinetics that currently commercially available asparaginase can be cloned from Streptomyces species" is a bit ambiguous. Please rewrite this sentence.

Round 2 Review

General Comments

The authors have addressed all reviewer comments and improved the manuscript. I have no further comments.

Conflicts of Interest

No conflict declared.

Reference

1. Baral A, Gorkhali R, Basnet B, Koirala S, Bhattarai HS. Selection of the optimal L-asparaginase II against acute lymphoblastic leukemia: an in silico approach. JMIRx Med 2021 Sep 7;2(3):e29844 [FREE Full text] [doi: 10.2196/29844]

Edited by E Meinert; submitted 27.08.21; this is a non–peer-reviewed article;accepted 27.08.21; published 08.09.21.

Please cite as:
Hardikar N
Peer Review of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach"
JMIRx Med 2021;2(3):e33215
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Peer-Review Report

Peer Review of “Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach“

Ariz Mohammad[1], PhD

Department of Genetics, Washington University in Saint Louis, St. Louis, MO, United States

Related Articles:

Companion article: https://www.biorxiv.org/content/10.1101/2020.10.13.337097v1

Companion article: https://preprints.jmir.org/preprint/29844

Companion article: https://med.jmirx.org/2021/3/e33217/

Companion article: https://med.jmirx.org/2021/3/e29844/

(JMIRx Med 2021;2(3):e33216) doi:10.2196/33216

This is a peer-review report submitted for the paper “Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach”.

Round 1 Review

General Comments

L-Asparaginase II (asnB) derived from *E coli* and *E chrysanthemi* is often used in the treatment of acute lymphoblastic leukemia (ALL). The manuscript submitted by Baral et al [1] outlines an in silico method to identify potential asnB from different species with potentially higher potency against suppressing the tumor and lesser side effects. Using over 100 asnB from a wide range of species, the authors identified a group of potential candidates and have taken them up for further analysis. Using homology modeling, the structures of these candidate proteins were built and were then used to calculate binding energies with asparagine. The authors also showed that the predicted binding energies have an inverse relationship with the reported experimental Km values of asnBs. This led authors to predict 3 asnBs from 3 different Streptomyces species.

The manuscript has systematically presented the findings and is nicely assembled. I have a few concerns.

Specific Comments

Major Comments

The figures need to be made compact and some should be combined into one (see below).

Minor Comments

1. Page 3, Introduction, line 2: Cite peer-reviewed article/review.
2. Page 3: Keep a space between text and citation parentheses.
3. Page 3, paragraph 2: First sentence is abrupt. Rewrite the paragraph, probably starting with the discovery of the guinea pig serum cure of ALL!
4. Page 5, line 1: Change “analyses” to analyze.
5. Figure 2: Should be rearranged and each plot should be labeled for species, and the unnecessary text should be removed like postscript file indicator, plot number, etc.
6. Figures 3-5b: Use an arrow to show the point.
7. Figures 3-5: Combine the three figures into one.
8. Figure 7: Figure needs to be combined and made compact. The insets are too big. Species name should be given on individual panels.
9. Figure 8: Figure needs to be combined and made compact.

Conflicts of Interest

No conflict declared.

Reference

1. Baral A, Gorkhali R, Basnet B, Koirala S, Bhattarai HS. Selection of the optimal L-asparaginase II against acute lymphoblastic leukemia: an in silico approach. JMIRx Med 2021 Sep 7;2(3):e29844 [FREE Full text] [doi: 10.2196/29844]

Abbreviations

ALL: acute lymphoblastic leukemia

Edited by E Meinert; submitted 27.08.21; this is a non–peer-reviewed article;accepted 27.08.21; published 08.09.21.

Please cite as:
Mohammad A
Peer Review of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach"
JMIRx Med 2021;2(3):e33216
URL: https://med.jmirx.org/2021/3/e33216
doi:10.2196/33216
PMID:

Peer-Review Report

Peer Review of “A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development”

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.09.13.20193599v1

Companion article: https://preprints.jmir.org/preprint/24630

Companion article: https://med.jmirx.org/2021/3/e32798/

Companion article: https://med.jmirx.org/2021/3/e24630/

(JMIRx Med 2021;2(3):e32796) doi:10.2196/32796

KEYWORDS

epidemiology; computational; model; COVID-19; modeling; outbreak; virus; infectious disease; simulation; impact; vaccine; agent-based model

This is a peer-review report submitted for the paper “A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development”.

Round 1 Review

General Comments

The paper [1] describes an agent-based model for investigating the COVID-19 spread in Lombardy. The importance of this study is evident. Additionally, it is interesting work. However, this manuscript needs to be enhanced more before publication. My main concerns are about the points below.

Specific Comments

Major Comments

1. The event of disease spread has been extremely simplified. As you know, the outbreak of a disease is affected by lots of factors.

2. The Introduction lacks enough references to previous research.

3. The model has not been validated and verified, which are the most important tasks in proving the correct performance of the model developed.

4. The movement of all agents has been considered randomly, while in reality, it does not happen in this way.

5. The materials and methods lack information about the way the model was developed. All necessary information about the model needs to be made known—attributes and behaviors of the agents, interactions between the agents, etc.

6. As you know, one of the advantages of the agent-based model approach is its consideration of the geography of the environment and simulation of the exact locations of people and places. The diversity of the population affects the spread of the disease as well as interactions. If the population density remains constant, but people do not have interactions with each other, the disease does not spread.

Minor Comments

1. The manuscript needs to be thoroughly proofread by a native English speaker.

2. The Abstract lacks results, which is an important part of the Abstract. Innovations and aims of the manuscript have not been expressed clearly as well as the contributions of the manuscript.

3. Figure 1 does not include any information.

4. The way the manuscript has been written is not appropriate. It has not been developed like a manuscript. It needs to be rewritten.

Conflicts of Interest

None declared.

Reference

1. Giacopelli G. A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development. JMIRx Med 2021 Sep 10;2(3):e24630 [FREE Full text] [doi: 10.2196/24630]

Edited by E Meinert; submitted 10.08.21; this is a non–peer-reviewed article;accepted 10.08.21; published 10.09.21.

Please cite as:
Anonymous
Peer Review of "A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development"
JMIRx Med 2021;2(3):e32796
URL: https://med.jmirx.org/2021/3/e32796
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Peer-Review Report

Peer Review of “A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development”

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2020.09.13.20193599v1

Companion article: https://preprints.jmir.org/preprint/24630

Companion article: https://med.jmirx.org/2021/3/e32798/

Companion article: https://med.jmirx.org/2021/3/e24630/

(JMIRx Med 2021;2(3):e32797) doi:10.2196/32797

KEYWORDS

epidemiology; computational; model; COVID-19; modeling; outbreak; virus; infectious disease; simulation; impact; vaccine; agent-based model

This is a peer-review report submitted for the paper “A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development”.

Round 1 Review

General Comments

This paper [1] is a great effort to apply agent-based modeling to the COVID-19 pandemic. The stated run times for this application are really quite good for such a large number of agents, and I believe that the publication of this paper, when revised, will be very useful to the disease-modeling community.

Specific Comments

Major Comments

1. Though I fully understand how difficult it is to write a scientific paper in a language that is not the primary language of the researchers involved, I am afraid I have to point out that this paper needs some serious revision in its usage of the English language. This is vital to a full understanding of the science applied and the knowledge gained as a result of this work.

2. I would like to see more details about the actual modeling simulation software, algorithms, mathematical functions, etc, used and how it was parallelized/distributed to achieve the efficiency stated in this work. I believe that these application details, rather than its results, are of even greater importance. It is fairly easy to make a model and simulation fit actual outbreak data, so the result is not of much importance when only applied to one set of data. Rather, what is important here is the application methods used to achieve your results as these can be applied to many other epidemiological situations that need to be modeled and simulated.

3. We need much more detail about parts of the model, such as the collision detection algorithm. For example, what was used to determine the result of this portion of the model (eg, what algorithm or mathematical function, etc?)? Please describe the model in detail.

Minor Comments

1. I do not believe that a 6-step-per-day model for the agents is too much, contrary to what the authors supposed might be interpreted by the reader. The collision detection and spread caused by an agent's movements throughout the day are likely in great need of many, many steps per day. Further, these “steps” per day could be modified, in future work, to illustrate the effects of movement control or quarantine on the agents of the model.

Conflicts of Interest

None declared.

Reference

1. Giacopelli G. A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development. JMIRx Med 2021 Sep 10;2(3):e24630 [FREE Full text] [doi: 10.2196/24630]

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Please cite as:
Anonymous
Peer Review of "A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development"
JMIRx Med 2021;2(3):e32797
URL: https://med.jmirx.org/2021/3/e32797
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Peer-Review Report

Peer Review of "Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review"

Alexis Beatty[1], MD, MAS

School of Medicine, University of California, San Francisco, San Francisco, CA, United States

Related Articles:

Companion article: https://preprints.jmir.org/preprint/21906

Companion article: https://med.jmirx.org/2021/3/e33179/

Companion article: https://med.jmirx.org/2021/3/e21906/

(JMIRx Med 2021;2(3):e33180) doi:10.2196/33180

KEYWORDS

cardiac rehabilitation; physical capacity; exercise; smartphone apps

This is a peer-review report submitted for the paper "Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review".

Review Round 1

General Comments

This paper [1] reviews published studies on use of smartphone apps for cardiac rehabilitation (CR). The authors reach interesting conclusions about integrating devices for monitoring physical activity and vital signs, which would be the main contribution of this paper. However, there are significant issues with the methods and a number of incorrect statements within the manuscript that are of concern.

Specific Comments

Major Comments

1. Please justify your statement in the abstract that apps reduce the cost of CR, or if unable to justify or cite a reference, remove this statement.

2. Would suggest citing newer references and original references for outcomes and rates of participation in CR: Ritchey MD, Maresh S, McNeely J, Shaffer T, Jackson SL, Keteyian SJ, Brawner CA, Whooley MA, Chang T, Stolp H, Schieb L, Wright J. Tracking cardiac rehabilitation participation and completion among Medicare beneficiaries to inform the efforts of a national initiative. Circ Cardiovasc Qual Outcomes 2020;13(1):e005902.

3. Would suggest reading and referencing the Home-Based Cardiac Rehabilitation Scientific Statement: Thomas RJ, Beatty AL, Beckie TM, Brewer LC, Brown TM, Forman DE, Franklin BA, Keteyian SJ, Kitzman DW, Regensteiner JG, Sanderson BK, Whooley MA. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. Circ 2019;140(1):e69-e89.

4. Your search strategy appears rather limited. Would suggest including additional terms, such as *mobile app*, *mobile phone*, and *digital health*.

5. You should exclude studies that were not randomized per your methods (eg, Forman [2], Layton [3], Worringham [4]).

6. You should distinguish between lack of improvement with smartphone CR and lack of significant difference versus CR—they are different things.

7. Your definition of CR phases is not how most view it—Phase I is typically thought of as inpatient, and it is now recommended that patients start Phase 2 within 21 days and participate for 12 weeks.

8. I suggest including "Phase of rehab" in your table rather than in the text.

9. In your table, you should display the numbers of the outcome measure rather than the word description of the comparison.

Review Round 2

The authors appropriately responded to comments and the revised manuscript is significantly improved.

Conflicts of Interest

None declared.

References

1. Tuttle K, Kelemen A, Liang Y. Use of smartphone apps for improving physical function capacity in cardiac patient rehabilitation: systematic review. JMIRx Med 2021 Sep 15;2(3):e21906 [FREE Full text] [doi: 10.2196/21906]
2. Forman DE, LaFond K, Panch T, Allsup K, Manning K, Sattelmair J. Utility and efficacy of a smartphone application to enhance the learning and behavior goals of traditional cardiac rehabilitation: a feasibility study. J Cardiopulm Rehabil Prev 2014;34(5):327-334. [doi: 10.1097/HCR.0000000000000058] [Medline: 24866355]
3. Layton AM, Whitworth J, Peacock J, Bartels MN, Jellen PA, Thomashow BM. Feasibility and acceptability of utilizing a smartphone based application to monitor outpatient discharge instruction compliance in cardiac disease patients around discharge from hospitalization. Int J Telemed Appl 2014;2014:415868 [FREE Full text] [doi: 10.1155/2014/415868] [Medline: 25574165]
4. Worringham C, Rojek A, Stewart I. Development and feasibility of a smartphone, ECG and GPS based system for remotely monitoring exercise in cardiac rehabilitation. PLoS One 2011 Mar 09;6(2):e14669 [FREE Full text] [doi: 10.1371/journal.pone.0014669] [Medline: 21347403]

Abbreviations

CR: cardiac rehabilitation

Edited by E Meinert; submitted 26.08.21; this is a non–peer-reviewed article;accepted 26.08.21; published 17.09.21.

Please cite as:
Beatty A
Peer Review of "Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review"
JMIRx Med 2021;2(3):e33180
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doi:10.2196/33180
PMID:

Peer-Review Report

Peer Review of “Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review”

Karla Goessler[1], PhD

Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil

Related Articles:

Companion article: https://preprints.jmir.org/preprint/21906

Companion article: https://med.jmirx.org/2021/3/e33179/

Companion article: https://med.jmirx.org/2021/3/e21906/

(JMIRx Med 2021;2(3):e33181) doi:10.2196/33181

KEYWORDS

cardiac rehabilitation; physical capacity; exercise; smartphone apps

This is a peer-review report submitted for the paper “Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review”.

Review Round 1

General Comments

This is a systematic review [1] investigating the utilization of smartphone apps for improving physical function capacity in cardiac rehabilitation (CR). Please find below my comments/suggestions.

Specific Comments

Major Comments

1. CR interventions seem to be quite different between studies, making future comparisons inappropriate (ie, for CR programs including exercise programs, I would expect improvements in cardiorespiratory fitness (CRF), while for programs including diet, this outcome might not change).

2. It is not clear how authors selected the papers. This process makes it difficult to understand the results, as the outcomes and types of interventions are quite different between studies. As the main outcome in CR is CRF, I would suggest making it your primary outcome for selection of the studies.

Minor Comments

Methods/Results

1. I would suggest including a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the study selection process. This is available at http://prisma-statement.org/prismastatement/flowdiagram.aspx.

2. Tables 2 and 3 are not clear.

Conflicts of Interest

None declared.

Reference

1. Tuttle K, Kelemen A, Liang Y. Use of smartphone apps for improving physical function capacity in cardiac patient rehabilitation: systematic review. JMIRx Med 2021 Sep 15;2(3):e21906 [FREE Full text] [doi: 10.2196/21906]

Abbreviations

CR: cardiac rehabilitation
CRF: cardiorespiratory fitness
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Edited by E Meinert; submitted 26.08.21; this is a non–peer-reviewed article;accepted 26.08.21; published 17.09.21.

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Goessler K
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JMIRx Med 2021;2(3):e33181
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doi:10.2196/33181
PMID:

Peer-Review Report

Peer Review of "Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study"

Ebrahim Sadeghi-Demneh[1], MD

Musculoskeletal Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Related Articles:

Companion article: https://preprints.jmir.org/preprint/30233

Companion article: https://med.jmirx.org/2021/3/e32248/

Companion article: https://med.jmirx.org/2021/3/e30233/

(JMIRx Med 2021;2(3):e32262) doi:10.2196/32262

KEYWORDS

tele-rehabilitation; video-consultations; assessment of movement; eHealth; technology; desktop robots; wide-angle webcams; physical health; rehabilitation; remote; assessment; assistive technology; evaluation; framework; webcam; telehealth; robots

This is a peer-review report submitted for the paper "Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study."

Round 1 Review

General Comments

Thank you for taking the time to submit this paper [1]. It is an interesting area for health care practitioners. This was an exploratory trial on the feasibility of video consultation with some off-the-shelf technologies in the United Kingdom. This manuscript is well structured and written, but the external validity of the results is limited. I have included some feedback on the different sections of the manuscript and hope the authors will find these comments helpful.

Specific Comments

Major Comments

1. Please consider that movement at least has four basic parameters, including force, range of motion/distance, rate (velocity/acceleration), and endurance (repeats until the mover is fatigued). I think authors could talk more about the shortcomings of their methods for comprehensive assessments of the parametric abilities of movements.

2. To further discuss the limitations of your study, please note that in resource-limited environments and developing countries, these results cannot be generalized.

Minor Comments

3. Please correct the spelling of "CINHAL".

4. Please explain why authors selected a time limit (since 2016) for their literature search.

5. The specification of products/instruments should include details (model, manufacturer company, country).

Conflicts of Interest

None declared.

Reference

1. Jones RB, Hubble S, Taylor L, Gunn H, Logan A, Rowland T, et al. Technologies to support assessment of movement during video consultations: exploratory study. JMIRx Med 2021 Sep;2(3):e30233 [FREE Full text] [doi: 10.2196/30233]

Edited by E Meinert; submitted 20.07.21; this is a non–peer-reviewed article;accepted 20.07.21; published 24.09.21.

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doi:10.2196/32262
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Peer-Review Report

Peer Review of “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study”

Immanuel Victor George[1], MSN, PGDANP

NHS WWL Foundation Trust, Wigan, United Kingdom

Related Articles:

Companion article: https://preprints.jmir.org/preprint/30233

Companion article: https://med.jmirx.org/2021/3/e32248/

Companion article: https://med.jmirx.org/2021/3/e30233/

(JMIRx Med 2021;2(3):e32263) doi:10.2196/32263

KEYWORDS

tele-rehabilitation; video-consultations; assessment of movement; eHealth; technology; desktop robots; wide-angle webcams; physical health; rehabilitation; remote; assessment; assistive technology; evaluation; framework; webcam; telehealth; robots

This is a peer-review report submitted for the paper “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study.”

Round 1 Review

General Comments

This paper [1] is an exploratory study on technologies to support video consultations assessing movement. It is not clear whether it explored the technology itself or the process of using various technologies.

Specific Comments

Major Comments

1. It is not clear why 4 specific devices were chosen and there is no explanation of the most widely used software. Is it technology or device exploration?

2. I was unable to identify clearly whether the hypothetical patients were physiotherapists or family members. Were the hypothetical patients briefed on what they should present for inference, or was the clinical condition identified as they presented?

3. How many hypothetical patients took part in the study?

Minor Comments

4. The experiences of the hypothetical patients were not detailed.

Conflicts of Interest

None declared.

Reference

1. Jones RB, Hubble S, Taylor L, Gunn H, Logan A, Rowland T, et al. Technologies to support assessment of movement during video consultations: exploratory study. JMIRx Med 2021 Sep;2(3):e30233 [FREE Full text] [doi: 10.2196/30233]

Edited by E Meinert; submitted 20.07.21; this is a non–peer-reviewed article;accepted 20.07.21; published 24.09.21.

Please cite as:
George IV
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doi:10.2196/32263
PMID:

Peer-Review Report

Peer Review of “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study”

Radu Ciorap[1], PhD

Department of Biomedical Sciences, Faculty of Medical Bioengineering, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

Related Articles:

Companion article: https://preprints.jmir.org/preprint/30233

Companion article: https://med.jmirx.org/2021/3/e32248/

Companion article: https://med.jmirx.org/2021/3/e30233/

(JMIRx Med 2021;2(3):e32265) doi:10.2196/32265

KEYWORDS

tele-rehabilitation; video-consultations; assessment of movement; eHealth; technology; desktop robots; wide-angle webcams; physical health; rehabilitation; remote; assessment; assistive technology; evaluation; framework; webcam; telehealth; robots

This is a peer-review report submitted for the paper “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study.”

Round 1 Review:

The paper [1] is well organized, and the length is appropriate.

The title is chosen correctly, and the abstract provides sufficient information to give a clear idea of what to expect from the paper.

The results are well highlighted, and the conclusions are adequate.

The technical depth of the paper meets the requirements for a scientific article published in a quality journal.

Conflicts of Interest

None declared.

Reference

1. Jones RB, Hubble S, Taylor L, Gunn H, Logan A, Rowland T, et al. Technologies to support assessment of movement during video consultations: exploratory study. JMIRx Med 2021 Sep;2(3):e30233 [FREE Full text] [doi: 10.2196/30233]

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Ciorap R
Peer Review of “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study”
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PMID:

Peer-Review Report

Peer Review of “Early Experience With Neutralizing Monoclonal Antibody Therapy for COVID-19: Retrospective Cohort Survival Analysis and Descriptive Study”

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.09.21255219v1

Companion article: https://preprints.jmir.org/preprint/29638

Companion article: https://med.jmirx.org/2021/3/e33496/

Companion article: https://med.jmirx.org/2021/3/e29638/

(JMIRx Med 2021;2(3):e33499) doi:10.2196/33499

KEYWORDS

infectious disease; monoclonal antibody therapy; COVID-19; experience; therapy; drug; patient outcome; risk; efficacy; approach; treatment; pandemic; antibody; immunotherapy; immune therapy

This is a peer-review report submitted for the paper “Early Experience With Neutralizing Monoclonal Antibody Therapy for COVID-19: Retrospective Cohort Survival Analysis and Descriptive Study.”

Round 1 Review

General Comments

In this paper [1], the authors study the effect of monoclonal antibodies and their benefit in patients with COVID-19. The authors conclude that, although this therapy may be an important treatment option for early mild to moderate COVID-19 in patients at high risk, further investigations are needed to define the optimal timing of monoclonal antibody treatment to reduce hospitalization and mortality.

Although this topic is not entirely new, the paper looks good to me and confirms other previously published data.

Specific Comments

As Tables 1 and 2 are quite complex, they need a clear legend and not just the title, as reported.

For greater clarity, the figures should also be better explained.

In the Introduction and Discussion when talking about COVID-19, for the sake of clarity, we need to better explain the inflammation that kills people and not just go straight to the monoclonal antibodies. Therefore, to make this paper more interesting for the readers of this important journal, the authors should expand the discussion on this subject a little to give a wider view to the reader.

Conflicts of Interest

None declared.

Reference

1. Jarrett M, Licht W, Bock K, Brown Z, Hirsch J, Coppa K, et al. Early experience with neutralizing monoclonal antibody therapy for COVID-19: retrospective cohort survival analysis and descriptive study. JMIRx Med 2021 Sep;2(3):e29638 [FREE Full text]

Edited by E Meinert; submitted 09.09.21; this is a non–peer-reviewed article;accepted 18.09.21; published 27.09.21.

Please cite as:
Anonymous
Peer Review of "Early Experience With Neutralizing Monoclonal Antibody Therapy for COVID-19: Retrospective Cohort Survival Analysis and Descriptive Study"
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doi:10.2196/33499
PMID:27629988

Peer-Review Report

Peer Review of "SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study"

Anonymous

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.27.21252790v1

Companion article: https://preprints.jmir.org/preprint/30176

Companion article: https://med.jmirx.org/2021/3/e31900/

Companion article: https://med.jmirx.org/2021/3/e30176/

(JMIRx Med 2021;2(3):e31904) doi:10.2196/31904

KEYWORDS

vaccination; COVID-19; incarcerated individuals; correctional facility; public health; pandemic; vaccine; carceral setting; vaccine implementation; correctional staff

This is a peer-review report submitted for the paper "SARS-CoV-2 Vaccination Uptake in a Correctional Setting".

Round 1 Review

General Comments

This paper [1] is an important addition to the literature. The authors discuss the rollout of COVID-19 vaccines in the Rhode Island Department of Corrections.

Specific Comments

Introduction

Are you sure you were the first state to offer vaccines? You might be the first to get a shot in the arm, but other states were offering in February 2021, and since the jail kept on getting new people, you never really completed offering testing. For the study, your cutoff was February 5, but I am guessing the first vaccines were still given on February 6, 7, 8, etc. You might want to specify that your study period of interest was from December 22 to March 5. This helps me believe your denominators as well.

I speak about this more in my review of the discussion, but I think this does not add to your paper, and, in fact, draws away from it. It gets braggy that you were the first. That is less important than being the best, unless you think the first and then best are related? Overall, I think the Introduction would be better by changing the second-to-last sentence to be the last sentence and removing the last sentence.

Methods

1. The first sentence of the Methods is really background/introduction information, not methodology.

2. I would appreciate more information about the process of deciding the phases, maybe a line about the stakeholders who convened to make the decision and whether any evidence or guidelines were used.

3. I recommend starting the Methods with "RIDOC is a unified…," then "SARS-CoV-2 vaccines offered…March 5," and then, "Staff… concurrently."

4. "Rounds" is colloquial; I need to know what you mean by this. Did you mean "rounding," like you offered it at rounds on the cellblock? Or was this another way to say phases?

5. The last paragraph, first line, needs rewriting.

6. More information on what type of education was provided at roll call and by whom is needed.

7. What was in the email? Could it be included as a supplement? It seems super successful, and I would think the wording of the email or the video should be shared to help other people inform their efforts.

Results

1. I think the line about the flu vaccination is out of place in the Results. It should be in the Discussion.

2. I do not think you need the word "approximately" in front of specific percentages (eg, 9.1).

3. Overall, I think you can just refer a lot to the table rather than writing out all of the numbers. Here, you use round 1 instead of phase 1.

4. "Second-dose vaccines were administered…": I don't think you need to discuss these first 2 sentences. They are not really results because you were not reporting on how well you kept

to the intended timeline. You also do not let us know how many doses. I recommend removing this.

5. I recommend starting this with 3 incarcerated individuals and 6 who received the first dose but did not take their second. This is amazing.

6. What is an overpull? I recommend taking this out. You have enough for a different paper about how you did this process. It draws away from your results to report this.

7. Should “Intake” be capitalized in “Intake facility”?

8. You do not report anywhere that part of your process was to track adverse events or what you defined as an adverse event. If you want to retain this, I recommend a line in the Methods. I feel like everything you report in the Results section should be linked to something you said you would do in the Methods.

Discussion

1. I do not think “efficient” is correctly used in the first line. We do not know if it was efficient. You were able to vaccinate the majority of people.

2. Lines 2 and 3 of the Discussion are separate thoughts. I would make them two separate thoughts and two separate statements.

3. What do you mean regarding the RIDOC being the first to offer? I think this statement draws away from the importance of the paper and makes it a little weirdly competitive. The first inmate to get a shot was in Rhode Island? I am not sure about that… I would take that statement out. If you highlight how amazing you are, then you take away from the goal that everyone should be able to do this, even the last state that is vaccinating.

4. Why the high decline rate in the Minimum and Women’s facilities. Are they younger?

5. They are not difficult to reach. I think calling them “difficult to reach” has been refuted and is sort of elitist. We know where they are. They are poor and in jail. They are not difficult to reach.

6. The comment about switching to 1-dose vaccines seems totally out of line with what you said before. You were able to do this very successfully. I would argue, especially with the issues with Johnson & Johnson, that your study shows it is possible to use 2 doses effectively. I recommend highlighting your low second-dose refusal rate. Why was that?

Conflicts of Interest

None declared.

Reference

1. Berk J, Murphy M, Kane K, Chan P, Rich J, Brinkley-Rubinstein L. SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study. JMIRx Med 2021 Sep 27;2(3):e30176 [FREE Full text] [doi: 10.2196/30176]

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Peer-Review Report

Peer Review of "SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study"

Benjamin A Howell, MD, MPH, MHS

Related Articles:

Companion article: https://www.medrxiv.org/content/10.1101/2021.04.27.21252790v1

Companion article: https://preprints.jmir.org/preprint/30176

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(JMIRx Med 2021;2(3):e31905) doi:10.2196/31905

KEYWORDS

vaccination; COVID-19; incarcerated individuals; correctional facility; public health; pandemic; vaccine; carceral setting; vaccine implementation; correctional staff

This is a peer-review report submitted for the paper "SARS-CoV-2 Vaccination Uptake in a Correctional Setting".

Round 1 Review

General Comments

This is an important manuscript [1] describing the efforts of the Rhode Island Department of Corrections (RIDOC) to roll out a vaccine program in their unified state correctional system. First, I would be careful in describing this as an "evaluation." It is a description of the rollout of the vaccine program, and I did not find any elements of an evaluation. Second, the manuscript could be much improved with increased clarity in the writing. Even as a reader who knows more about the RIDOC correctional system than the average reader, I got confused at times about what the authors were referring to. Adding more details on the RIDOC (and how it compares to other correctional systems) will aid generalizability, and also adding more details about the RIDOC vaccination program will help readers contextualize their findings. I recommend rewriting this manuscript with a more general public health audience in mind (who will likely know less about correctional systems).

Specific Comments

Major/Minor Comments

Introduction

1. "Correctional outbreaks have substantially contributed…" While I agree that is likely true, this statement relies on the citation of one study that describes county-level infection rates based on infection rates in one (very large) county jail. I would hedge more with the language here as done in the Discussion section.

2. "The goal of this study was to evaluate…" As mentioned above, I would not call this an "evaluation" per se. Even as a largely descriptive piece, the data reported here are important, so I do not think the authors need to oversell it as an "evaluation." Evaluation implies that they attempted to figure out differences in vaccine acceptance rate or why/how the program worked/did not work or something like that. There is none of that here.

Methods

1. "From the beginning…" What makes RIDOC procedures around testing and isolation "aggressive"?

2. "The RIDOC is…" First, the authors should be consistent using "RIDOC" or "The RIDOC." Second, I think this is where more work can be done to explain the RIDOC to general public health audiences. For example, the term "security facilities" will likely be opaque to many. Third, the authors used "sentenced…individuals" here, but in the next sentence refer to the same people as "incarcerated people who had received a sentence after a criminal trial," which is confusing.

3. "This includes individuals…" This is vague, and I believe this is included to make the results from the RIDOC generalizable to other states, but more clarification of why this sentence is included would be helpful. The authors could also use this section to describe where a typical "jail" population is housed in the RIDOC system (ie, the Intake facility).

4. "Among incarcerated people, a general system of "Rounds"…" Is "Rounds" here a synonym for what is described as "phases" in the next paragraph? It is unclear what is meant by this term. Also, they should be clearer about what they mean by "opt-out." More descriptions of how this process was rolled out will be helpful for readers hoping to implement similar

programs. How did they approach individuals who were incarcerated? What education was provided?

5. More details in the paragraph on phases would be helpful, for example, in the sentence beginning “In phase 2...” If more description of the RIDOC facilities is given, they can refer to that here. To people unfamiliar with the RIDOC, what a “smaller facility” means would be confusing. This is also the case with the next sentence and the reference to “Medium Security.”

6. “Among corrections staff…” As above, I think being clearer about what is meant by “opt-in” here would be helpful, especially as it contrasts with the “opt-out” system described for incarcerated individuals.

Results

1. The sentence on influenza does not need to be in parentheses.

2. “…declined the offer of vaccine.” This is awkward—may be missing an indefinite/definite article or needs to be phrased differently (ie, “declined the offer of a vaccine” or “declined to be vaccinated”).

3. “A total… did not opt-in for the initial vaccine offering.” The authors mean “did not opt in for a vaccine during the initial vaccine offering,” not opting in for the vaccine offering.

4. “Due to logistics…due to vaccine delivery times and staffing availability.” The sentence is awkwardly structured. The “logistics” are the “delivery times and staffing availability,” or are they referring to something else?

5. “At the time…” The reference to the Intake facility will be confusing to people who are not aware of the structure of the RIDOC. The authors may want to flag “Intake” as being equivalent to a “jail” population in other states that has a mix of “awaiting-trial” and “sentenced” individuals. If the Intake facility only has awaiting-trial individuals, this should be clearer. As it is referred to here, it is vague and confusing.

Discussion

1. “Vaccination was efficient…” What about it was efficient? I think the authors mean that they vaccinated 70% of the population within 4 months, but this should be more explicitly stated if that is what they meant.

2. “This aligns…” I would break this sentence into two sentences. There are two important points being made here and they should highlight both: (1) the RIDOC is on target to achieve herd immunity and (2) concerns about vaccine hesitancy in incarcerated populations may be overstated. Also, this second point makes a description of how they structured the education and approach to incarcerated individuals that much more important.

3. “The pandemic has devastated correctional settings…” This sentence is awkward, and the use of devastated needs to be qualified (as is, it feels too subjective).

4. “Similarly…” This sentence is awkward. The authors mean to say that both mass incarceration and COVID-19 have disproportionately impacted communities of color, but they should say it more clearly. Also, they should be consistent using “Covid-19” or “COVID-19.”

Tables

1. Table 1: Alignment of the “group description” here and what is described in the text. For example, phase 2 here refers to the specific facility but in the text, these are referred to as “smaller facilities,” requiring the reader to make this logical connection. Phase 3 here includes “individuals awaiting transfer,” which is not referred to in the text.

2. Table 1: There is no attached asterisk to where the footnote is referring to.

3. Table 2: It should be made clearer that general individuals in the Intake facility (as being an awaiting-trial population) were not included in the vaccine rollout phases (or was this not true?).

4. Table 2: The population on what day? These populations probably change every day (or even every hour). The authors should flag this in the title of the table when these numbers were collected.

Round 2 Review

General Comments

The authors have addressed all my concerns with this revision of their manuscript. My only suggestion is to rereview for typographical or grammatical errors. This revision introduced a couple of errors that I think should be fixed before this paper is fully accepted. For example: in the Abstract/Objective section, “...to describe the a state-wide vaccination...” and in the first sentence of the second paragraph of the Introduction, “From the beginning of the pandemic, the Rhode Island collaborated...”

Conflicts of Interest

None declared.

Reference

1. Berk J, Murphy M, Kane K, Chan P, Rich J, Brinkley-Rubinstein L. SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study. JMIRx Med 2021 Sep 27;2(3):e30176 [FREE Full text] [doi: 10.2196/30176]

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Authors' Response to Peer Reviews

Authors' Responses to Peer Reviews of "In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study"

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Companion article: https://med.jmirx.org/2021/3/e24645/

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KEYWORDS

modified early warning score; MEWS; AVPU scale; Korle-Bu Teaching Hospital; KBTH; Ghana; critical care; vital signs; global health

This is the authors' response to peer-review reports for "In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study."

Round 1

The authors of the manuscript [1] are grateful to the editor and reviewers [2-4] for their invaluable input and feedback.

Reviewer AK

Major Comments

1. Thank you for your suggestion. We have simplified the statement of the objectives and have clarified the motivation for the study in the background, including explaining why both the modified early warning score (MEWS) and the limited MEWS (LMEWS) are included. We have revised the objectives both in the *Abstract* and in the main text. Mortality has been specified as the measured outcome of clinical deterioration and MEWS and LMEWS as the predictors. The *Methods* section has been clarified to explain the relationship between MEWS and LMEWS.
2. Thank you for your suggestion. We have modified the *Methods* section to make the statistical approach clearer to readers.
3. Thank you for your valuable suggestion. In all instances where comparisons are made, we have proceeded with MEWS followed by LMEWS, in that order.

Minor Comments

1. Thank you for your suggestion. We have addressed all grammatical errors.

Reviewer BO

Major Comments

1. Thank you for your suggestion. We have included a power and sample size calculation in the statistical analysis (see above response to Reviewer AK [2]). Typically, patients are discharged in possession of their paper health records (electronic health records are not used, limiting study size), accounting for the smaller number of available records; we clarified this as well. However, the power calculation puts the number we were able to review in context as being 50% more than would have been needed for a significant result.
2. Thank you for drawing our attention to the lack of emphasis on the efferent arm in the study. In fact, there is no rapid response team and therefore response to deterioration is not standardized. Thus, there may be biases in the survival (eg, sicker patients getting less attention because of their perceived poor prognosis). We have now included this in the discussion of the limitations of the study.

Reviewer CM

Major Comments

1. Thank you; please see the response to reviewer AK [2] as we have now included the power calculation in the *Methods* section.
2. Thank you for your observation. Missing data were only seen for the variable "organ system" and accounted for <1%. We have now included this in the *Statistical Analysis* section.
3. Thank you for your comments about blind assessment. Blind assessment of the predictors was not carried out as these are measured values retrospectively extracted from the record. Therefore, MEWS and LMEWS are not subjective—in real time when consciousness is assessed, there may be observer bias, but we did not have any such data. Since our data is randomly interpolated based on published population proportions, lack of blinding should not be an issue. We did perform a sensitivity analysis on the threshold for MEWS and LMEWS to test the published parameters in this population in case there was a source of bias that might make such cut-points variable.
4. Thank you for your observation. The maximum duration of follow-up was 32 days (included in the first paragraph of the *Methods*). We have included a flow chart of how the cohort was generated (Figure 2).
5. Thank you for your concern. The confidential nature of patient information, the protection of anonymity, and consent are paramount in record reviews; as such, ethical approval was obtained from the Institutional Review Boards (IRB) of Johns Hopkins University and the Korle-Bu Teaching Hospital (KBTH), and clearance was obtained from the Scientific and Technical Committee of the KBTH. Although reporting was anonymous, patients' records were not, so the researchers involved in data collection and handling needed to sign a confidentiality clause. This is now captured in the *Methods* section. Data access is limited to me; I abstracted the data and ran the study analysis for a limited duration.

Round 2

Reviewer CM

Major Comments

1. Thank you for allowing us to clarify the sample size question. The study proposal submitted to the IRB required a mandatory sample size calculation. As such, this was calculated a priori based on a publication by Kyriacos et al [5]. Based on this study, a power of 80% to detect clinical deterioration in postoperative inpatients, with a significance level of .05 and a delta value of 0.45, will give us a minimum sample size of 46. A post–data collection power analysis was also performed, based on a chi-square test comparing two independent proportions. Based on the resulting analytic sample of 112 participants, with 31 in the significant MEWS category and 81 in the nonsignificant MEWS category, our study achieves a power of 95% to detect a difference in outcome percentages of at least 37% between these two groups.
2. Thank you.
3. Thank you for your suggestion. As with all retrospective study designs, the measurement of outcomes occurred prior to the start of the study; as such, we had no control over how assessments were made including choice of measurement tools, whether tools were valid and reliable, and how results were interpreted and recorded. Blinding of outcome assessors serves to limit detection bias, but this was unemployable in our retrospective chart review, and the determination of which predictors to use in our analysis is based solely on the conceptual framework described in Figure 1.
4. Thank you for your ethical concerns and the effort to maintain the highest standards in clinical research. The confidential nature of patient information, protection of

anonymity, and consent are paramount in record reviews; as such, ethical approval was obtained from the IRB of Johns Hopkins University and the KBTH, as well as clearance from the Scientific and Technical Committee of the KBTH. In addition, we received a “waiver of documented (signed) permission,” which waives the requirements to obtain documented (signed) parent or guardian permission under the same conditions that apply to waiving signed consent from adult subjects. Documentation of assent and permission for adolescents 13 to 17 years of age involves being fully informed about a study and giving a signed assent to participation in a research study. They are, however, equally subject to a waiver of signed permission.

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis"

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KEYWORDS

COVID-19; health information; informational support; online health; online health communities; online platform; pandemic; social support

This is the authors' response to peer-review reports for "The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis".

Round 1 Review

Responses to Editors

M. Addressed [1].

Q. Addressed.

U. Addressed.

Reviewer AB [2]

Specific Comments

Major Comments

1. Addressed.

2. Addressed.

3. Addressed.

4. Addressed.

5. Addressed. What we were trying to convey is that people who offered information were more likely to post more than once judging by their action of responding to others' information requests.

6. Emotional support is an interesting topic, but it is out of the scope of this study.

7. We are unable to address this comment at this moment, as studies on other public health emergencies with comparable findings are limited.

Minor Comments

8. Addressed.

9. Addressed.

10. Addressed.

11. Addressed.

12. Addressed.

Anonymous [3]:

General Comments

1. Addressed.

2. We are unable to address this comment at this moment.

3. Please refer to the *Methodology* section, where previous studies on which our coding ontology is based are cited.

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1. Jong W, Liang OS, Yang CC. The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis. JMIRx Med 2021 Jul 22;2(3):e27485 [FREE Full text] [doi: 10.2196/27485]
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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study"

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KEYWORDS

cutaneous leishmaniasis; outbreak; Iraq; risk factors; risk; disease; infectious disease; disease prevention; prevention

This is the authors' response to peer reviews of "Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study."

Round 1 Review

Reviewer O

1. Thanks for raising this issue [1]. Being a control does not mean that they should not share the risk factors. A control here [2] is a person with no current lesions or history of lesions.

4. Would you please highlight the repeated paragraph, as we reviewed it more than once but did not find it.

Reviewer T

2. Because we have so many risk factors to talk about, we did not put the odds in the Abstract.

6. Because this study was part of an outbreak investigation, we did not use the traditional methods for sample size calculation. Instead, we included as many as possible of both cases and controls to have more insight into the risk factors.

8. If the reviewer can kindly point out which table he meant [3], we will correct it accordingly.

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study"

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KEYWORDS

social media; opinion; COVID-19; case study; polarization; communication; Twitter; echo chamber

This is the authors' response to peer-review reports for "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study."

Round 1 Review

Reviewer L

General Comments

First, we would like to thank this reviewer [1] for their insightful comments on our paper [2]. Although endogeneity may be an issue of concern for these types of framings, our methodology builds on numerous studies (now cited in the revised paper) that—after controlling for many correlated variables—show how the emergence of online echo chambers is partly due to contagion dynamics, partly due to homophily, partly due to influence effects, and is not simply explained by one single mechanism (eg, political ideology alone). Nevertheless, our strategy has been proven effective to separate network structure from information spread dynamics. In the revised manuscript, we explained the various assumptions of the model, some potential limitations related to endogeneity, and referred to work illustrating the robustness of the adopted approach.

The reviewer is absolutely correct in that the real-world political ideology distribution may not match the one on Twitter. In fact, in the revised manuscript, we now refer to various studies that confirmed the same skewed online ideology distribution we observed in our study of Twitter. Since the data we observed is heavily left skewed, we used binning to facilitate comparison between left- and right-partisan users. This approach is consistent with prior work, which we now cite in the revised paper. We should note that as our study is restricted to Twitter, any insights we gleaned should only be assumed to be applicable to this platform—an important limitation that we now underscore in the revised manuscript, which, however, we do not think takes away from the importance of our work given the prominence of Twitter in political and public health discourse. The findings of how people share political information on Twitter may not necessarily generalize to other online platforms (or real-world offline networks). In the future, we will study the cross-platform dynamics of political information sharing. We clarified these limitations in the revised paper.

To clarify, we are not hypothesizing or postulating that COVID-19 (mis)information spreads differently from other information. We believe that studying the spread of (mis)information in the case of COVID-19 specifically is paramount due to the fact that it can have tangible effects on public health and how people behave in the offline world, with respect to health behaviors (eg, mask wearing, etc). We have illustrated some of these specific examples in the work we recently published (cited and further detailed in the revised manuscript). As for this specific paper, to avoid duplication, we limited the amount of discussion on specific content. Conversely, we wanted to concentrate specifically on the interplay between political ideology and COVID-19 online discourse to characterize how pre-existing polarization due to political divide may further exacerbate the spread of misinformation or potentially alter the dynamics of (factual and/or incorrect) information in the presence of echo chambers. To our knowledge, our study is the first to characterize this interplay and its effect on COVID-19 online discourse.

Reviewer R

General Comments

We would like to thank this reviewer [3] for their feedback.

The motivation of the paper is to understand the role social media polarization plays in contributing (mis)information spread regarding COVID-19. This is of particular importance currently as inaccurate information may undermine public health efforts. Since prior works show that attitude toward COVID-19 is linked to political ideology, understanding the extent of polarization will be helpful for relaying information and debunking misinformation. In the revised manuscript, we added to the Introduction to strengthen our motivation for the paper, as well as to the Discussion for an in-depth discussion of the implications of our work.

We added more detailed explanations for all the models mentioned in the paper, including word embeddings, transformers, S-BERT, and network embeddings in the Methods section.

Specific Comments

Major Comments

1. Thank you for this comment. In our revised manuscript, we clarified the research questions to better reflect their relevance to COVID-19.
2. Thank you for this comment. In "Related Work," we have added explanations of word embeddings, transformers, and network embeddings so that readers can have a high-level understanding of these models.
3. Thank you for this comment. In our revised manuscript, we have added more layman explanations of each model when we introduce them in the Methods section. We believe this helps give readers a more intuitive understanding of word embeddings, transformers, etc.
4. Thank you for this comment. We removed the most bot-like users as is customarily done when dealing with potentially bot-infused data. If bots infiltrated users of different partisanship equally, then we expect to find a similar distribution of bot scores across all users. Since this is not what Figure 2B shows, it suggests there may be more right-leaning bots. In our revised manuscript, we clarified what we expect to find to highlight what we observed in terms of bot score distributions.
5. We thank the reviewer for this insight. In our paper, we use the term "partisan users" to refer to users who are strong supporters of a party, which could be very left or very right. As such, this is corroborated precisely by the U-shaped distributions in Figure 3B, C, and D. Figure 3A and E only shows that left-leaning users are influential, which could be attributed to Twitter's left bias as a platform (giving more verified status to left-leaning users) and the larger left-leaning user base. In our revised manuscript, we added a suggestion that the phenomenon could be attributed to the large left-leaning user base.
6. Thank you!
7. Thank you!
8. We agree with the reviewer's comment. We have added a paragraph on the implications of our work for health and wellness.

Minor Comments

1. We defined "AUC" along with a short explanation of why it was chosen (over accuracy, etc).
2. "NLP" has been replaced with "natural language processing."
3. The reviewer is right; this mistake in the caption has been corrected.
4. Thank you. You can find out more about this from: Garimella K, De Francisci Morales G, Gionis A, Mathioudakis M. 2017. Quantifying controversy on social media. ACM Trans Soc Comput, 1 (1) Article 1. DOI: 10.1145/3140565

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1. Gadarian S. Peer Review of "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study". JMIRx Med 2021 Aug;2(3):e32268 [FREE Full text] [doi: 10.2196/32268]

2. Jiang J, Ren X, Ferrara E. Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study. JMIRx Med 2021 Aug;2(3):e29570 [FREE Full text] [doi: 10.2196/29570]
3. Buente W. Peer Review of "Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study". JMIRx Med 2021 Aug;2(3):e32267 [FREE Full text] [doi: 10.2196/32267]

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Authors’ Response to Peer Reviews

Authors’ Response to Peer Reviews of “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

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(JMIRx Med 2021;2(3):e31568) doi:10.2196/31568

This is the author’s response to peer-review reports for the paper “Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method”

This paper [1] first underwent review as two separate manuscripts: one on transfusion adverse events and the other on time-based adverse events.

In addition to responding to the reviewers’ comments [2-5], we made the following changes:

Round 1 Review: Transfusion Adverse Events

Anonymous [2]

General Comments

1. We believe our title matches the study contents. We do not understand how the results of using a new method, applied in a new area (blood transfusion adverse events [AEs]), are “self-evident.” We prefer to keep the title unchanged.
2. Please see the new subsection “Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling” at the end of the *Discussion* section:
   “We were unable to find published instances of LDA topic modeling applications for adverse event detection.

Furthermore, we found none that apply LDA topic modeling to words or phrases in documents in the group of interest that are filtered to terms that most significantly distinguished a patient group of interest from a comparison group. This filtering process was essential for identifying topics describing the unique qualities of transfused vs nontransfused groups. Also, to our knowledge, we are the first to check the interpretation of documents with large numbers of topics with nontrivial scores."

3. Please see the new subsection "Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling" at the end of the *Discussion* section for a summary of the use of latent Dirichlet allocation (LDA) topic modeling in electronic health record (EHR) data and how the Shakespeare method compares.
   We agree that natural language processing (NLP) is indispensable to finding potential AEs in unstructured text. Please see the new subsection "Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling" at the end of the *Discussion* section for the new text:
   "LDA topic modeling has been used for a variety of NLP tasks [6,7] (although it can also be used on other high-dimension data) such as text classification and filtering [8]."
   We state in the *Conclusions* section that the final step, manual interpretation of selected original notes, could benefit from adaptation of more sophisticated NLP methods.
4. As described, LDA topic modeling is one step in the Shakespeare method.
   In the *Discussion* section, "Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling subsection, we now say:
   "We were unable to find published instances of LDA topic modeling applications for adverse event detection. Furthermore, we found none that apply LDA topic modeling to words or phrases in documents in the group of interest that are filtered to terms that most significantly distinguished a patient group of interest from a comparison group. This filtering process was essential for identifying topics describing the unique qualities of transfused vs nontransfused groups. Also, to our knowledge, we are the first to check the interpretation of documents with large numbers of topics with nontrivial scores."
5. Thank you for pointing out this error. We have made the correction to five steps.
6. We have clarified this sentence in the *Introduction* section, "EHRs for Postmarketing Surveillance" subsection, and made a similar change to the *Background* section in the abstract. The new paragraph is:
   "Many methods for finding AEs in text [9-34] rely on predefining possible AEs before searching for prespecified words and phrases or manual labeling (standardization) by investigators. Crucially, events described in text may not necessarily be attributed to AEs [19,35,36]. We wanted to develop a method to identify possible AEs, even if unknown or unattributed, without any prespecifications or standardization of notes."

Anonymous [3]

General Comments

We have clarified our statements in the *Introduction* section, "Selection of Case of Blood Transfusion" subsection, to indicate that some transfusion AEs were established in the literature by 2002 while others were gaining recognition over the time of the data set (2001-2012).

Specific Comments

Major Comments

1. We are in the process of publishing the code and expect to have a permanent citation in a few weeks. We now cite it as reference 54 in the *Methods* section, "The Shakespeare method" subsection.
2. The details are in another paper we cited (reference 57).
3. We added some explanation to the *Methods* section, "Step 4. Model Topics" subsection:
   1. "An important consideration for LDA is that the number of topics must be selected a priori. The results of topic modeling change depending on the number of topics assigned to a corpus—this is an iterative (hyperparameter tuning) process that requires human judgment to interpret the topics (based on the top terms in each topic) and determine which number of topics best fits the corpus. With too few topics assigned, topics are not cohesive and do not add any clarity or information to an analysis. With too many topics assigned, "incoherent" topics that do not capture terms common to the member documents proliferate; also, useful topics are likely split among smaller, more specific topics, although that does not limit the ability to analyze true clusters in the corpus.
      To tune the hyperparameters of the LDA model, we calculated models with the following numbers of topics: 25, 35, 45, 55, 65, 75, 85. We observed (data not shown):
      In the *Discussion* section, "Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling" subsection, we added:
      "The chosen number of topics was effective for identifying a range of PTAEs. Evaluation of the overlap of topics and contents of documents identified for varying numbers of topics has not been reported in the literature. Our iterative approach to evaluating different hyperparameters demonstrated to our satisfaction the relative stability of PTAEs indicated by topics.
      We determined the number of topics based on our experience of tuning the hyperparameters, the number of TAEs reported in the literature, and the complexities of critical care patients. We were satisfied with the number because there was both overlap of topics that simultaneously had high word and document scores and some incoherent topics with low scores. As the number of topics gets too large, additional topics are uninterpretable, and that as data set size increases, more robust topics are generated [37]."

2. In the *Discussion* section, "Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling" subsection, we added:
   "Systematic evaluation of the number of topics and other hyperparameters is always necessary for LDA topic modeling in a new setting."
3. In the *Methods* section, "Step 4. Model Topics" subsection, we added:
   "Topic modeling is an unsupervised method commonly used in NLP to extract the most relevant terms for each topic (cluster) of similar documents [6,7]. We chose latent Dirichlet allocation (LDA) [8] to accomplish topic modeling of the T documents. LDA is a generative probabilistic model that results in interpretable dimensionality reduction, which means that we reduced 41,664 terms to 45 topics for our data. A topic is a multimodal distribution of terms over an entire vocabulary (in our case, all the filtered terms). A topic consists of co-occurring terms in this corpus of T documents. Each document can have a mixture of these topics. Each topic contribution in a document is a probability (we refer to this as a document topic score); thus, the scores of all topics for a document sum to 1 (see Figure 3D)."

4. In the new *Discussion* section, "Use of Classification to Filter Document Vectors" subsection, we added:
   "As noted before, we were initially surprised that primarily unigrams (and not the longer sequences) appeared to play a significant role in distinguishing transfusion from control texts. We believe it is possible that enough unigrams that were part of meaningful phrases were also in other phrases or were significant on their own to result in relatively higher scores. For example, although "mechanical ventilation" conveys more meaning than just "mechanical" or "ventilation," each word occurs singly or in phrases other than "mechanical ventilation." Because bigrams and phrases were important in other LDA studies [38,39], we do not conclude that our unigram finding is necessarily applicable to other study settings. In this data set and blood transfusion situation, including only unigrams would not be expected to have changed the particular unigrams selected during the ensemble classification step. In other studies, it might be important to include n-grams where n>1."
   In the new *Discussion* section, "Use of Classification to Trim Document Vectors" subsection, we added:
   "In this data set and blood transfusion situation, including only unigrams would not be expected to have changed the particular unigrams selected during the ensemble classification step. In other studies, it might be important to include n-grams where n>1."
   In the new *Discussion* section, "Use of Classification to Trim Document Vectors" subsection, we added:
   "Because bigrams and phrases were important in other LDA studies [38,39], we do not conclude that our unigram finding is necessarily applicable to other study settings."
5. We agree. In the *Conclusion* section, we added:
   "We present our use of the Shakespeare method for a different surveillance question elsewhere [40]."
6. The renamed *Methods* subsection "Step 3. Extract Significant Terms" now explains the filtering (trimming) method in more detail.
   In the new *Discussion* section, "Use of Classification to Filter Document Vectors" subsection, we added:
   "Filtering the vectors to only terms that were important for focusing the topics on clinical conditions specific to transfusion, including reasons for and consequences of transfusion, was important for identifying PTAEs."

Minor Comments

1. We simplified the statement to:
   "We chose the case of transfusion adverse events (TAEs) and potential TAEs (PTAEs) because new TAE types were becoming recognized during the study data period, so we anticipated an opportunity to find unattributed TAEs in the notes."
2. Thank you for finding this mistake, which we corrected to "five steps."
3. Thank you for finding this typo in the *Conclusion* section. "Her" should have been "EHRs" and has been corrected.

Round 2 Review: Transfusion Adverse Events

We finalized the citation for the Shakespeare method software in reference 54, and submitted manuscripts with and without tracked changes that show our changes.

We believe we addressed the reviewer's [2] concerns. We apparently did not because some of the prior concerns remain in this review round. We are puzzled by the newly restated comments and would like more clarity on his/her points so that we can be sure to address the concerns. We provide more details about our questions as individual responses below.

Anonymous [2]

General Comments

We disagree that the Shakespeare method is an alternative to NLP, because we leverage NLP, which includes many methods. As part of the Shakespeare method, we used the following NLP methods: n-gram formation, count vectorization, supervised learning, and LDA topic modeling. We mentioned another NLP method, word/phrase searches, in the *Introduction* section, thus demonstrating our understanding of that method; we also discussed why we did not choose to use it. To form the transfused and nontransfused groups, we created and used a dictionary of transfusion terms. Outside of our paper, we are, indeed, familiar with many other NLP methods (stemming, sentence boundary recognition, part-of-speech tagging, parsing, semantics, sentiment analysis, word sense disambiguation, language models, language translation, and neural network–based machine learning) that are a menu of methods that may or may not be useful for a particular application. We do not understand why the reviewer thinks we do not understand NLP, why the reviewer thinks NLP is the preferred alternative to the Shakespeare method, and why that means we might be making mistaken conclusions.

Specific Comments

Major Comments

1. The reviewer seems to agree that the dictionary method relies on predefined possible AEs, which could rely on, for example, the Unified Medical Language System vocabulary list and could miss important terms. We are proposing an alternative method to find both expected and unexpected possible AEs, as we state in the *Introduction* section. We do not understand what the criticism is.
2. We agree and state in the *Discussion* section that in addition to possibly causal TAEs, the Shakespeare method identified reasons for transfusion, consequences of reasons for transfusion, and possibly noncausal PTAEs. We agree and state that the PTAEs need manual review to distinguish among these groups. As we state, the difference from the NLP dictionary method is that the Shakespeare method found PTAEs that were not described as related to transfusion in the notes or billing codes. The dictionary method cannot find potentially important terms and phrases that are not in the dictionary.
3. The application of the Shakespeare method to blood transfusion is a use scenario, so we do not understand why the reviewer thinks a potential use scenario needs to be included; however, we did include reference 107 as an additional scenario. We do not understand why or how manual review is an example of a potential use scenario. We reported our manual review of the results, so we do not understand what the reviewer means by asking "will more manual reviews be needed for the results."

Round 1 Review: Time-Based Adverse Events

Reviewer CD

General Comments

1. We changed the beginning of the sentence to "We examined whether."
2. Thank you!
3. We already stated some limitations. In the subsection "Discussion of Time Periods Case," we pointed out that removing numerals from alphanumeric words had resulted in the creation of a "junk" topic that we would not recommend doing again. Additionally, in the *Conclusions* section, we mentioned that further development of tools for evaluating the reports would be very helpful. Furthermore, in the subsection "Use of Classification to Filter Document Vectors," we added our observation that only unigrams survived the classification process in both the transfusion and time periods cases, and declined to recommend only using unigrams in other settings.

Reviewer CI

General Comments

We appreciate the reviewer's praise and hope we have satisfied the concerns.

Specific Comments

Major Comments

1. We agree that it would be great to know the accuracy of the Shakespeare method. Please see "Top-Scoring Documents for Each Transfusion Topic," where we reviewed a random selection of transfusion admissions and compared them to the transfusion documents with high topic scores.

Minor Comments

1. We trimmed the list of keywords.
2. We are satisfied with the current state of the *Conclusions* section.

Conflicts of Interest

None declared.

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1. Bright RA, Dowdy K, Rankin SK, Blok SV, Palmer LAM, Bright SJ. Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method. JMIRx Med 2021 Aug 11;2(3):e27017 [FREE Full text] [doi: 10.2196/27017]
2. Anonymous. Peer Review of "Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method". JMIRx Med 2021 Aug 11;2(3):e31547 [FREE Full text] [doi: 10.2196/31547]
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Abbreviations

AE: adverse event
EHR: electronic health record
LDA: latent Dirichlet allocation
NLP: natural language processing

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Authors' Response to Peer Reviews

Author's Response to Peer Reviews of "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study"

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KEYWORDS

COVID-19; pandemic; vaccination; vaccine; strategy; vaccination strategy; hospitalization; mortality rates; older adults; mortality

This is the author's response to peer-review reports for "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study."

Round 1 Review

The author of the manuscript [1] is grateful to the editor and reviewers [2,3] for their invaluable input and feedback.

Anonymous Reviewer [2]

Specific Comments

Major Comments

1. Thank you for your comment. I have updated the title based on the suggestion.
2. Thank you for your suggestion. I have added arguments and statistics to the Introduction.
3. I have developed a section for measures.
4. Thank you for your recommendation. I have developed a Methods section based on your suggestion.
5. Thank you for your comment; it is an important point. My preliminary analysis showed that the results were fairly consistent up to the first month of vaccination. Additionally, it takes time to see the effectiveness of vaccination. Therefore, this study began on the first day of vaccination.

Minor Comments

1. Thank you. I have reviewed the writing and have improved it.
2. I have changed it.
3. I have changed it.
4. Thank you. I have changed the language.

Anonymous Reviewer [3]

Specific Comments

Major Comments

1. I have added in a study that discusses another methodology, which was different from the US vaccine policy.
2. Thank you. I have developed a section for measures and statistical analysis.
3. Thank you. I have added a section on implications.

Minor Comments

1. I have reviewed the paper's write-up.

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2. Anonymous. Peer Review of "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study". JMIRx Med 2021 Aug;2(3):e32461 [FREE Full text] [doi: 10.2196/32461]
3. Anonymous. Peer Review of "The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study". JMIRx Med 2021 Aug;2(3):e32462 [FREE Full text] [doi: 10.2196/32462]

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis"

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KEYWORDS

infectious disease; COVID-19; strain; virus; Romania; transmission; spread; mutation; impact; case study; genome; sequencing; genetics; epidemiology; variant; virology; lineage

This is the authors' response to peer-review reports for "Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis."

Round 1 Review

Responses to Reviewers

Reviewer 1 [1]

1. The manuscript [2] needs some revision of English. It is generally well prepared, but there are several instances in which it could benefit from a professional revision.

Response: Per the reviewer's [1] comment, we have revised the manuscript throughout with an eye toward improving the English, format, and syntax.

Reviewer 2 [3]

1. In the Materials and Methods section, authors mentioned that "Twenty samples, collected from patients in the cities of Cluj, Craiova and Suceava counties from Romania were selected for analysis, including patients with possible contacts with UK infected individuals." In the Introduction section, the authors also described the first few possible UK variant cases in Romania.

Are these 20 cases sequenced by authors related to those cases mentioned in the Introduction? If not, can authors provide some details about the subjects' past travel history? For example, did they stay in UK for more than 2 weeks before they traveled to Romania? And when were these samples collected? The timeline is important to understand how the disease spread and whether they are the first strains of B.1.1.7 in Romania.

Response: We thank the reviewer [3] for his/her comment. The 20 cases sequenced were selected by our laboratory in Suceava as part of the ongoing effort of monitoring SARS-CoV-2 spread in Romania. Among the 20 samples, one—later referred to as EPI_ISL_869241 (Suceava)—was carrying the new UK strain.

The other four samples presented in the Results section were sequenced by other laboratories in the country, so there is no connection with the 20 samples sequenced by us.

Information regarding the travel history of the patients was added, where appropriate. Sample collection dates were added to the table in Multimedia Appendix 1.

2. The authors claimed that "the Romanian strains bearing the particular ORF8 mutations described above clearly originated in the UK, which is also supported by the fact that the patient from Suceava county arrived in Romania from the UK." I have a similar question about the travel details of the patient as well as the timeline.

Response: Information regarding the Romanian patient bearing the ORF8 mutation was added in the Results section.

3. From a public health standpoint, how did the authors deal with the "news" of the new variant? Was there any communication with local officials or support for contact tracing?

Response: This information was added to the text. In addition, we mentioned that our laboratory is 1 of 4 (at the moment of writing the paper) that reports weekly genomic data to government agencies. These data are then integrated with epidemiological data to inform public health agencies.

4. In the Discussion section, the authors described that "Many European countries, including Romania, lag in genomic sequencing". Can the authors provide more details about why Romania lags in genomic sequencing for COVID? For example, cost, equipment, access to labs/institutes. This can help readers and other researchers to understand the issue.

Response: The information was added to the text.

References

1. Apetrei C. Peer Review of 'Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis'. JMIRx Med 2021 Aug;2(3):e32296 [FREE Full text] [doi: 10.2196/32296]
2. Lobiuc A, Dimian M, Sturdza O, Filip R, Covasa M. Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis. JMIRx Med 2021 Aug;2(3):e28049 [FREE Full text] [doi: 10.2196/28049]
3. Guo L. Peer Review of 'Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis'. JMIRx Med 2021 Aug;2(3):e32299 [FREE Full text] [doi: 10.2196/32299]

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Authors' Response to Peer Reviews

Author's Response to Peer Reviews of "Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study"

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Companion article: https://med.jmirx.org/2021/3/e31927/

Companion article: https://med.jmirx.org/2021/3/e28843/

(JMIRx Med 2021;2(3):e31910) doi:10.2196/31910

KEYWORDS

COVID-19; pandemic; public health; mortality; infection; risk; risk factors; age; epidemiology; infectious disease

This is the author's response to peer-review reports submitted for the paper "Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study".

Round 1 Review

Author's response to the review of the manuscript:

1. The Abstract and body of the text of the manuscript [1] have been restructured to conform with the standard format of the journal (ie, Background, Objective, Method, Results, Conclusions).
2. The revised text is based on the updated manuscript as recommended by the editor.
3. Figures that were suggested for deletion have been removed. All figures have been sized and reformatted per journal policy.
4. All footnotes have been removed, and the relevant information has been made part of the text or a numbered reference.
5. Equations are numbered for appropriate reference in the text.
6. I have added some quantitative values in the Results section of the Abstract.
7. I have removed the author-defined acronym, "CFR," for apparent case fatality ratio.
8. Two references have been added in the Summary section.
9. The Summary and Conclusions have been expended to suggest potential effects of new SARS-CoV-2 variants.

Conflicts of Interest

None declared.

Reference

1. Barletta WA. Risk factors of SARS-CoV-2 infection: global epidemiological study. JMIRx Med 2021 Aug 18;2(3):e28843 [FREE Full text] [doi: 10.2196/28843]

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Authors' Response to Peer Reviews

Authors' Responses to Peer Reviews of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study"

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Companion article: https://med.jmirx.org/2021/3/e31896/

Companion article: https://med.jmirx.org/2021/3/e29062/

(JMIRx Med 2021;2(3):e31892) doi:10.2196/31892

KEYWORDS

respiratory; medicine; nasal therapy; COVID-19; mechanical ventilation; ventilators; mortality; morbidity; intubation

This is the authors' response to peer-review reports for the paper "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study".

Round 1 Review

Reviewer G

Specific Comments

Major Comments

Thank you, Reviewer G [1], for your comments on our paper [2]. We appreciate your wonderful feedback.

1. The Methods section was modified to clarify the inclusion criteria further. There were two stages to our screening process; hence, the inclusions and exclusions were written to reflect a step-by-step method of achieving the final N.

The CONSORT (Consolidated Standards of Reporting Trials) diagram at the end further clarifies the process.
2. The 35 L/min flow was the starting point for the HFNT (high-flow nasal therapy) initiation protocol. Immediately, adjustments were made based on the patient's tolerance and oxygenation. The "33.5, SD 11.7" value in the Results section is the average first flow rate documented in our Electronic Medical Record (EMR).
3. The first two paragraphs were written as a summary of the overall results as stated by the journal guidelines for the discussion. We revised the first two paragraphs to make the summary more concise.

Minor Comments

1. The error was corrected.
2. Those with high clinical suspicion were indeed negative by PCR (polymerase chain reaction). This was added to the Methods section.
3. The confidence interval was 0.994 to 4.591. We adjusted the language of the paper to reflect the above results in a more appropriate way.
4. In other words, our analysis showed that any lack of improvement or negative change in ROX (ratio of oxygen saturation) index was predictive of intubation. The sentence was rewritten to explain this better.
5. We will change the reported values to AUC (area under the receiver operating characteristic curve) in the paper.

Reviewer R

Major Comments

Thank you, Reviewer R [3], for your wonderful comments. We appreciate your feedback.

1. We have changed the objective to be distinguishable from the key question.
2. The paragraphs were separated to highlight the two sections.
3. We refined the Methods section with the goal of improving it. The subsections were redefined to improve this section. The treatment protocols will be moved to the supplementary materials section. We are happy to redact more, if necessary.
4. This was a retrospective observational study. Hence, the authors made no contribution to the actual treatments of patients. We used the data available to us afterward to evaluate the ROX index. It was not until we had analyzed our data that we started using the ROX index in our intensive care unit routinely.
5. Noted. Changes have been made as per the suggestions.
6. Our Discussion section includes a section specifically on strengths and limitations. We are happy to separate it out as a different section, if needed.
7. The ROX index is a noninvasive score that can easily be applied at any hospital without the addition of any new parameters. It includes pulse oximetry, fraction of inspired oxygen, and respiratory rate. All hospitals will always have these parameters available to them. Thus, ROX gives physicians a noninvasive tool during a pandemic when minimizing exposure is key to preventing transmission.
8. Our figures were submitted separately from the main submission per the submission guidelines. We will include all the images with the main document in the revised version.
9. We are happy to provide our data analysis to the reviewer separately, if needed. We feel discussing all the details of how we generated our results step by step will dilute the importance of the results highlighted in the Results section. Moreover, we feel this might not be ideal for a reader who has only a basic statistical background.
10. All the results mentioned in the paper have been presented in textual and graphical forms (graphs and tables), wherever applicable. The majority of the discussion involves a review of previous data and an explanation of our results, which will be difficult to write in a tabular form. We are happy to rearrange portions in a tabular format if the reviewer would be kind enough to point out a specific section.
11. As mentioned above, we are happy to provide all the derivative equations to the reviewer if that helps. However, we felt that some of these derivatives are complex and take away from the results of the paper. Moreover, the majority of studies written usually do not provide the actual calculations of their results. Most studies have the data analysis available upon request, which we are happy to provide.
12. Thank you.
13. Thank you for the wonderful feedback.

Minor Comments

1. The majority of typos and grammatical issues have been corrected.
2. The article was restructured according to the points made by the reviewer.
3. We will review the guidelines again and try to conform to those guidelines.
4. The images will be made available at the end of the paper per the submission guidelines.
5. We are happy to provide data sets upon request. We do not want our data sets to be publicly available, but we are happy to share them on a case-by-case basis. We do mention this in our paper.
6. We corrected this section to accommodate your request.

Conflicts of Interest

None declared.

References

1. Sehgal M. Peer review of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study". JMIRx Med 2021 Aug 18;2(3):e31896 [FREE Full text] [doi: 10.2196/31896]
2. Patel M, Chowdhury J, Mills N, Marron R, Gangemi A, Dorey-Stein Z, et al. Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study. JMIRx Med 2021 Aug 18;2(3):e29062 [FREE Full text] [doi: 10.2196/29062]
3. Roy A. Peer review of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study". JMIRx Med 2021 Aug 18;2(3):e31895 [FREE Full text] [doi: 10.2196/31895]

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Authors' Responses to Peer Reviews of "Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study"
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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-sectional Web-Based Study"

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Companion article: https://med.jmirx.org/2021/3/e28158/

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This is the authors' response to peer-review reports for "Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-Sectional Web-Based Study".

Round 1 Review

The responses and changes made to the manuscript in reply to the reviewers' comments [1,2] are below:

Major comments

1. The novelty of this study [3] is justified in the manuscript in detail.
2. The grammatical errors in the manuscript have been corrected.
3. The keywords have been corrected.
4. The *Introduction* part has been revised with all the relevant information provided during the data collection time in India.
5. The literature review for this study has been expanded with relevant scholarly articles.
6. The concurrent validity of the Fear of COVID-19 Scale with the Generalized Anxiety Disorder-7 scale and the Patient Health Questionnaire-9 have been compared with the available prior evidence.

Minor comments

1. Footnotes have been provided for the abbreviations in the table.
2. Other correlation values have been added to Table 4 along with *P* values.
3. For very small *P* values, *P*<0.001 has been written.

4. For Tables 4 and 5, the format has been corrected with clarity and written as per journal guidelines.
5. Less scholarly journal articles have been removed and references are written as per guidelines.

Round 2 Review

Minor comment

1. * and *** to indicate significance levels in the Abstract have been removed.
2. GAD-7 is the Generalized Anxiety Disorder Scale and PHQ-9 is the Brief Patient Health Questionnaire; this is indicated clearly in the main text in addition to the footnotes of the table. Different terms for the two scales have been removed and corrected.
3. Articles about university students regarding their psychological distress have been cited more, including Pramukti et al [4].
4. The reference category for the categorical independent variable is indicated in Table 4.

References

1. Anonymous. Peer review of "Exploring the Utility of Google Mobility Data During the COVID-19 Pandemic in India: Digital Epidemiological Analysis". JMIRx Med 2021 Sep 02;2(3):e32952 [FREE Full text] [doi: 10.2196/32952]
2. Anonymous. Peer review of "Exploring the Utility of Google Mobility Data During the COVID-19 Pandemic in India: Digital Epidemiological Analysis". JMIRx Med 2021 Sep 02;2(3):e32953 [FREE Full text] [doi: 10.2196/32953]
3. Chaudhary AP, Sonar NS, TR J, Banerjee M, Yadav S. Impact of the COVID-19 pandemic on the mental health of college students in India: cross-sectional web-based study. JMIRx Med 2021 Sep 02;2(3):e28158 [FREE Full text] [doi: 10.2196/28158]
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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach"

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Companion article: https://med.jmirx.org/2021/3/e29844/

(JMIRx Med 2021;2(3):e33217) doi:10.2196/33217

This is the authors' response to peer-review reports for the paper "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach".

Round 1 Review

Authors' Response to Anonymous [1]

Major Comments

1. The formatting has been changed to make the paper [2] more concise and in line with proper journal formatting standards.
2. We constructed our tree using the maximum likelihood method. Maximum likelihood is a probability-based phylogenetic tree construction method. It allows the user to choose a model of evolution and constructs the tree based on the probabilities associated with the sequences. The maximum likelihood method considers a tree more preferable if the sequences are more probable in that tree. Thus, it is a sequence-based tree.
   - Lines 15-26 of page 9: We have added to the paper our reasoning and relevant literature references explaining how sequence-only–based screening is sufficient to link immunology in our study.
3. The number of initial candidates studied, numbers of candidates selected/screened, and the reasoning behind their selection has been added for each step where screening took place.
   - Lines 9-14 of page 9: Screening based on tree
   - Lines 5-7 of page 22: Screening from docking and binding energy

Minor Comments

1. Page 10: A higher quality version of the phylogenetic tree was added to the manuscript, and squares were used for highlighting.

2. Lines 7 and 8 of Page 9: The mistakes were corrected, and the positions of the commercially available (at the top) and our candidate (at the bottom) organisms mentioned in accordance with the tree (and its legend) is present in the manuscript.
3. Sites were identified by superimposing and aligning the candidate sequences with the sequence of 1nns asparaginase using PyMOL. This has been explained in the Methods section (line 11 of page 7).
4. Page 19: * was replaced with proper multiplication signs in the table.

Authors' Response to Reviewer S [3]

Major Comments

1. Lines 11-14 of page 6: An explanation of Blastp was added. The purpose of using blastp in this method is explained.
2. Lines 4-10 of page 23: A figure of the sequence alignment of our optimal enzyme candidates and the *E coli* (subject) sequence has been added with an explanation.
3. Lines 8-25 of page 29: A segment regarding relevant studies that support our findings was added to the Discussion section. The added segment uses previous studies on enzyme screening/optimization, especially L-asparaginase, to support the tools we used and the results we have obtained.
4. Line 17 of page 31: The Conclusion section was edited to be clearer on the finding of this study. A proper summery of our work and our results were added.

Minor Comments

1. Lines 5-7 of page 7: The full forms and meaning of DOPE and SOAP have been added.
2. Line 6 of page 30: The 6 species with Kms have been added to the Discussion section.
3. Line 26 of page 30: The sentence was rewritten to be clearer on its meaning.

Authors' Response to Reviewer T [4]

Major Comments

We have edited all our figures to remove unnecessary parts and make them appropriately compact. Several related figures have been combined together for compactness.

Minor Comments

1. Line 2 of page 3: A peer-reviewed paper was cited.
2. A space was added between the text and citation.
3. Lines 7-11 of page 3: The paragraph was rewritten. A better and more contextual opening sentence was used.
4. Line 26 of page 4: Analyses was changed to analyze.
5. Pages 12 and 13: Plot labelled for species; figures edited to only include relevant information.
6. Pages 14-16: Arrows added to highlight points.
7. Pages 14-16: The three figures were combined and edited.
8. Pages 25 and 26: Species' names were added to each panel. Multiple figures were combined and edited to be more compact.
9. Page 27: All figures were combined into one. The figures were edited to be more compact.

References

1. Anonymous. Peer review of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach". JMIRx Med 2021 Sep 7;2(3):e33214 [FREE Full text] [doi: 10.2196/33214]
2. Baral A, Gorkhali R, Basnet B, Koirala S, Bhattarai HS. Selection of the optimal L-asparaginase II against acute lymphoblastic leukemia: an in silico approach. JMIRx Med 2021 Sep 7;2(3):e29844 [FREE Full text] [doi: 10.2196/29844]
3. Hardika N. Peer review of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach". JMIRx Med 2021 Sep 7;2(3):e33215 [FREE Full text] [doi: 10.2196/33215]
4. Mohammad A. Peer review of "Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach". JMIRx Med 2021 Sep 7;2(3):e33216 [FREE Full text] [doi: 10.2196/33216]

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Authors' Response to Peer Reviews

Author's Response to Peer Reviews of "A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development"

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KEYWORDS

epidemiology; computational; model; COVID-19; modeling; outbreak; virus; infectious disease; simulation; impact; vaccine; agent-based model

This is the author's response to peer-review reports for "A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development".

Round 1 Review

The authors of the manuscript [1] are grateful to the editor and reviewers [2,3] for their invaluable input and feedback.

Anonymous [2]

Major Comments

1. I agree with the reviewer, but the underlying idea of the paper is to create a model using just simple open-access data, like population density and estimations made on publicly available ensemble data (eg, number of contagions, number of deaths, etc). The author knows perfectly that this amount of data is not sufficient to fully depict epidemic behavior, but the idea is that on a very large scale, this information along with a fitting on the free parameters can approximate epidemic behavior. This has been explained better:

"The random walk behavior must be intended as an approximation of the actual motion of people during the day; this approximation was introduced to reduce the amount of information required to run the model and is widely used in many fields of science (eg, ideal gas theory)…"

2. References to previous models have been added:

"In particular, agent-based modeling in epidemiology has been used widely in the past. However, due to its computational limitations, approaches based on differential equations like SIR (susceptible-infected-recovered) models have often been preferred. The latest advances in computer science and engineering and the outbreak of COVID-19 have led to the use of ABM for simulating small community epidemic behavior…"

3. The model has been compared with an SIRD (susceptible-infected-recovered-deceased) model fitted on the outbreak scenario in terms of the rooted mean squared error in the infected, recovered, and deaths curves, outperforming the SIRD model in fitting the recovered curve and obtaining higher but comparable distances in the infected and deaths curves. It must be pointed out that even if the performance of the proposed model is comparable to the SIRD model, it has many advantages over the SIRD model (as pointed out in the paper):

"The proposed model has been compared with the classical SIRD model [33] fitted with parameter exploration on outbreak data. The result can be seen in Figure 2. It can be seen that the results are comparable: in terms of the rooted mean squared error from the data, the SIRD model has an error of 150 for the infected, 71 for the recovered, and 18 for deaths. The proposed model exhibits an error of 535 for the infected, 58 for the recovered, and 34 for deaths. This means that the model has comparable performance with the SIRD model (outperforming in the recovered), but it is not ODE mediated, so it is suitable to test alternative scenarios."

4. This is true, but it can be approximated (like in ideal gas theory) with the idea that even if the behavior of each person is not random, the interaction for large numbers of people can be approximated with a random walk. Future work could aim to reconstruct people's behavior in a more realistic way; however, it would require additional data (usually covered by privacy laws) that are not in the public domain. This would, unfortunately, contradict the aim of the paper of constructing a model based on public-domain information, making the model available for anyone. So, the random walk should be intended as an assumption and not as a ground truth.

"The random walk behavior must be intended as an approximation of the actual motion of people during the day; this approximation was introduced to reduce the amount of information required to run the model and is widely used in many fields of science (eg, ideal gas theory)…"

5. The following has been added to the paper:

"The creation of this algorithm was a challenging aspect of this study. The idea was to use matrix optimization in order to speed up the computation. The territory was subdivided into 20-km–long cells, and the cells in every frame were completely independent, with the supposition that, on average, every cell contains *m* people. In order to compute the distance between all nodes in the network, we had to compute the order of N^2 pairwise distances.

"With this scheme, we had to only compute the order of m^2 distances for each block multiplied by the number of blocks (which is about *N/m*) that is an order of *Nm*. Considering *m* small in comparison with *N*, it can be said that the scheme has a complexity near the order of *N* (for large *N* and small *m*). However, determining in which cell a person is located was also challenging because of the large size of the population. For these reasons, a simple grid scheme was used to locate nodes inside the cells. We used the following idea—supposing a segment from 0 km to L_C=2 km with N_c=4 cells:

1. From 0 km to 0.5 km
2. From 0.5 km to 1 km
3. From 1 km to 1.5 km
4. From 1.5 km to 2 km

"If, for example, the point *p*=0.6 km needed to be located, the formula used to calculate this would be $id_p=ceil(N_c p/L_c)$. The result is 2, indicating the second cell. Applying this formula for the x-axis and y-axis allows the algorithm to locate people in the cells. Although this algorithm may appear to be simple, it requires few calculations to be computed, which can make a substantial difference when a large number of agents is concerned."

6. The density of the population has been taken into account from publicly available data. Additionally, the variation in the density of the population has been taken into account, but because of the limited length of the daily path of the nodes in their random walk, the variability in population density is not very notable. This work has not accounted for the demographic profile of the population, but because of the agent-based nature of the model, it could be easily implemented (given an accurate spatial demographic profile and detailed demographic-dependent statistics about COVID-19, which are not publicly available to the best of the author's knowledge). This has been pointed out in the following:

"The displacement of the particles follows the density of inhabitants in Lombardy (ie, publicly available data). Even if more accurate data on people displacement and movement could be used, privacy concerns may not permit the open-source and open-access distribution of this data."

Minor Comments

1. The paper has been revised.

2. The abstract has been revised.

3. Fixed in the text:

"Figure 1: The 3-layer structure of the model. The first layer, environment and agents, represents the motion of the inhabitants. The second layer represents social interaction between people in terms of collision detection. The third layer represents the virus dynamic in terms of epidemic behavior."

4. The paper has been organized into Introduction, Methods, Results, and Discussion.

Anonymous [3]

Major Comments

1. The language of the paper has been revised.

2. The model has been depicted more clearly in terms of a mathematical description. The model, as it is, outlines a general procedure to approach an epidemic. Most of the data used to create the model are realistic, starting from geographic distribution (that is, as realistic as possible to reproduce

population displacement but, on the other hand, is not demanding in terms of the data required to run the model) and virus characterization. In the text, I have underlined a general procedure to deploy the model in different scenarios:

"Moreover, in this paper, since most of the parameters are realistic, the model can be run for a general epidemic upon collecting the few parameters required (which in this case were all open access) and fitting the two parameters left. However, the model can be made more precise by adding additional realistic data, which most of the time are not fully open access; this, however, is out of the scope of this study."

3. I thank the reviewer for this comment because I think it is the key point of the paper. More details have been added (see response #5 to Anonymous [2]).

Minor Comments

1. I agree with the reviewer, and I have added the following to the Future Works section:

"This work provides a novel, efficient, and low-demanding (in terms of computational resources) population model. Many features remain to be introduced in the model, like an age-dependent virus model, the ability to introduce an age parameter in the model or a more precise spatial simulation based on big data, and the ability to simulate the habits of the population. In conclusion, future work could be done to increase the number of frames per day, thereby improving the performance of the agents."

Conflicts of Interest

None declared.

References

1. Giacopelli G. A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development. JMIRx Med 2021 Sep 10;2(3):e24630 [FREE Full text] [doi: 10.2196/24630]
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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review"

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Companion article: https://med.jmirx.org/2021/3/e21906/

(JMIRx Med 2021;2(3):e33179) doi:10.2196/33179

KEYWORDS
cardiac rehabilitation; physical capacity; exercise; smartphone apps

This is the authors' response to peer-review reports for the paper "Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review".

Round 1 Review

I. We went through the PRISMA checklist and made changes for better compliance. Some items on the list are not applicable to our article [1].

II. We created the PRISMA diagram as requested by the reviewers.

III. We have done that.

IV. We are fine with transferring to *JMIR Cardio* as suggested by some reviewers.

V. We extended the Abstract as requested.

Reviewer F [2]

General Comments

Thank you for the encouraging comments [2]. We made significant changes in our effort to correct those incorrect statements.

1. We opted to take the sentence out of the Abstract and instead focus more on it within the Introduction. Citations are not typically placed in the Abstract, and cardiac rehabilitation is sometimes covered by insurance plans if eligible. However, not all patients have insurance, so cost can be a deterring factor. This is mentioned as a barrier in the Introduction now.

2. We added this reference [3] and others.

3. Done.

4. Done. We made additional searches as suggested and reported this in the paper.

5. The Forman [4], Layton [5], and Worringham [6] studies were 3 non–randomized controlled trials. We removed them

from the Results section. However, they are still mentioned in the Introduction and Discussion sections as support articles, since some vital information was drawn from them.

6. Done.

7. We made these changes as suggested. Depending on location, guidelines and duration can slightly vary. This is now mentioned in the paper.

8. The phase of rehabilitation is included in Table 3. We removed it from the text as requested.

9. We interpret this request by the reviewer to create new numeric codes for the individual outcome measures. Then, we use those codes only in the table and use a legend below the table for the codes. Do we understand it correctly? We slightly disagree with that option; it would make the table itself neat and clean, but it would require a longer time for a reader to read and understand the content and would increase the length of the paper. Nevertheless, we are happy to do this if the reviewer feels strongly about this change. Simply listing the citations after the outcome measures is insufficient, since there are more than 2 options for table cells. However, we significantly simplified Tables 2 and 3. Maybe the current version provides enough simplicity, clarity, and readability for publication.

Reviewer AI [7]

General Comments

1. A complicated problem such as heart failure takes multiple interventions to treat. Although diet does not seem to be directly related to cardiac functional capacity, high sodium diets can aid in retaining fluid in the body, further propagating heart issues, as the heart is too weak to pump the excess fluid. Excess fluid will then push on the chest and sit on the lungs, making exercise difficult, causing shortness of breath while walking, and ultimately making the heart weaker. Multiple interventions are used in treating heart issues, as recommended by the American Heart Association and American College of Cardiology, because it is a complicated organ. Therefore, it is appropriate for smartphone app interventions to include more than one component of cardiac rehabilitation. We added some of this information to the manuscript.

2. Cardiac rehabilitation functional capacity is the primary outcome and was narrowed down to the two main measurements of a 6-minute walk test or peak oxygen uptake in this revised version of our paper. Other outcomes are briefly mentioned in the discussion.

3. We created a PRISMA flow diagram for the study selection process.

4. We deleted the corresponding paragraphs, which were confusing. Also, we simplified the tables to increase their clarity and to better align with our research topic.

References

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Abbreviations

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

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Authors' Response to Peer Reviews

Authors’ Response to Peer Reviews of “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study”

Ray B Jones[1], PhD; Suzanne Hubble[2], BSc, MRES; Lloyd Taylor[1], MSc; Hilary Gunn[2], PhD; Angela Logan[2,3], PhD; Tim Rowland[4], BSc; Hannah Bradwell[1], PhD; Luke J Connolly[2], PhD; Kim Algie[2], BSc; Krithika Anil[2], PhD; Bradley Halliday[2], BSc; Sandra Houston[5], MSc; Rachel Dennett[2], BSc; Sarah Chatfield[6], BSc; Sarah Buckingham[2], PhD; Jennifer Freeman[2], PhD

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KEYWORDS

tele-rehabilitation; video-consultations; assessment of movement; eHealth; technology; desktop robots; wide-angle webcams; physical health; rehabilitation; remote; assessment; assistive technology; evaluation; framework; webcam; telehealth; robots

This is the authors’ response to peer-review reports for “Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study.”

Round 1 Review

Response to reviewers, June 7, 2021

Reviewer K [1]

1. We acknowledge that this exploratory study [2] has been carried out by just one team and that further work by others would help validate our approach and conclusions. We have added a sentence to the paragraph headed *Limitations* to that effect.

2. Thank you. We are of course aware of the various aspects of movement, and these were taken into account in our literature

search and methods. This perhaps was not clear to the reviewer, so we have added sentences to the *Introduction*, *Methods*, and Multimedia Appendix 1 to address this point.

3. Acknowledged, and we have added a sentence to the *Limitations* section to address this point. Thank you.

4. We have not been able to find this misspelling (ie, “CINHAL”) anywhere. CINAHL seems to be correctly spelled both in the main text and in Multimedia Appendix 1.

5. Actually, we realize there is a mistake in the text of the main paper in that our literature review was 2017-2021 inclusive. We have added a justification for the choice of date to Multimedia Appendix 1. The reasons for starting with 2017 are as follows:

(1) The routine use of video calls in clinical consultations is relatively recent. Starting with a very simple search of Web of Science on *video consultations* gives 2465 results, half of which are from 2017 onward. However, if the search is changed to *video consultation* AND *physiotherapy*, Web of Science only returns 21 results, all but one of which are from 2017 onward.

(2) Kubi was introduced to the market in 2012. It was likely that any study making use of it in clinical video consultations was not going to reach press until 2015 at the earliest.

(3) As we were also searching via Google and had had a “watching brief” on technology developments related to telepresence robots over the last decade, we thought a 5-year review of the literature was adequate.

6. Multimedia Appendix 2 gives considerable detail on each of the products.

Reviewer AB [3]:

1. We have added “use of” to the objectives in the Abstract to clarify our focus.

2. Our justification for focusing on these four devices (Kubi and Pivo desktop robots, Facebook Portal TV, wide-angle webcam) is provided in the *Introduction* (pages 2 and 3), where we describe how we were aware of the Kubi and Pivo, how we carried out a literature search (as well as various Google searches), and that as far as we were aware, these were the only “off-the-shelf” technologies available at the time.

3. The “hypothetical patients” were “hypothetical” (ie, they were “mental constructs” that we made by taking the technology use and skills, various disabilities and physical limitations, and other characteristics of family members of the authors and “mentally” combining these with typical clinical conditions encountered by the therapists in the team. We have expanded the description of this in the text just before Table 3 for clarification.

4. None—they were hypothetical (ie, a mental construct). All testing was between the coauthors.

5. As explained above, we have added a sentence to the *Methods* section to clarify “hypothetical patients.”

Reviewer AC [4]

Thank you (:>).

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Early Experience With Neutralizing Monoclonal Antibody Therapy for COVID-19: Retrospective Cohort Survival Analysis and Descriptive Study"

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KEYWORDS

infectious disease; monoclonal antibody therapy; COVID-19; experience; therapy; drug; patient outcome; risk; efficacy; approach; treatment; pandemic; antibody; immunotherapy; immune therapy

This is the authors' response to peer-review reports for "Early Experience With Neutralizing Monoclonal Antibody Therapy for COVID-19: Retrospective Cohort Survival Analysis and Descriptive Study."

Round 1 Review [1]

1. Formatting in paper [2] changed as requested
2. Figures changed
3. Added suggested contextualization
4. Fortified Discussion
5. Although we added references and discussion of the inflammatory response to cytokines, it should be recognized that these antibodies work by neutralization of the virus, not by affecting cytokines.

References

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study"

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KEYWORDS

vaccination; COVID-19; incarcerated individuals; correctional facility; public health; pandemic; vaccine; carceral setting; vaccine implementation; correctional staff

This is the authors' response to peer-review reports for the paper "SARS-CoV-2 Vaccination Uptake in a Correctional Setting".

Round 1 Review

The authors of the manuscript [1] are grateful to the editor and reviewers [2,3] for their invaluable input and feedback.

Anonymous [2]

General Comments

Thank you. We agree this is an important contribution.

Specific Comments

Introduction

Thank you for this comment. The first vaccine was administered on December 22, 2020, which, to our knowledge, was the first. At the beginning of the submissions process (at the time of the preprint server submission), this was meant to showcase that correctional facilities could and are offering vaccines. Now, as the vaccine is more widely available, we agree that there is less value added to showcasing Rhode Island as "the first," and, therefore, this has been removed as suggested. The study period was made clearer as suggested as well.

Methods

1. This sentence (“From the beginning of the pandemic…”) has been moved to the Background section.

2. We have added a line that the Rhode Island Department of Corrections (RIDOC) leadership prioritized vaccine allocation based on guidance from the Centers for Disease Control and Prevention (CDC) and the Department of Health.

3. This change was made.

4. We agree this term is unhelpful and informal. We have changed “round” to “phase” to refer to all subsequent vaccination groups.

5. Thank you for identifying this confusion. The line has been rewritten to say: “This vaccine campaign exemplified adherence to public health principles: vaccinate where spread and disease can best be prevented.” A citation was added to clarify.

6. We agree these details can be important. We have added specifics that the education during roll call addressed information on signing up and have added a link to the video and uploaded the email as a supplement.

Results

1. This sentence has been moved to the Discussion.

2. The word “approximately” has been removed.

3. The details on uptake have been removed from the text, which now references only the table.

4. Details on second doses have been removed as suggested.

5. We agree this is an important finding and is now the topic sentence of its own paragraph.

6. An overpull is the phenomenon that most 10-dose vials actually had 11 or 12 doses that could be used, which was recommended by the CDC. This caused some headaches in logistics planning. This has therefore been left in but with a parenthetical explanation: “During this time “overpulls” (ie, a common 11th dose of vaccine could be pulled from a 10-dose vial)…”

7. Thank you for this clarification. Typically, it is capitalized when referring to the specific facility (ie, Intake facility) as opposed to a general intake facility.

8. The section was removed. We followed all Vaccine Adverse Event Reporting System (VAERS) protocols for tracking adverse events but had none, and this may therefore take away from the core part of the results.

Discussion

1. Agreed. We have removed the efficiency description and appreciate this feedback.

2. Agreed. These have now been split into two sentences, and we agree that they read much more clearly now.

3. As mentioned above, we have removed the discussion on the RIDOC being the first to vaccinate. We appreciate this feedback.

4. They were not. It is unclear and is most likely due to cultural issues in each facility. This would be a great topic for another paper. The Women’s Facility, on average, does have a shorter length of stay than the other sentenced facilities, but identifying factors of vaccine hesitancy among our own population is a topic of future research.

5. Thank you for this; we appreciate it. We used “difficult to reach” to refer to the overall demographics of individuals with limited access or uptake of vaccines, which often refers to BIPOC (black, indigenous, and other people of color) communities, which are also disproportionately affected by mass incarceration. Clearly, however, we would not want this to be misconstrued in any way and so “difficult to reach” has been removed from the manuscript.

6. Agreed. We have put less emphasis on switching to the single dose, particularly now with the complications of the Johnson & Johnson vaccine. Single-dose vaccines, however, do play a role in larger, short-term, jail-like facilities, and this was more explicitly said. The low second-dose refusal rate likely corresponds to community averages, although I do not believe there is strong data on this currently, and we, unfortunately, do not have detailed data explaining the reasons for refusals of the second dose. We agree this would be another wonderful future topic of research.

Reviewer B

General Comments

We appreciate this opportunity to clarify and have removed the term “evaluation” and added a section regarding the RIDOC that I believe makes the writing clearer. Thank you for this feedback.

Specific Comments

Major/Minor Comments

Introduction

1. This is very reasonable, and we appreciate the critique. This language has been changed to state: “Correctional outbreaks have been shown to contribute to the community and statewide spread of infection.”

2. We agree. The term “evaluation” has been removed.

Methods

1. The term “aggressive” has been removed.

2. We have worked to make referencing “the RIDOC” more consistent as colloquially it is referred to both as “RIDOC” and as “the RIDOC.” It is now referred to consistently as “the RIDOC” when used as a noun or as “RIDOC” when used as an adjective (eg, “RIDOC nurses”). We have changed the wording to better define “security facility” and now consistently refer to the group of individuals as “sentenced individuals.”

We have added a description: “The Rhode Island Department of Corrections (RIDOC) is a unified (combined prison and jail) statewide correctional facility that currently houses approximately 1500 sentenced and 500 awaiting-trial individuals across 6 facilities among a spectrum of security levels, including Minimum Security, Medium Security, Maximum Security, and High Security.)”

3. This sentence has been taken out as the majority of this paper focuses on the sentenced population. A better description of the Intake facility is included.

4. The term "rounds" has been replaced by "phases" as mentioned above. The term "opt-out" was removed, and a better description of the public health educators is included. Most of the education was tailored to the individual, and so we have added a statement regarding answering questions. This is now described as: "Two RIDOC public health educators provided education on the vaccine, answered questions, and provided consent before the vaccine clinic day. All eligible individuals were offered the vaccine in this way with the option to accept or defer."

5. Thank you for identifying this. We now explicitly state the names of each smaller facility in the text: "In phase 2, smaller facilities (ie, facilities with a smaller average daily population: Women's Facility; Minimum, Maximum, and High Security facilities) were offered the vaccine…"

6. Thank you for this opportunity to clarify. We have changed the wording to explain opt-in via email: "Among corrections staff, individuals were vaccinated with an opt-in system (signing up via email)."

Results

1. The parentheses have been removed.

2. We have added the article. Thank you for catching this.

3. Thank you, this wording has been changed as suggested.

4. This sentence has been removed to avoid confusion.

5. This section was removed and now references Table 1 (as recommended by Anonymous).

Discussion

1. We have removed the term "efficient," as also recommended by Anonymous.

2. This is appreciated and was also suggested by Anonymous. The change has been made to split this into two sentences: "This aligns with necessary immunization rates modeled to achieve herd immunity [8]. More importantly, this is a departure from some concerns of high vaccine hesitancy rates, including a recent CDC publication estimating only a 45% willingness to receive the vaccine among incarcerated people [9]."

3. The term "devastated" has been removed to avoid editorializing.

4. This sentence has been changed to say, "Additionally, both COVID-19 and mass incarceration have disproportionately impacted communities of color [11]." We have made changes to consistently use "Covid-19" rather than "COVID-19," although we also defer to the journal's editorial preference.

Tables

1. Table 1: Thank you for identifying this. This is now clarified in the text to align with the table.

2. Table 1: The asterisk (regarding the type of vaccine used) has been removed and added to the text.

3, 4. Table 2: The reviewer is completely correct that the Intake population, being more jail-like, adds some confusion to the paper and takes awareness from the core focus, which was on the immediate vaccination of sentenced individuals (some of whom just happened to be at our jail-like Intake facility). Table 2, therefore, has been removed, as it does not further elaborate on the key findings of the research and only adds questions.

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3. Howell BA. Peer Review of "SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study". JMIRx Med 2021 Sep 27;2(3):e31905 [FREE Full text] [doi: 10.2196/31905]

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Original Paper

In-hospital Mortality and the Predictive Ability of the Modified Early Warning Score in Ghana: Single-Center, Retrospective Study

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Abstract

Background: The modified early warning score (MEWS) is an objective measure of illness severity that promotes early recognition of clinical deterioration in critically ill patients. Its primary use is to facilitate faster intervention or increase the level of care. Despite its adoption in some African countries, MEWS is not standard of care in Ghana. In order to facilitate the use of such a tool, we assessed whether MEWS, or a combination of the more limited data that are routinely collected in current clinical practice, can be used predict to mortality among critically ill inpatients at the Korle-Bu Teaching Hospital in Accra, Ghana.

Objective: The aim of this study was to identify the predictive ability of MEWS for medical inpatients at risk of mortality and its comparability to a measure combining routinely measured physiologic parameters (limited MEWS [LMEWS]).

Methods: We conducted a retrospective study of medical inpatients, aged ≥13 years and admitted to the Korle-Bu Teaching Hospital from January 2017 to March 2019. Routine vital signs at 48 hours post admission were coded to obtain LMEWS values. The level of consciousness was imputed from medical records and combined with LMEWS to obtain the full MEWS value. A predictive model comparing mortality among patients with a significant MEWS value or LMEWS ≥4 versus a nonsignificant

MEWS value or LMEWS <4 was designed using multiple logistic regression and internally validated for predictive accuracy, using the receiver operating characteristic (ROC) curve.

Results: A total of 112 patients were included in the study. The adjusted odds of death comparing patients with a significant MEWS to patients with a nonsignificant MEWS was 6.33 (95% CI 1.96-20.48). Similarly, the adjusted odds of death comparing patients with a significant versus nonsignificant LMEWS value was 8.22 (95% CI 2.45-27.56). The ROC curve for each analysis had a C-statistic of 0.83 and 0.84, respectively.

Conclusions: LMEWS is a good predictor of mortality and comparable to MEWS. Adoption of LMEWS can be implemented now using currently available data to identify medical inpatients at risk of death in order to improve care.

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KEYWORDS

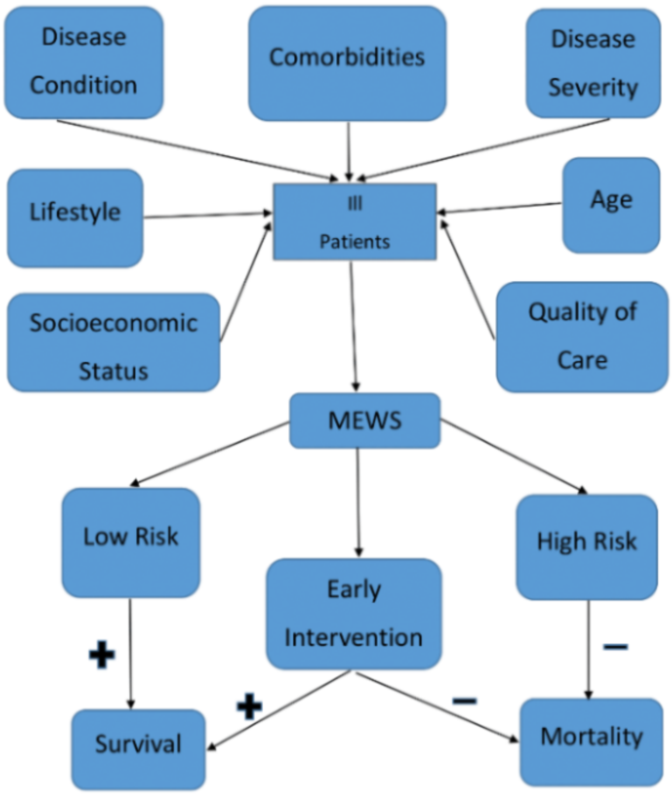
modified early warning score; MEWS; AVPU scale; Korle-Bu Teaching Hospital; KBTH; Ghana; critical care; vital signs; global health

Introduction

Critical illness is a leading cause of morbidity and mortality in sub-Saharan Africa, including Ghana [1]. Low- and middle-income countries have a disproportionately higher burden of critical illness with over 90% of global maternal deaths and deaths from trauma and infections [1-3]. In Ghana, the critical care burden is high. Historically, financial investment has been skewed toward primary health care. Less commitment to critical care means that resources for intensive medical care are limited, and their thought-out and appropriate allocation is important [4].

One of the main reasons why patients deteriorate and die in hospitals is delayed recognition of illness severity in understaffed inpatient wards. Early warning tools to help identify patients at the highest risk of death could help countries like Ghana with resource allocation and clinical decision making (Figure 1).

Figure 1. Conceptual framework showing predictors of in-hospital mortality and the role of the modified early warning score (MEWS) among ill patients.



Multiple studies have shown that critical illness and serious adverse events in hospitalized patients are preceded by signs of clinical deterioration in up to 80% of those affected [5-8]. Therefore, changes in physiological parameters can be used to predict adverse events such as shock, cardiac arrest, death, and unplanned intensive care unit (ICU) admissions [9].

MEWS is a commonly used illness severity score that is calculated by combining five physiologic bedside parameters: systolic blood pressure, heart rate, respiratory rate, temperature, and level of consciousness assessed by the AVPU (alert, [responds to] voice, [responds to] pain, unresponsive) scale or RASS (Richmond Agitation Sedation Scale) score. These four vital signs and the observation of consciousness are individually scored and summed to yield a combined score between 0 and 14, with higher scores representing increased illness severity.

In a systematic review conducted by Smith et al [10] in 2014, early warning scores, including MEWS, had strong predictive ability for death and cardiac arrest within 48 hours in academic urban hospitals in economically advanced countries. Early warning scores have also been shown to provide precise, concise, and unambiguous means of identifying and communicating about clinical deterioration to help clinical staff provide special attention and care to patients who need it most (justifiable appropriation of care) [11]. As a result, scoring systems such as MEWS have been adopted in most developed countries and some African countries [12-14].

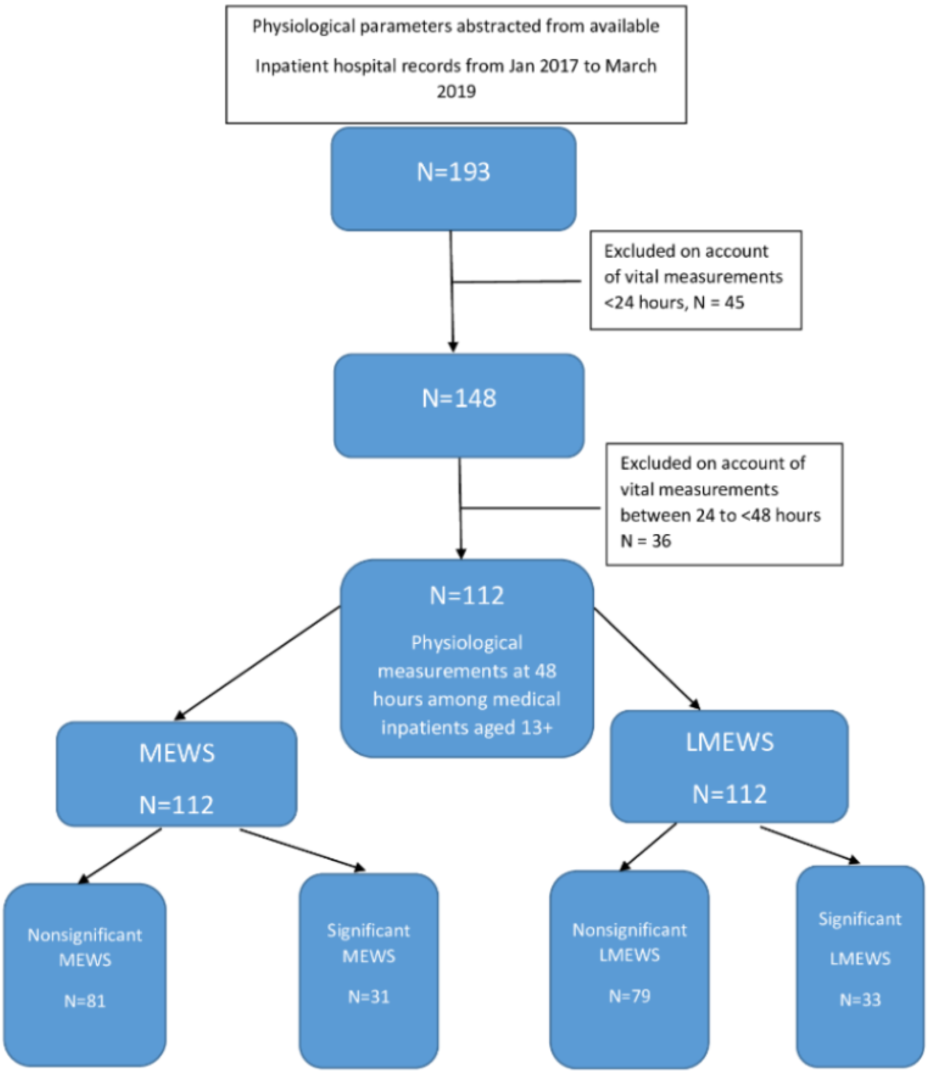
This study sought to validate the use of MEWS as a clinical decision-making tool to improve early identification of hospitalized medical patients at increased risk for death in Ghana. In addition, since level of consciousness is not routinely recorded in current clinical practice, we aimed to investigate the predictive utility of a limited MEWS (LMEWS) calculation based on vital signs alone. Most studies in similar settings have found that the level of consciousness is generally high (ie, the patient is well oriented) even when other aspects of the MEWS value are abnormal [2]. We therefore hypothesized that the physiologic data currently being monitored in Ghana may be sufficient to improve the early detection of critical illness and help guide resource allocation among inpatients in this setting.

Methods

Study Design and Population

This was a retrospective chart review study of hospitalized medical patients, aged ≥13 years, admitted to the Korle-Bu Teaching Hospital in Accra, Ghana. The Korle-Bu Teaching Hospital is the national hospital of Ghana and the leading tertiary care referral center in the country [15]. Medical inpatients hospitalized there for at least 48 hours whose medical records were still available from the period of January 2017 to March 2019 were included in the study. During this period, the standard practice was to discharge patients in possession of their written medical records; copies were not often retained. This practical limitation accounts for the smaller study size than might be expected for a tertiary facility. Pediatric patients, defined as those aged less than 13 years of age by the Ghana Ministry of Health guidelines, were not included. Patients with more than one hospital admission in the past month, or those who were admitted for conditions other than medical ones, were also excluded (Figure 2). The maximum in-hospital stay was 32 days, and no follow-up data were collected post discharge.

Figure 2. Flow chart demonstrating the creation of the modified early warning score (MEWS) cohort. LMEWS: limited MEWS.



Demographic data were collected to analyze covariates. Patients' vital signs recorded at 48 hours after admission were recoded and scored to generate the LMEWS value, using thresholds as previously described (Table 1) [2]. To compare the utility of LMEWS with the full MEWS in the absence of routine observation of consciousness and recording of AVPU scores, we generated a full MEWS value using imputation by randomly assigning 92% of the sample to a status of "alert" (AVPU score=0) and the rest to scores between 1 and 3. These percentages were determined based on the findings of a study by Subbe et al [2], which used a similar patient population.

Our study was based on the conceptual framework depicted in Figure 1, which identifies correlational patterns of how different events and experiences may predict mortality in a hospitalized patient. A predictive model was designed using multivariable logistic regression and validated for model accuracy to compare patients with significant MEWS to patients with nonsignificant MEWS, where a significant MEWS was defined as a score ≥4, and a nonsignificant MEWS was defined as a score <4 in the absence of the AVPU [3,16,17]. This cut-off did not vary for the LMEWS versus MEWS values since for most individuals the level of consciousness is normal and therefore contributes 0 points to the total MEWS value.

Due to the confidential nature of patient information, and the need to protect anonymity and obtain consent during health record reviews, ethical approval and waiver of documented permission was obtained from the Institutional Review Board (IRB) of Johns Hopkins University, and from the Scientific and Technical Committee (KBTH-STC 00017/2019) and the IRB of the Korle-Bu Teaching Hospital. Although reporting was anonymous, patients' records were not, so researchers involved in data collection and handling also signed a confidentiality clause.

Table 1. Scoring scale for the modified early warning score (MEWS) adopted form Subbe et al [2].

Physiological parameter	MEWS value						
	3	2	1	0	1	2	3
Systolic blood pressure (mmHg)	<70	71-80	81-100	101-199	—[a]	≥200	—
Heart rate (bpm)	—	41-50	41-50	51-100	101-110	111-129	≥130
Respiratory rate (cpm)	—	—	—	9-14	15-20	21-29	≥30
Temperature (°C)	—	—	—	35-38.4	—	≥38.5	—
AVPU[b] score	—	—	—	Alert	Reacting to voice	Reacting to pain	Unresponsive

[a]Not applicable.

[b]AVPU: alert, voice, pain, unresponsive.

Statistical Analysis

Data were analyzed using STATA (version 15.1, StataCorp LLC). The estimated sample size was determined a priori based on work by Kyriacos et al [18], which yielded a minimum sample size of 46 based on a significance level of .05, delta value of 0.45, and power of 80% to detect clinical deterioration in postoperative patients using MEWS. Post–data collection power analysis was also performed, based on a chi-square test comparing two independent proportions. Based on the resulting analytic sample of 112 participants, with 31 in the significant MEWS category and 81 in the nonsignificant MEWS category, our study achieves a power of 95% to detect a difference in outcome percentages of at least 37% between these two groups. Testing for associations with survival to discharge versus in-hospital mortality was conducted using a two-sample *t* test for each of the individual continuous physiological parameters. The chi-square test was used to test for differences in the proportion of patients with each outcome in the categories of significant versus nonsignificant MEWS and LMEWS. Univariable log-binomial regression analysis was used to estimate unadjusted risk ratios between each predictor and mortality. Multivariable Poisson regression with robust variance was used due to the failure of convergence of the log-binomial regression model. Logistic regression analysis (odds ratio [OR]) was used to identify an appropriate predictive model. A *P* value of <.05 was considered statistically significant. The accuracy of the prediction model was determined using the receiver operating characteristic (ROC) curve and C-statistic (where a C-statistic of 0.5 implies the model performs no better than random chance and a score of 1.00 perfectly discriminates between categories). Adjustment was made for the following potential confounders: age, sex, duration of admission, admission to the ICU, presence or absence of other comorbidities, and the organ system involved in the disease process. The Hosmer-Lemeshow test was used to determine model fit for both the MEWS and LMEWS models, with *P* values ≥.05 implying satisfactory fit. A sensitivity analysis was done using a cut-off of ≥5 to distinguish significant from nonsignificant MEWS and LMEWS values. Missing values were limited to the reason for admission (organ system) and represented <1% (1/112).

Results

The sample comprised 112 patients admitted for medical reasons during the study period. Of these, 62% (69/112) were male with a mean age of 47 years (SD 17.5), and 38% (43/112) were female with a mean age of 52 years (SD 20) (Table 1). Overall mortality was 41.1% (46/112) and increased with age. Every year increase in age was associated with a 3% increase in mortality rate after adjusting for MEWS (IRR [incidence rate ratio]=1.03, 95% CI 1.02-1.04). For patients who survived, the most common admission diagnoses were genitourinary system abnormalities (17/65, 26.2%), whereas neurologic conditions were most common among patients who died (18/46, 39%). The longest length of in-hospital stay was 32 days, with an average of 8 days.

At 48 hours post admission, patients' mean systolic blood pressure was 125 mmHg (SD 2.9), average pulse rate was 91 mmHg (SD 2), mean axillary temperature was 36.9°C (SD 0.1), and average respiratory rate was 24 cpm (SD 4.7). Only temperature and respiratory rate were individually associated with mortality (Table 2). Physiological parameters measured at 48 hours produced an average LMEWS value of 3 (range 0-11). Imputation of randomly assigned AVPU values increased mean scores by 8% overall, producing an average MEWS of 3 (range 0-14).

A significant MEWS was associated with a relative risk of 2.01 (95% CI 1.33-3.04) for death in the univariable analysis, while a significant LMEWS had a relative risk of 2.19 (95% CI 1.46-3.30) in the univariable analysis (Table 3).

Table 2. Showing baseline characteristics.

Characteristic	Survival to discharge (n=66)	Death in hospital (n=46)	*P* value[a]
Sex (male), n (%)	45 (68.2)	24 (52.2)	.09
Age (years), n (%)			<.001
25-64	46 (69.7)	27 (58.7)	
≥65	7 (10.6)	18 (39.1)	
Disease type by system involved, n (%)			.01
Cardiopulmonary	15 (23.1)	13 (28.3)	
Neuroendocrine	11 (16.9)	18 (39.1)	
Hemaoncological	11 (16.9)	1 (2.2)	
Physiological parameter at 48 hours, mean (SD)			
Systolic blood pressure (mmHg)	127.8 (29.4)	120.7 (32.1)	.23
Pulse rate (bpm)	89 (17.6)	94 (18.1)	.17
Axillary temperature (°C)	36.7 (0.7)	37.3 (1.2)	.002
Respiratory rate (cpm)	23 (4.7)	25 (6.9)	.03
Average length of admission	7 (6.3)	8 (7)	.60

[a]*P* values obtained via the *t* test and the chi square test.

Table 3. Multivariable logistic regression of death using full modified early warning score (MEWS) and the limited MEWS (LMEWS).

Covariate	MEWS, odds ratio (95% CI)	LMEWS, odds ratio (95% CI)
Age	1.08 (1.04-1.12)	1.08 (1.04-1.12)
Sex (male)	0.44 (0.16-1.23)	0.40 (0.14-1.13)
MEWS (significant)	6.33 (1.96-20.49)	8.22 (2.45-27.56)
Duration of admission	0.99 (0.93-1.07)	1.01 (0.94-1.08)
Diseased organ system	0.59 (0.31-1.13)	0.59 (0.31-1.12)

The death rate calculated by the Poisson regression after adjusting for only age was 2.02 (95% CI 1.40-2.91) times higher in patients with a significant MEWS compared to those with a nonsignificant MEWS. The death rate for a significant MEWS value using LMEWS was 2.13 (95% CI 1.48-3.07) times that of nonsignificant MEWS after adjusting for age.

In the multivariable predictive model adjusting for age, sex, duration of admission, admission to the ICU, organ system involved, and comorbidities, the odds of death among patients with a significant MEWS was 6.33 (95% CI 1.96-20.50) times that of patients with a nonsignificant MEWS. The death rate among patients with a significant LMEWS was 8.2 (95% CI 2.5-27.6) times that of patients with a nonsignificant LMEWS in the multivariable analysis. The best multivariable regression model was selected based on the Akaike Information Criteria, with a value of 116.4. The odds of death for every year increase in age was 8% (OR 1.08, 95% CI 1.04-1.12). Other covariates were not statistically significant.

Both MEWS and LMEWS were found to have good discrimination based on the ROC curves, with a C-statistic of 0.833 and 0.838, respectively (Figures 3 and 4), using a cut-off of ≥4. The Hosmer-Lemeshow goodness-of-fit test yielded *P* values of .16 and .25 for MEWS and LMEWS, respectively, implying that our model fits the data well (the null hypothesis being that the prediction model is correctly specified).

Sensitivity analyses using a significant MEWS or LMEWS cut-off score of ≥5 yielded a multivariable OR of 12.4 (95% CI 2.5-61.2) and 15.1 (95% CI 2.5-91.8), respectively. The ROC curves for MEWS and LMEWS was found to be 0.838 and 0.840, respectively, when a cut-off of ≥5 was adopted, as captured in Figures 5 and 6. The Hosmer-Lemeshow test to assess goodness of fit yielded *P* values of .51 versus .77 for MEWS and LMEWS, respectively, when a cut-off of ≥5 was used.

Figure 3. Receiver operator characteristic (ROC) curve for the modified early warning score (MEWS) using a cut-off of 4.

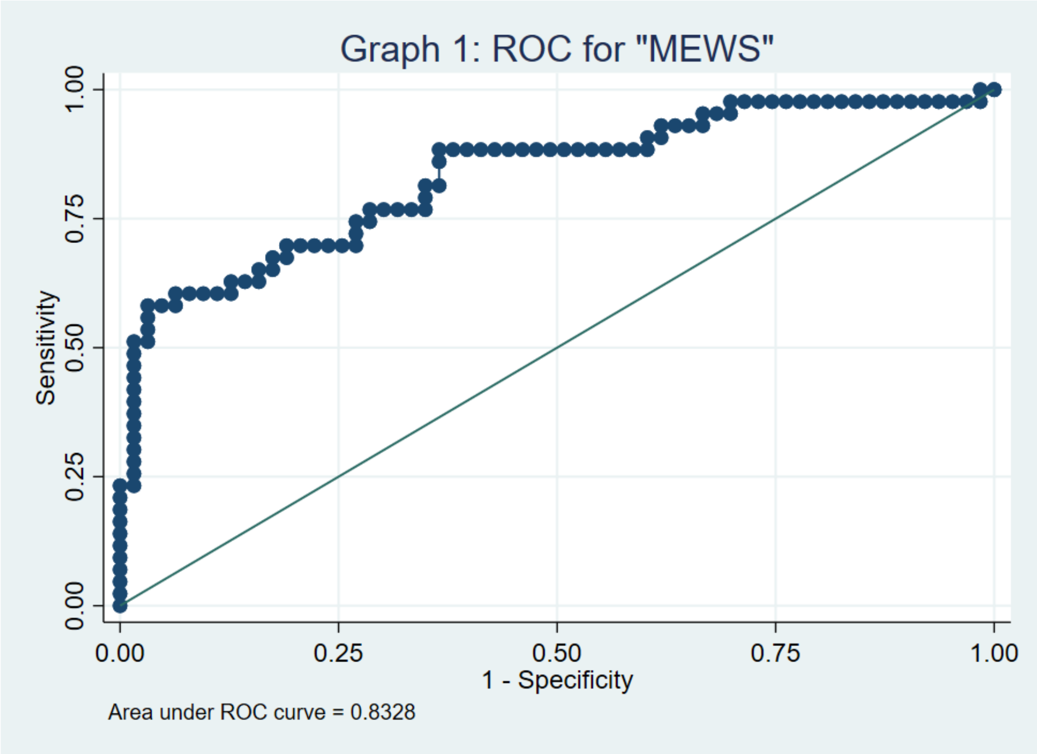


Figure 4. Receiver operator characteristic (ROC) curve for the limited modified early warning score (LMEWS) using a cut-off of 4.

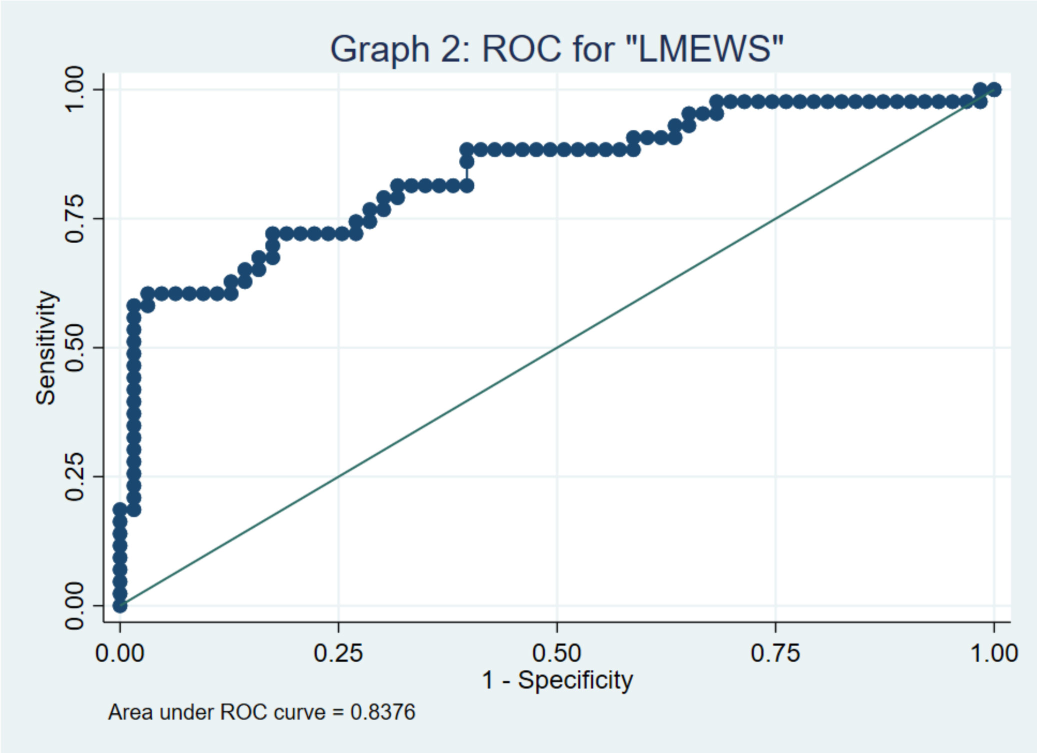


Figure 5. Receiver operator characteristic (ROC) curve for the modified early warning score (MEWS) using a cut-off of 5.

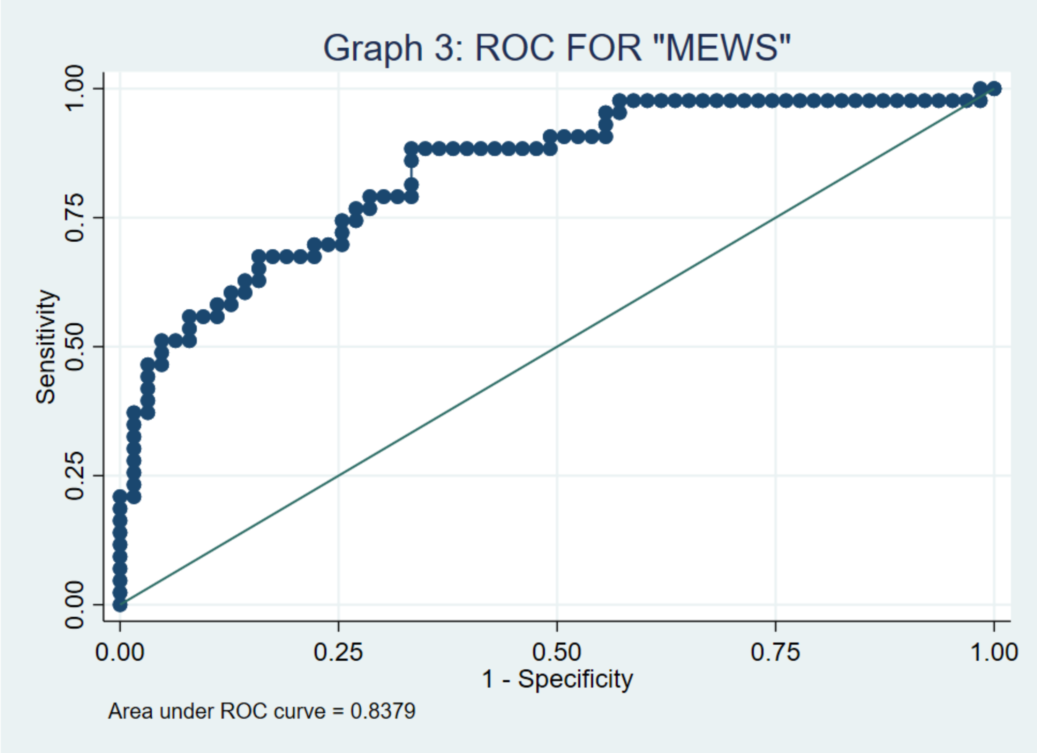
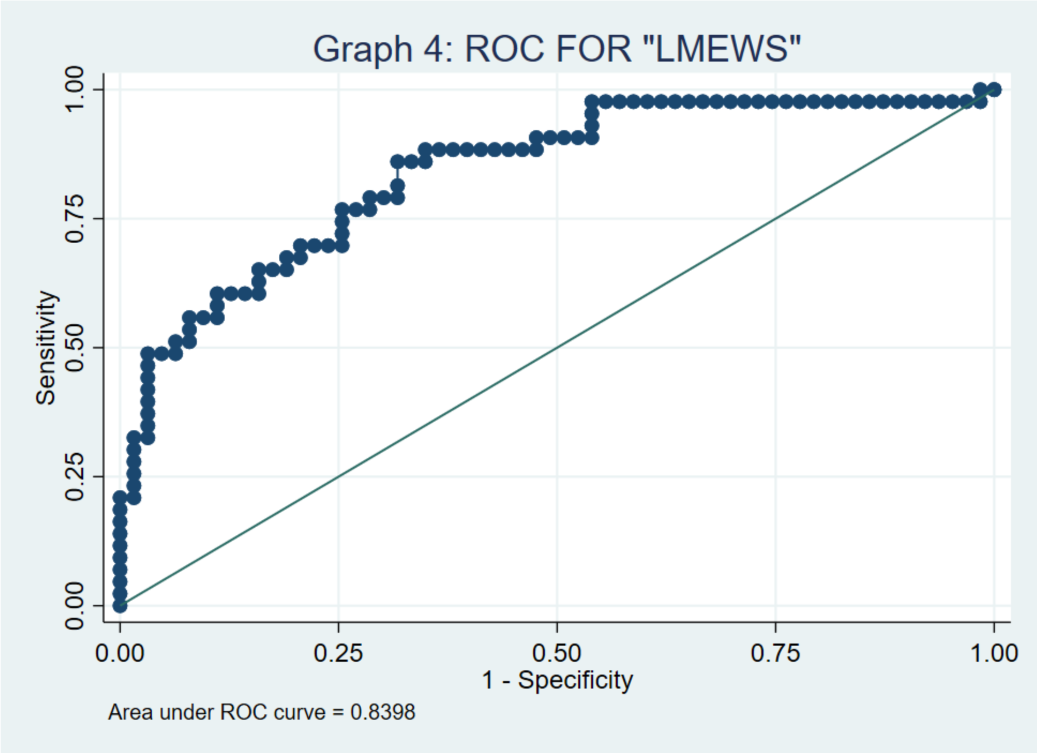


Figure 6. Receiver operator characteristic (ROC) curve for the limited modified early warning score (LMEWS) using a cut-off of 5.



Discussion

Principal Findings

MEWS has been validated in several settings as a robust predictor of both clinical deterioration and death in hospital [2,18]. This study demonstrates that the approach is useful even in the absence of an observed level of consciousness. Vital signs data collected routinely at the bedside in most facilities in Ghana and throughout sub-Saharan Africa can be used to generate LMEWS, which also has a high predictive value.

Serious adverse events and some portion of in-hospital mortality can be prevented by limiting human error, such as failure to recognize the early warning signs of a deteriorating patient or failure to act on this information in a timely manner [19].

MEWS is a low-cost tool that utilizes easy-to-measure bedside parameters to generate a singular value that can identify at-risk patients. This value can be used as a preset trigger in the context of a reporting algorithm.

We found that, in this setting, having a LMEWS value of 4 or greater was highly associated with in-hospital mortality. The area under the curve (AUC) of 0.84 for the LMEWS is consistent with good model accuracy in the discrimination of patients who are critically ill. The combination of LMEWS with clinical judgment is therefore likely to be as effective in Ghana as it has been in other similarly resourced settings [20]. This is encouraging since LMEWS can be implemented without additional training of staff on how to score the level of consciousness and without changing standardized documentation forms already in use for patient monitoring.

The standard inpatient vital signs monitoring charts used in many Ghanaian hospitals includes a 4-hourly graphic to plot temperature, pulse rate, respiratory rate, and blood pressure. Additional parameters may also be serially recorded in some instances or centers; however, the typical bedside observation chart does not record the level of consciousness for patients, as captured in the MEWS by including either the AVPU or RASS score.

Although the original description defined a significant MEWS as any single score ≥5, or any increase of 2+ points in patients with initial scores above 5, a cut-off of 4 was adopted for this study [2,16]. Arguably, a lower threshold for detection would increase the burden of patient re-examination and reassessment on health care providers, potentially making use of the score impractical in settings with severely limited human resources. The decision to adopt a cut-off score of 4 as the definition of a significant MEWS was based on previous work done by Gardner-Thorpe et al [16] in 2006, which showed that raising the threshold reduces the sensitivity to unacceptable levels for patient safety, though an increase in specificity would be observed. Using a cut-off of 4, the number of individuals with a significant MEWS value was 33 (out of 112), and 31 had a significant LMEWS value. In other words, nearly 30% of the patients in our study would have been categorized as high risk for clinical deterioration in the context of a MEWS-based reporting algorithm.

Interestingly, using MEWS or LMEWS with a cut-off of ≥5 did not only yield higher discrimination, based on the C-statistics, but also had better calibration in terms of correctly assessing the risk of disease severity. Based on the receiver operating characteristics and the Hosmer-Lemeshow goodness-of-fit test, LMEWS with a cut-off of ≥5 was superior to both MEWS and LMEWS with a cut-off of ≥4.

Encouraging complete, accurate documentation and a standardized interpretation of vital signs with appropriate actions by nurses, doctors, and other allied staff can potentially improve the outcomes of patients admitted to hospitals, even in a setting that lacks rapid response teams. Many interventions such as fluids or antibiotics do not require advanced equipment or costly supplies, making the implementation of the afferent arm of a rapid response system important even in settings where the efferent arm is more limited [21].

Limitations

This study is subject to all the limitations of a single-center, retrospective chart review. Sources of bias include the potential for differential clinical care based on perceived patient status in the absence of a standardized rapid response team or protocol. In addition, the study only examined vital signs collected at a single time point for each patient. Changes in serially measured physiological parameters were not evaluated. A study published by Ludikhuize et al [22] recommends the calculation of MEWS at least 3 times daily to detect the development of physiological abnormalities. Our study could not have detected any significant MEWS values that may have developed after the first 48 hours upon admission. However, missing additional patients who may have worsened later and then died would bias the study toward the null hypothesis. This makes our study design a conservative one, with results consistent with previously published literature on the topic [2,16].

More prospective research is needed to help define the utility of LMEWS for physicians looking to allocate resources and develop rapid response teams that can act on predictive information to improve patient outcomes and patient care.

Conclusion

This study was the first to examine the ability of an early warning system to predict inpatient mortality based on routinely collected clinical data in a low-resource setting. Early recognition of clinical status decline is critical even in low-resource settings, where bedside interventions may prevent ICU admissions and disease complications including death. Though the MEWS system provides good discrimination, the LMEWS provides better discrimination and calibration in the prediction of mortality and can identify critical illness among inpatients with primarily medical diagnoses. Additional prospective studies will be useful to validate LMEWS among other categories of inpatients and to investigate its impact on health resource allocation and clinical outcomes in low-resource settings.

Acknowledgments

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We are grateful to the Korle-Bu Teaching Hospital, medical department staff, and clientele for making patient charts available for data collection, as well as Drs Benjamin Sena Fenu and Oforiwaa Amoah, who contributed to data collection and on-site follow-up for ethical and technical committee approval; Victor Nortey, who was instrumental in guiding us through the ethical review processes at the Korle-Bu Teaching Hospital; and George Mwinnyaa and Seth Bennett, who reviewed the statistical analysis.

Authors' Contributions

EJA was responsible for the concept, study design, partial data collection, analysis and interpretation, and writing of the manuscript. PA, JSRM, MC, and SES participated in concept development, critical revision, and review of the manuscript. PA, JSRM, and MC also served as academic mentors, while SES was the on-site preceptor as well.

Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the curve
AVPU: alert, voice, pain, unresponsive
ICU: intensive care unit
IRB: Institutional Review Board
IRR: incidence rate ratio
LMEWS: limited modified early warning score
MEWS: modified early warning score
OR: odds ratio
RASS: Richmond Agitation Sedation Scale
ROC: receiver operating characteristic

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Original Paper

Impact of Modifiable Risk Factors on the Occurrence of Cutaneous Leishmaniasis in Diyala, Iraq: Case-Control Study

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Abstract

Background: In 2018, an outbreak of cutaneous leishmaniasis (CL) occurred in Diyala Province in Iraq. Several risk factors of CL were identified in a prior study; however, the impact of removing modifiable risk factors on the occurrence of the disease was not measured.

Objective: The aim of this study is to measure the impact of removing modifiable risk factors of CL on the occurrence of the disease.

Methods: We conducted a population-based unmatched case-control study in two conveniently selected districts in Diyala Province. All cases of CL were included. Controls were chosen preferentially according to the site where the cases occurred. A structured questionnaire was used to collect data. The unadjusted odds ratios (ORs) and 95% confidence intervals for each risk factor were calculated using binary logistic regression. We also calculated the attributable fractions and 95% confidence intervals of the modifiable risk factors. A *P* value <.05 was considered statistically significant.

Results: Data from 844 persons (432 cases, 51.2%) were analyzed. Cases were more likely than controls to report a history of previous displacement (OR 5.18, 95% CI 3.84-6.98), electricity supply for less than 12 hours per day (OR 1.94, 95% CI 1.47-2.55), living in a rural area (OR 1.91, 95% CI 1.45-2.51), living in a clay house (OR 2.41, 95% CI 1.59-3.66), having an unpainted indoor living space (OR 2.14, 95% CI 1.51-3.02), having rodents inside the house (OR 5.15, 95% CI 3.56-7.47), having chickens, sheep, or both (OR 3.44, 95% CI 2.48-4.75), having a mixture of dogs and sheep or of dogs and chickens within a distance of less than 100 meters (OR 3.92, 95% CI 2.59-5.94), fogging (OR 2.11, 95% CI 1.40-3.19), bed net use (OR 1.72, 95% CI 1.08-2.72), and sleeping outside or a mixture of inside and outside (OR 4.01, 95% CI 1.32-12.19). The data show that the exposure of approximately 70% to 80% of cases was associated with displacement, the presence of rodents inside the house, the presence of animals within 100 meters of the house, the presence of animals (chickens/sheep/both or a mixture of dogs and sheep or of dogs and chickens), and sleeping outside. Approximately 40%-50% of the cases reported living in a clay house, living in a rural area, having an unpainted indoor space, having an electricity supply for less than 12 hours, and using a bed net.

Conclusions: Prevention and control of CL requires a multifaceted approach that relies on changing environmental conditions, housing conditions, and human behavior. Fogging and bed net use were not effective because the underlying housing characteristics and human behavior provided a good culture for the disease. We recommend conducting a study to identify the species, reservoirs, and vectors of CL in Iraq; studying vector behaviors before applying environmental control measures; and educating the public on how and when to use bed nets as well as how to accompany their use with behavioral changes.

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KEYWORDS

cutaneous leishmaniasis; outbreak; Iraq; risk factors; risk; disease; infectious disease; disease prevention; prevention

Introduction

Cutaneous leishmaniasis (CL) is a neglected tropical disease for which approximately 500,000 to 1,000,000 new cases are reported per year worldwide [1,2]. Furthermore, it causes an estimated 2.4 million disability-adjusted life years, placing it among the top 10 in a global analysis of infectious diseases [3]. Countries in the Eastern Mediterranean region contribute approximately 57% of the total CL burden, where *Leishmania tropica* and *Leishmania major* are endemic in 18 countries and territories (including Iraq). Moreover, more than 100,000 new cases of CL are reported annually to the World Health Organization by countries in the Eastern Mediterranean region; however, the actual incidence is estimated to be 3 to 5 times higher [1,4,5]. In Iraq, surveillance data after the 1970s showed an average of 10x00 cases per year [6]. According to internal technical reports released by the Iraqi Ministry of Health, the last country-wide outbreak started at the end of 2014 and continued throughout 2017, when the number of cases per year reached an average of 16,000. In 2018, the number of cases started to decline steadily and reached approximately 11,000.

There are more than 20 *Leishmania* species that can be transmitted to humans, and more than 90 sand fly species that can transmit the protozoa to humans; moreover, approximately 70 animal species, including humans, are natural reservoir hosts of *Leishmania* parasites [7]. The transmission cycle of the parasite in nature can be either zoonotic or anthroponotic [8,9]. In Iraq, data are lacking regarding the most common *Leishmania* species, reservoirs, and vectors. However, evidence from nearby countries suggests that both transmission cycles of CL (zoonotic and anthroponotic) are common in Iraq [5,10,11].

Risk factors for developing CL include residence in rural areas, climate changes, movement of people, conflict areas, deforestation, house characteristics, and human behavior [9,12-14]. Prevention and control of leishmaniasis requires a combination of intervention strategies because transmission occurs in a complex biological system involving the human host, parasite, sand fly vector, and, in some cases, an animal reservoir host. Key strategies for prevention are early diagnosis and effective case management, vector control, effective disease surveillance, control of animal reservoir hosts, and social mobilization and strengthening partnerships among all concerned institutions [14].

Although CL is a self-healing disease, it is potentially disfiguring [1]. The only drug licensed by the Iraqi Ministry of Health to treat CL is sodium stibogluconate, a pentavalent antimony compound.

The recent outbreak affected most Iraqi provinces variably, with an overall incidence rate of $0.9/10^3$ population. The highest incidence rate was in Diyala Province ($4/10^3$ population), while the lowest incidence rate was in Duhok Province ($0.01/10^3$ population). According to internal reports and discussion with the zoonotic diseases section at the Iraq Communicable Diseases Control Center, the lack of infrastructure and municipal services, the presence of hard-to-reach areas, and a lack of prevention programs were blamed for the occurrence of the outbreak. Diyala was subjected to terrorist and military operations from 2014 to 2016, when most of its residents were displaced. Meanwhile, it also encountered a wave of a *Leishmania* epidemic that started in November 2014, reached its peak during 2015, and continued throughout 2017. In response to the rapid escalation of the outbreak, the outbreak response team investigated the outbreak to identify possible risk factors and the impact of removing these factors on reducing the number of cases.

Methods

This is a population-based unmatched case-control study. A case of CL was defined as any person who showed clinical signs (skin or mucosal lesions) and was diagnosed by a dermatologist with CL. A control person was defined as any person (or family member) who was proved to be free of these skin or mucosal lesions. Controls were chosen preferentially according to the site where the cases occurred (from the neighboring house or village). The study was conducted in two conveniently selected districts in Diyala Province (Al-Muqdadiya and Al-Mansuriya). Those two districts were selected as part of the on-job outbreak investigation because surveillance data detected an increase in the number of CL cases in these areas, and those areas were in the recovery process after security instability. Approval for conducting the study was obtained from the Public Health Directorate/Ministry of Health and Diyala Directorate of Health. Oral consent was obtained from the cases and controls themselves or from their caretakers.

Field epidemiology training program students interviewed cases and controls using a modified questionnaire of the case investigation form of the zoonotic section of the Iraq Communicable Diseases Control Center. The questionnaire contained questions about the main demographic (age, sex, occupation), clinical (date of onset, signs and symptoms, presence of other cases within the family, treatment, previous visits, number and site of skin lesions), and epidemiological characteristics (displacement history, house and residency data [information about the type of residency area; house construction materials, such as wall type; electricity provided; animals living within the house; painting of indoor areas; presence of rodents inside or around the house]), sleeping habits, and preventive measures implemented in the area (fogging and use of bed nets).

A total of 866 persons were interviewed within the 717 families visited: 451 cases (292 from Al-Mansuriya District and 159 from Al-Muqdadiya District) and 415 controls (182 Al-Mansuriya District and 233 from Al-Muqdadiya District). However, we excluded 22 persons from the sample due to incomplete information. The final sample size used was 844 persons (cases=432, controls=412), with a ratio of almost 1 case to 1 control.

Univariate analysis was used to describe the study sample. Bivariate analysis was used to detect possible associations between each of the risk factors and the disease (CL) using the chi-square test of independence. The unadjusted odds ratio (OR) and 95% confidence interval of each risk factor were calculated using binary logistic regression. The attributable fractions and their corresponding 95% CIs were calculated for the modifiable risk factors. A *P* value <.05 was considered statistically significant.

Epi Info, version 7.2 was used for data entry and SPSS, version 25 (IBM Corporation) was used for data analysis.

Results

Data from 844 persons (432 cases, 51.2%) were analyzed. There were no gender differences between cases and controls. Cases were more likely than controls to report a history of previous displacement, electricity supply for less than 12 hours per day, and living in a rural area. Regarding house characteristics, cases were more likely than controls to report living in a clay house, living in unpainted indoor areas, and the presence of rodents inside the house. As for animal ownership and the distances of the animals from the house, cases were more likely than controls to have chickens only, sheep only, or both and a mixture of animals (dogs and sheep or dogs and chickens) within a distance of less than 100 meters. Regarding possible preventive measures, cases were more likely to report fogging, bed net use, and sleeping outside or a mixture of inside and outside than controls.

Almost all the risk factors were statistically significantly associated with higher odds of having CL. Nevertheless, the strength of the association varied, as it was stronger (4 to 5 times higher odds of having CL) for factors such as displacement, having animals within 100 meters of the house, and sleeping outside the house. Factors that were associated with a 2 to 3 times increase in the odds of having CL included living in a clay house, having an unpainted indoor area, sleeping in a mixed pattern (inside and outside the house), having animals (whether chickens only, sheep only, or both, or mixtures of dogs and sheep or dogs and chickens), and, interestingly, using a bed net and fogging/unknown fogging status. In fact, the use of a bed net was associated with 72% higher odds of having CL in comparison to the lack of use of a bed net (OR 1.72, 95% CI 1.08-2.72). Likewise, fogging and unknown fogging status were associated with statistically significant 2-fold higher odds of having CL compared to no fogging (*P*<.001).

Regarding the impact of removing modifiable risk factors, our results show that approximately 70% to 80% of the cases were associated with displacement, the presence of rodents inside the house, the presence of animals within 100 meters of the house, the presence of animals (whether chicken only/sheep only/both or a mixture of dogs and sheep or dogs and chickens), and sleeping outside. Similarly, approximately 40% to 50% of the exposure of the cases was associated with living in a clay house; living in a rural area; having an unpainted indoor space; having an electricity supply for less than 12 hours per day; and, interestingly, using a bed net. Unexpectedly, approximately 10% to 20% of the exposed cases reported fogging or unknown fogging status. That is, fogging and unknown fogging status were negatively associated with the occurrence of CL.

The characteristics of the study sample are shown in Table 1. The risk factors for CL in the study population are summarized in Table 2.

Table 1. Characteristics of the study sample.

Characteristic	Total (N=844), n (%)	Cases, (n=432, 51.2%), n (%)	Controls (n=412, 48.8%), n (%)	*P* value
Demographics				
Age group (years)				<.001
<15	607 (71.9)	358 (82.9)	249 (60.4)	
≥15	237 (28.1)	74 (17.1)	163 (39.6)	
Gender				.74
Male	437 (51.8)	226 (52.3)	211 (51.2)	
Female	407 (48.2)	206 (47.7)	201 (48.8)	
Residency				<.001
Rural/semiurban	464 (55)	271 (62.7)	193 (46.8)	
Urban	380 (45)	161 (37.3)	219 (53.2)	
Characteristics				
Previous displacement				<.001
Yes	493 (58.4)	332 (76.9)	161 (39.1)	
No	351 (41.6)	100 (23.1)	251 (60.9)	
Building material of the house				<.001
Clay	117 (13.9)	81 (18.8)	36 (8.7)	
Block/brick	727 (86.1)	351 (81.3)	376 (91.3)	
Indoor space				<.001
Not painted	178 (21.1)	117 (27.1)	61 (14.8)	
Painted	666 (78.9)	315 (72.9)	351 (85.2)	
Electricity supply (hours per day)				<.001
<12	394 (46.7)	236 (54.6)	158 (38.3)	
≥12	450 (53.3)	196 (45.4)	254 (61.7)	
Animals				<.001
Dogs only	14 (1.7)	8 (1.9)	6 (1.5)	
Chickens only/sheep only/both	254 (30.1)	169 (39.1)	85 (20.6)	
Mixture of dogs and sheep or dogs and chickens	134 (15.9)	93 (21.5)	41 (10)	
No animals	442 (52.4)	162 (37.5)	280 (68)	
Distance of animals from house (meters)[a]				<.001
All	436 (51.7)	301 (69.7)	135 (32.8)	
<100	305 (70)	253 (84.1)	52 (38.5)	
100-300	111 (25.4)	39 (13)	72 (53.3)	
>300	20 (4.9)	9 (3)	11 (8.1)	
Presence of rodents in the house				<.001
Yes	648 (76.8)	388 (89.8)	260 (63.1)	
No	196 (23.2)	44 (10.2)	152 (36.9)	
Use of fogging				<.001
Yes	127 (15)	85 (29)	42 (10.2)	
Unknown	220 (26.1)	104 (24.1)	116 (28.2)	
No	497 (58.9)	243 (56.3)	254 (61.7)	
Use of bed net				<.001

Characteristic	Total (N=844), n (%)	Cases, (n=432, 51.2%), n (%)	Controls (n=412, 48.8%), n (%)	*P* value
Yes	108 (12.7)	55 (12.7)	53 (12.8)	
Unknown	127 (15)	67 (15.5)	60 (14.5)	
No	609 (72.3)	310 (71.7)	299 (72.5)	
Sleeping habits				<.001
Inside the house	668 (79.1)	318 (73.6)	350 (84.9)	
Outside the house	19 (2.2)	15 (3.6)	4 (1)	
Inside/outside the house	157 (18.6)	99 (22.9)	58 (14.1)	

[a]Percentages in this category are calculated based on the “All” values.

Table 2. The odds ratios, attributable fractions, and 95% confidence intervals of the modifiable risk factors.

Risk factor	Odds ratio (95% CI)	Attributable fraction (%) (95% CI)
Displacement	5.18 (3.84 to 6.98)	80.6 (73.7 to 85.8)
Clay house	2.41 (1.59 to 3.66)	58.5 (36.7 to 72.7)
Residence in rural region	1.91 (1.45 to 2.51)	47.6 (31 to 60.1)
Unpainted interior	2.14 (1.51 to 3.02)	53.3 (33.8 to 66.9)
Electricity for <12 hours per day	1.94 (1.47 to 2.55)	48.30 (31.9 to 60.8)
Animals		
Dogs only	2.30 (0.79 to 6.76)	56.5 (–28.2 to 85.2)
Chickens only/sheep only/both	3.44 (2.48 to 4.75)	70.9 (59.7 to 78.9)
Mixture of dogs and sheep or dogs and chickens	3.92 (2.59 to 5.94)	74.5 (61.4 to 83.2)
Distance of animals from the house (meters)		
<100	5.95 (2.35 to 15.07)	83.2 (57.4 to 93.4)
100-300	0.66 (0.25 to 1.73)	–51.5 (–3 to 42.1)
Presence of rodents in the house	5.15 (3.56 to 7.47)	80.6 (71.9 to 86.6)
Use of fogging		
Yes	2.11 (1.40 to 3.19)	52.6 (28.6 to 68.6)
Unknown	2.25 (1.43 to 3.56)	55.5 (30.1 to 71.9)
Use of bed net		
Yes	1.72 (1.08 to 2.72)	41.9 (7.4 to 63.2)
Unknown	1.49 (0.86 to 2.60)	32.9 (–16.3 to 61.5)
Sleeping habits		
Outside the house	4.01 (1.32 to 12.19)	75.1 (24.2 to 91.8)
Inside/outside the house	2.07 (1.43 to 3)	51.7 (30.1 to 66.7)

Discussion

Principal Findings

To our knowledge, this is the first large population-based case-control study performed in Iraq to determine the risk factors of CL and the impact of changing modifiable risk factors. We identified the main domestic and behavioral characteristics associated with increasing the odds of contracting CL, which provides a guide for preventive and control measures.

The main modifiable risk factors were displacement, having animals within 100 meters of the house, and sleeping outside the house. In fact, the exposure of 70% to 80% of the cases was associated with displacement, animals in the house, animals within 100 meters of the house, and sleeping outside. In contrast, preventive measures, such as bed net use and fogging, were not successful in preventing CL, as both were associated with increased odds of having CL. In fact, assuming a causal relationship and no bias, the data show that approximately 42% of the cases who used a bed net and 10% of the cases who reported fogging would not have contracted CL if they had not used bed nets or fogging. This finding could be explained by inappropriate timing of fogging, that is, fogging occurred after people returned to liberated areas and had already been bitten by sand flies. In addition, fogging may have been performed in the afternoon, when sand flies are inactive, and the flies were consequently not affected. Bed net use was also not an effective measure of preventing CL, possibly because the patients went to bed late, when the sand flies were not active, and therefore had already been bitten.

The findings in our study regarding displacement, poor housing conditions, and sleeping outside the house agree with findings from studies of risk factors in developing and developed countries [15],[16] (retracted), [17]. Displacement increases individuals' risk of exposure to environmental and personal risk factors of developing CL. In addition, areas from which people are displaced, usually war zones, provide a suitable culture for the growth of both vectors and reservoirs of CL because of the accumulation of wastes and the destruction of infrastructure, such as sewage systems [7]. These findings suggest that preventing CL requires a multifaceted approach that focuses on modifying environmental, domestic, and peridomestic characteristics and on changing human behaviors. Our findings are similar to findings from studies of risk factors of CL in Morocco [18,19], Spain [20], and Ghana [20].

Our study has several strengths. First, it is the first large population-based case-control study of a leishmaniasis outbreak. We identified the main risk factors and their attributable fractions, providing an estimate of the public health impact of the disease. In addition, the findings from our study help to guide preventive and control measures as to the timing of fogging, keeping animals outside houses, painting indoors, and sleeping inside houses.

Our study also has a few limitations. First, the duration of the study was limited, as all data were collected in only 4 days; this led to missing information for some of the variables in the original sample, and they were thus excluded. Second, two important variables were missed, namely, time of fogging and time of sleep, which led us to hypothesize that both actions were undertaken at the wrong time and consequently both surfaced as risk factors rather than preventive factors for the disease. Third, the hazardous security situation limited the movement of the team to only safe areas, which could have obscured other risk factors we are not aware of. Finally, no species were identified from the patients, reservoirs, or vectors to establish the linking of the transmission cycle; therefore, the link is only epidemiologic. None of these limitations could have affected findings from our study; nevertheless, they are worth mentioning to direct future studies in Iraq regarding variables to consider.

Conclusions and Recommendations

CL is an important public health problem in Iraq, especially in Diyala Province. Most of the cases in our study could have been prevented if they were not exposed to displacement, animals inside the house, animals within 100 meters of the house, or rodents in the house. In addition, the timing of fogging and using bed nets is an important consideration. Prevention and control of CL require a multifaceted approach that relies on changing environmental conditions, housing conditions, and human behavior. Fogging and bed net use were not effective because the underlying housing characteristics and human behavior provided a good culture for the disease.

We recommend conducting a study to identify the species, reservoirs, and vectors of CL in Iraq, studying vector behaviors before applying environmental control measures, and educating the public on how and when to use bed nets and accompany their use with behavioral changes, such as using insect repellents and wearing long sleeves. Furthermore, we recommend studying vector and reservoir behaviors before implementing control measures. In addition, we recommend implementing preventive measures, such as fogging and rodent control, in abandoned areas before people resettle after displacement.

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Conflicts of Interest

None declared.

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Abbreviations

CL: cutaneous leishmaniasis
EMPHNET: Eastern Mediterranean Public Health Network
OR: odds ratio

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Original Paper

Emergence of the First Strains of SARS-CoV-2 Lineage B.1.1.7 in Romania: Genomic Analysis

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Abstract

Background: The United Kingdom reported the emergence of a new and highly transmissible SARS-CoV-2 variant (B.1.1.7) that rapidly spread to other countries. The impact of this new mutation—which occurs in the S protein—on infectivity, virulence, and current vaccine effectiveness is still under evaluation.

Objective: The aim of this study is to sequence SARS-CoV-2 samples of cases in Romania to detect the B.1.1.7 variant and compare these samples with sequences submitted to GISAID.

Methods: SARS-CoV-2 samples were sequenced and amino acid substitution analysis was performed using the CoV-GLUE platform.

Results: We have identified the first cases of the B.1.1.7 variant in samples collected from Romanian patients, of which one was traced to the region of the United Kingdom where the new variant was originally sequenced. Mutations in nonstructural protein 3 (Nsp3; N844S and D455N) and ORF3a (L15F) were also detected, indicating common ancestry with UK strains as well as remote connections with strains from Nagasaki, Japan.

Conclusions: These results indicate, for the first time, the presence and characteristics of the new variant B.1.1.7 in Romania and underscore the need for increased genomic sequencing in patients with confirmed COVID-19.

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KEYWORDS

infectious disease; COVID-19; strain; virus; Romania; transmission; spread; mutation; impact; case study; genome; sequencing; genetics; epidemiology; variant; virology; lineage

Introduction

A new SARS-CoV-2 variant, with an N-Y substitution in the 501 position of the spike (S) protein, was detected in the United Kingdom in the fall of 2020. An initial variant of the virus, termed 501 N, with fewer mutations, occurred in late September in Wales, followed by the current variant (VUI-202012/01), giving rise to lineage B.1.1.7, which began to spread rapidly in the United Kingdom and then globally [1]. The new variant has 18 particular mutations, of which several have biological significance and are of epidemiological interest. Among the most notable mutations is N501Y, within the S protein, which corresponds to the receptor binding domain of the virus, where attachment to the host ACE2 enzyme takes place. Other important mutations are the deletion of two amino acids, histidine and valine, at positions 69 and 70, and a substitution at position 681, within the same spike protein. Of great concern is the increased transmissibility and disease severity compared to older variants, raising questions concerning its potential avoidance of successful nucleic acid amplification for diagnostic tests or even reduced vaccine effectiveness [2]. On January 8, 2021, Romania confirmed the first case of COVID-19 infection with the new strain, in a patient from Giurgiu (in South-East Romania) without a history of travel to the United Kingdom or contact with individuals from the United Kingdom. On January 22, 2021, two additional individuals from Bucharest were identified to have the new strain. They reported no travel history, were in good clinical condition, and were isolated at home under the supervision of a family physician. A fourth case was reported in Suceava County, in North-East Romania, on January 25, 2021, in an individual who arrived from the United Kingdom. A fifth reported case was confirmed on January 26, 2021, in a patient from Constanta, South-East Romania, with no travel history or contact with individuals infected with the new strain. Considering when B.1.1.7 was identified in Europe, its faster transmission compared to earlier strains, and the lack of genomic sequencing in Romania, there exists the possibility that the new variant is far more widespread in Romania than confirmed. In this paper, we report the identification of the new B.1.1.7 SARS-CoV-2 variant in Romania and present its characteristics in sequenced genome samples with the aim of enabling further comparison of transmission.

Methods

Overview

A total of 20 samples, collected from patients in the cities of Cluj and Craiova and Suceava County in Romania were selected for analysis, including patients with possible contacts with infected individuals from the United Kingdom. Sample viral titers and RNA amounts were quantified using quantitative polymerase chain reaction (qPCR) and Qubit fluorometers (Thermo Fisher Scientific), respectively. RNA extracts were reverse transcribed and libraries were prepared using AmpliSeq (Thermo Fisher Scientific) SARS-CoV-2 primer panels and workflow. Automatic library templating was performed using Ion Chef equipment and sequencing was carried out on Ion GeneStudio S5 with Ion 540 chips. Sequencing reads and assemblies were checked for quality using Ion Torrent Suite software plugins. Amino acid substitution analysis was performed using the CoV-GLUE platform. The B.1.1.7 SARS-CoV-2 sequence was uploaded into GISAID, under the ID EPI_ISL_869241. The consensus sequence and available Romanian sequences (from different laboratories) belonging to clade B.1.1.7 in Romania were aligned in GISAID to the reference strain using the MAFFT algorithm and maximum likelihood trees were obtained with MegaX software.

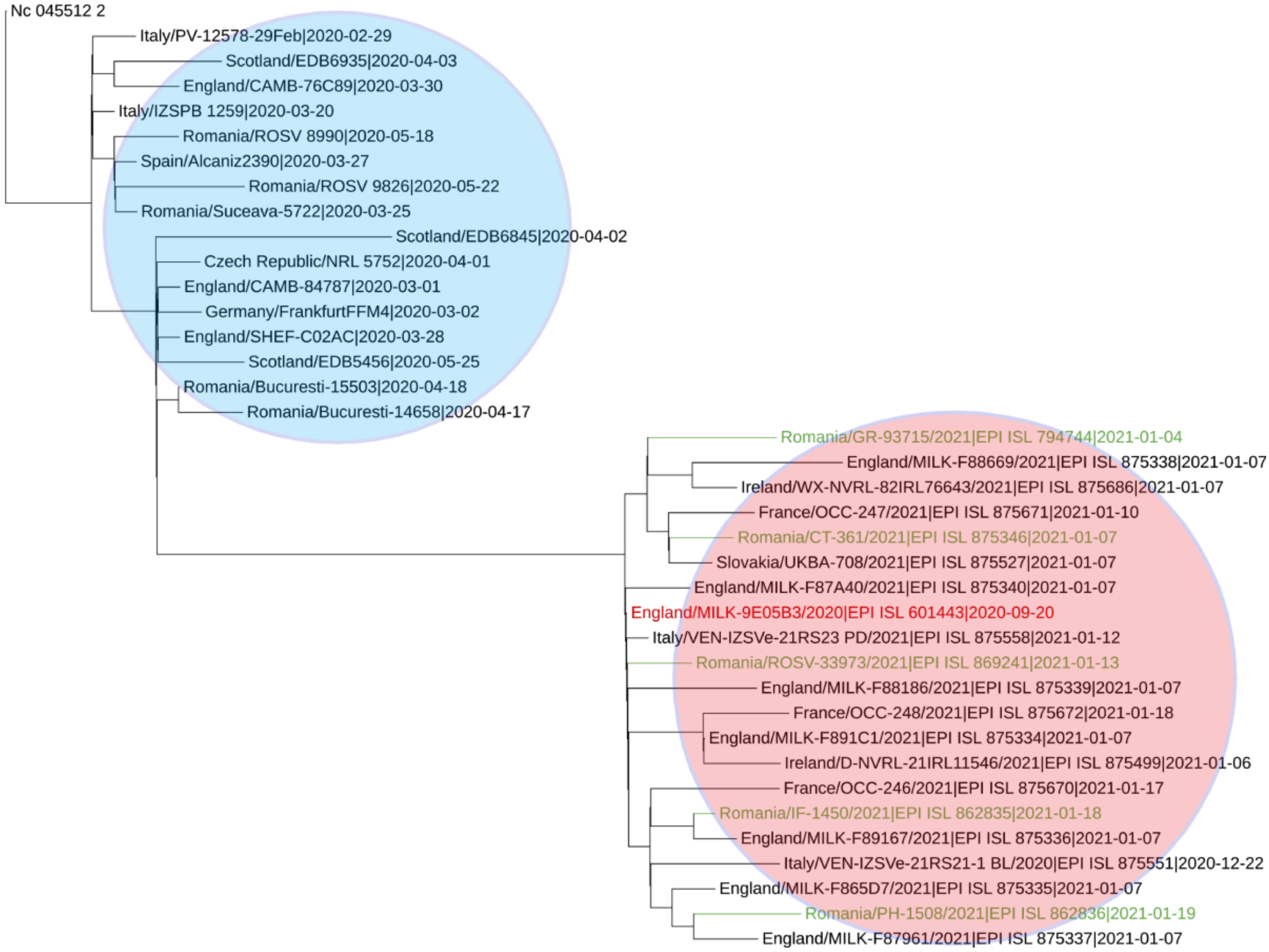
Ethics Approval and Consent to Participate

The study was approved by the ethics committee of University Stefan cel Mare of Suceava, Romania (protocol 11733/14.07.2020) and of Suceava County Emergency Hospital (protocol 17669/13.07.2020). All participants provided individual informed consent.

Results and Discussion

Among the 20 samples sequenced by our laboratory, one presented characteristic mutations of the B.1.1.7 SARS-CoV-2 variant. Phylogenetic placement of this sample, as well as others from Romania within the same lineage included in GISAID, shows the clear distinction of this lineage from the early 2020 strains, including the ones from England and Wales (Figure 1).

Figure 1. Phylogenetic placement of pre-B.1.1.7 samples (blue area) and B.1.1.7 samples (red area) from different European countries, including Romanian strains (green text).



A synopsis of all mutations found in all Romanian GISAID entries belonging to this clade was constructed (Multimedia Appendix 1). All Romanian samples share all 18 mutations characteristic of the B.1.1.7 strain; however, some of them have additional ones.

One such mutation is present only in the sample originating from Suceava, affecting the ORF8 protein, where a stop codon is gained by changing a C nucleotide to a T nucleotide in position 27,945 in the genome. According to CoV-Glue, this mutation has already been encountered in over 580 samples from April to October 2020. Of these, 73% (n=313) belong to specimens collected in the United Kingdom [3]. A second ORF8 truncation, not currently described for B.1.1.7 strains, appears in the samples from Giurgiu and Constanta, in position 68, also gaining a stop codon. Previous occurrences of this mutation are seen in 279 samples from CoV-Glue, of which 91% (n=256) are from the United Kingdom and 27% (n=76) originate from Milton Keynes laboratories, where the original B.1.1.7 strain was sequenced [4]. Such mutations indicate that, although B.1.1.7 originates in the United Kingdom, the set of characteristic viral alterations appeared much earlier and was grafted onto several different already circulating strains in the region. This idea is supported by the fact that, although the first sequenced samples carrying the new strain originated in Kent and Greater London, on September 20 and 21, 2020, respectively [5], the hallmark N501Y mutation first appeared in Italy in August 2020 [6]. However, at this point, the Romanian strains bearing the particular ORF8 mutations described above clearly originated in the United Kingdom, which is also supported by the fact that the patient from Suceava County resides in the United Kingdom and arrived in Romania shortly before the sample was sequenced. One other patient (EPI_ISL_794744) had no history of recent travel abroad but lived in a small city with a high number of individuals working abroad, including in the United Kingdom [7]. The remaining three patients from whom samples were sequenced had no travel history abroad or data were not available.

Strains without a functional ORF8 protein are considered to have epitope loss, which may decrease the accuracy of serological testing, whereas ORF8 antibodies could offer information on both acute and convalescent antibody response. Furthermore, ORF8 truncated proteins decrease disease severity and asymptomatic or mild cases might not be detected [8]. As such, the significance of ORF8 truncations in the context of B.1.1.7 strains should be promptly investigated, considering that mutations in the S gene characteristic to this lineage, particularly the deletion at positions 69-70, may elude detection by polymerase chain reaction (PCR) with certain diagnostic kits that have been used in the United Kingdom for a while [9]. This type of behavior could be indirectly but significantly linked to increased transmissibility of the virus, as potentially infected individuals might not have been accurately identified as such.

Another noteworthy mutation is N844S within nonstructural protein 3 (Nsp3) present in the Suceava sample, which is recorded in only 8 other samples sequenced so far, most of them also from England [10]. The sample from Prahova also has a mutation in Nsp3 (D455N), which has been recorded in only one other sample, collected in Japan [11] in April 2020, belonging to clade B1.1. The Prahova sample is again distinct from others in Romania through the appearance of L15F in ORF3a, a mutation recorded in 5 samples from Nagasaki, Japan, sampled in April 2020, among 243 samples collected worldwide, mostly from the United Kingdom [12]. Although the Japanese samples do not belong to the B.1.1.7 lineage, the coincidental presence of these mutations might indicate common ancestry with the Prahova sample. Other individual mutations in the Giurgiu and Ilfov samples are commonly observed in sampled UK strains. The Constanta sample displays two additional mutations not encountered in other Romanian samples. The first, in Nsp2, is a change from A to V in position 306, a mutation seen in other 209 GISAID samples. These samples were collected in the United Kingdom, Norway, Denmark, the United States, and Belgium [13]. The second mutation is in Nsp12 and is a change from K to N in position 160, which has been encountered in other 27 samples, including ones from the United States, Italy, and Scotland [14].

At the moment, there are over 32,500 B.1.1.7 accessions deposited in GISAID, out of which approximately 30,000 are from the United Kingdom and 5 are from Romania. This lineage is of major interest, due to the fact that three of its mutations might contribute to higher infectivity and transmissibility. Namely, the N50Y mutation of the S gene significantly increases its interaction force and number of interactions with the human receptor ACE2 [15,16]. The deletion of two amino acids at positions 69 and 70 in the same S gene leads to systematically biased diagnostic tests and doubles the reproductive advantage of the virus and viral particle numbers [17]. Furthermore, the P681H mutation of the S protein might influence the cleavage of the S protein due to its proximity to the S1/S2 furin cleavage site [18]. Identification of new mutations is crucial for designing diagnostic reagents [19], slowing transmission, and reconfiguring vaccines against new variants. In addition, particular mutations, besides those specific to B.1.1.7, may in the future aid in tracing virus movements across Romania and worldwide. The genomic data obtained by various laboratories throughout the country, including ours, are centralized by the National Centre for Surveillance and Prevention of Communicable Diseases, and transmitted to national and regional departments of public health. This, together with epidemiological data, helped public health officials to institute quarantine measures and other restrictions to control the transmission and spread of the virus.

However, many European countries, including Romania, lag in genomic sequencing and the European Union recommends increased focused sequencing based on epidemiological data, transmission rates, infectivity, treatment failure, and S-gene dropout in PCR testing. Several factors affected the timely acquisition of genome sequence data in Romania, such as a relatively small number of genomic laboratories in the country, the high costs associated with equipment and analyses, and a lack of specialized laboratory personnel. However, a thorough characterization of strains circulating in Romania is required, as it contributes to developing usable diagnostic tests and vaccines, especially in light of notable differences between strains belonging to the same clade and the evolutionary capacity of SARS-CoV-2.

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Authors' Contributions

AL, MD, and MC contributed to the conception and design of the study. AL, OS, and RF contributed to the acquisition of data. AL and MC drafted the article. All authors revised the article for important intellectual content and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Mutation analysis.
[DOCX File , 21 KB - xmed_v2i3e28049_app1.docx]

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Abbreviations

Nsp: nonstructural protein
PCR: polymerase chain reaction
qPCR: quantitative polymerase chain reaction
S: spike

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Original Paper

Finding Potential Adverse Events in the Unstructured Text of Electronic Health Care Records: Development of the Shakespeare Method

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Abstract

Background: Big data tools provide opportunities to monitor adverse events (patient harm associated with medical care) (AEs) in the unstructured text of electronic health care records (EHRs). Writers may explicitly state an apparent association between treatment and adverse outcome (“attributed”) or state the simple treatment and outcome without an association (“unattributed”). Many methods for finding AEs in text rely on predefining possible AEs before searching for prespecified words and phrases or manual labeling (standardization) by investigators. We developed a method to identify possible AEs, even if unknown or unattributed, without any prespecifications or standardization of notes. Our method was inspired by word-frequency analysis methods used to uncover the true authorship of disputed works credited to William Shakespeare. We chose two use cases, “transfusion” and “time-based.” Transfusion was chosen because new transfusion AE types were becoming recognized during the study data period; therefore, we anticipated an opportunity to find unattributed potential AEs (PAEs) in the notes. With the time-based case, we wanted to simulate near real-time surveillance. We chose time periods in the hope of detecting PAEs due to contaminated heparin from mid-2007 to mid-2008 that were announced in early 2008. We hypothesized that the prevalence of contaminated heparin may have been widespread enough to manifest in EHRs through symptoms related to heparin AEs, independent of clinicians’ documentation of attributed AEs.

Objective: We aimed to develop a new method to identify attributed and unattributed PAEs using the unstructured text of EHRs.

Methods: We used EHRs for adult critical care admissions at a major teaching hospital (2001-2012). For each case, we formed a group of interest and a comparison group. We concatenated the text notes for each admission into one document sorted by date, and deleted replicate sentences and lists. We identified statistically significant words in the group of interest versus the comparison group. Documents in the group of interest were filtered to those words, followed by topic modeling on the filtered documents to produce topics. For each topic, the three documents with the maximum topic scores were manually reviewed to identify PAEs.

Results: Topics centered around medical conditions that were unique to or more common in the group of interest, including PAEs. In each use case, most PAEs were unattributed in the notes. Among the transfusion PAEs was unattributed evidence of transfusion-associated cardiac overload and transfusion-related acute lung injury. Some of the PAEs from mid-2007 to mid-2008 were increased unattributed events consistent with AEs related to heparin contamination.

Conclusions: The Shakespeare method could be a useful supplement to AE reporting and surveillance of structured EHR data. Future improvements should include automation of the manual review process.

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KEYWORDS

epidemiology; electronic health record; electronic health care record; big data; patient harm; patient safety; public health; product surveillance, postmarketing; natural language processing; proof-of-concept study; critical care

Introduction

Background

Avoidable patient harm continues to be a significant problem [1]. To learn of adverse events (AEs), that is, patient harm, related to US Food and Drug Administration (FDA)–regulated products, the FDA relies on spontaneous reports from manufacturers, health care providers, and the general public. Published deficiencies of these reports [2-10] include nonstatistical representativeness of harm and problems. Now that electronic health care records (EHRs) are very common [11] and often more informative than billing codes from payment claims [7,12,13], we have an opportunity to leverage them for automated surveillance of patient harm [3,7,14,15]. We had two inspirations for naming the method after William Shakespeare: (1) in his play *Macbeth* [16], a king named Macbeth is surprised by an attack on his castle by soldiers camouflaged by trees, even though he had been warned that his downfall would come when the woods moved; and (2) scholars have been using word-frequency methods to discuss the true authorship of works from Shakespeare's time [17].

EHRs for Postmarketing Surveillance

Many methods for finding prespecified AEs in text [6,7,9,18-40] rely on predefining potential AEs (PAEs) before searching for prespecified words and phrases or manual labeling (standardization) by investigators. Crucially, events described in text may not necessarily be attributed to AEs [14,25,41]. We wanted to develop a method to identify PAEs, even if unknown or unattributed, without any prespecifications or standardization of notes.

There are many challenges to automated use of EHRs:

- Diagnosis codes may be "invalid, insensitive or non-specific" [20]
- "Often the notes contain medical and non-medical abbreviations, acronyms, numbers and misspelled words, which make it difficult to recognize the critical information in the notes. In other words, certain types of information such as ADEs [adverse drug events], indications, and signs and symptoms are harder to detect than other information such as drug names" [24]
- Medical entities in EHRs notes "can span across multiple words" [24]
- "… there is a lot of ambiguity among relevant named entities. Depending upon the context, the same exact phrase can be an ADE, indication, or a sign and symptom" [24]
- Periods do not always indicate the end of a sentence ("Dr.," "1.23," etc) [24]
- "…notes are frequently ungrammatical and are often inconsistently formatted. Ambiguity is common: MS, for example, can mean mitral stenosis or multiple sclerosis" [12]
- EHRs are "…subject to access restrictions…" [6]
- "…[N]ot all events and outcomes are consistently captured…" [15]
- We observed that different medical specialties, nurses, and other health care providers used different vocabulary.

We used the Medical Information Mart for Intensive Care III (MIMIC-III) EHR data set [42,43] because it is available to scientists with human subjects research training. MIMIC-III focuses on critical care in a major Boston teaching hospital. A published report using MIMIC-III noted [36]:

> *...several sentence segmentation tools available in popular NLP [natural language processing] toolkits, such as NLTK31 and spaCy, were tested and did not work well in clinical notes. In clinical notes, sentences do not always end with regular punctuation marks such as a period or question mark. More specifically, both regular punctuation marks and newline characters can serve as sentence breakers; however, newline characters can also be used for text wrap. Moreover, enumeration-like and list-like formats are also common in clinical notes, especially for physical exam and list of medications.*

Many medical care AEs occur at higher frequency in hospital critical care settings and are related to complex illnesses, invasive procedures, and relatively long lists of treatments [44,45].

General Methods

Preprocessing

We used EHRs for critical care admissions within an adult hospital, the Beth Israel Deaconess Medical Center in Boston, MA. The Massachusetts Institute of Technology worked with the hospital to process EHRs from 2001 to 2012, including unstructured notes, into the MIMIC-III data set, which is publicly available to those meeting certification requirements. The research was designated as not human subjects research by the FDA Institutional Review Board under the Code of Federal Regulations, Title 45, Part 46 [46].

We removed admissions of patients aged <16 years and admissions without notes from the total of 58,976 hospital admissions, resulting in 49,284 admissions.

We noted during our initial manual review of the notes for dozens of admissions—to familiarize ourselves with the data—that discharge summaries did not include all PAE information in the progress notes. We decided to use all available notes for each study admission and created one document by concatenating them chronologically. The notes in the MIMIC-III database contained duplicated paragraphs, sentences, and lists. These duplications distort statistical analyses of terms used and hamper manual review of the notes. We applied the Bloatectomy package to remove the duplicate text from each admission document [47].

We removed the personally identifying information mask string and lowercased the text. We retained punctuation, numerals, and stop words because they convey clinical information and are sometimes components of abbreviations.

The Shakespeare Method

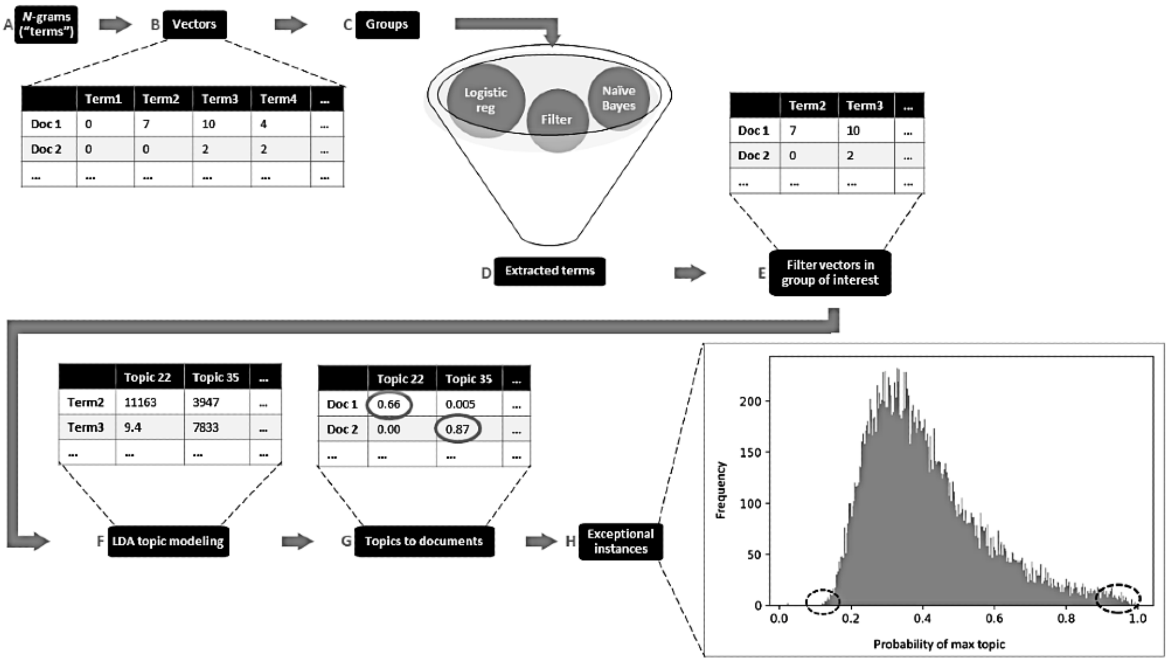
The Shakespeare method has five steps:

1. Convert each document into a vector of n-gram (term) frequencies.
2. Create groups of vectors: target and comparison.
3. Extract terms in the target group that are significant for the target group.
4. Apply topic analysis to the target group–filtered vectors.
5. Review the original documents that have topic scores of interest to interpret the topics and find PAEs.

We have published the code [48].

We selected two use cases to demonstrate the Shakespeare method: (1) comparing patients who received blood transfusion to those who did not and (2) comparing patient experiences in 1 year to the prior year. They shared step 1 (create n-gram vectors) of the Shakespeare method; we used the collocation detection skip-gram method for extracting the n-grams with n=1-5 consecutive words [49,50] (Figure 1A). We vectorized each document using a bag-of-words representation, where each dimension is represented by the frequency (count) of each n-gram (Figure 1B), resulting in a set of 7,422,044 words.

Figure 1. The Shakespeare method process with truncated examples. Step 1 (create n-gram vectors) includes (A) n-grams (terms) and (B) form vectors. Step 2 (create two groups) is (C) form groups. Step 3 (extract significant terms) is (D) extracted terms and (E) trim vectors in the group of interest. Step 4 (model topics) includes (F) latent Dirichlet allocation (LDA) topic modeling and (G) topics to documents. Step 5 (review topics) includes (H) identification of exceptional instances.



The Transfusion Case

Introduction

We decided to compare critical care patient admissions that involved blood transfusion (T) to comparison (C) admissions that had no transfusion events. An earlier version of the data set showed a higher risk of near-term mortality for patients receiving red blood cell transfusion compared to nontransfused patients [51]. By 2002, many transfusion AEs (TAEs) had been described [52]. During the time period covered by the data set, the transfusion research community recognized new TAE types—transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO)—that prompted new guidelines to reduce the use of transfusion [53]. Simultaneously, far fewer reports were coming to the FDA than would have been expected, considering the level of professional concern [54-56].

Study Objective

Our objective was to develop a method of using EHR notes to find recognized and unrecognized potential TAEs (PTAEs), which incidentally might also uncover other anomalies. We wanted our method to operate in the setting of the above-noted challenges.

Methods

We followed step 1 (create n-gram vectors) as described in *TheShakespeare Method* subsection of the *General Methods* section.

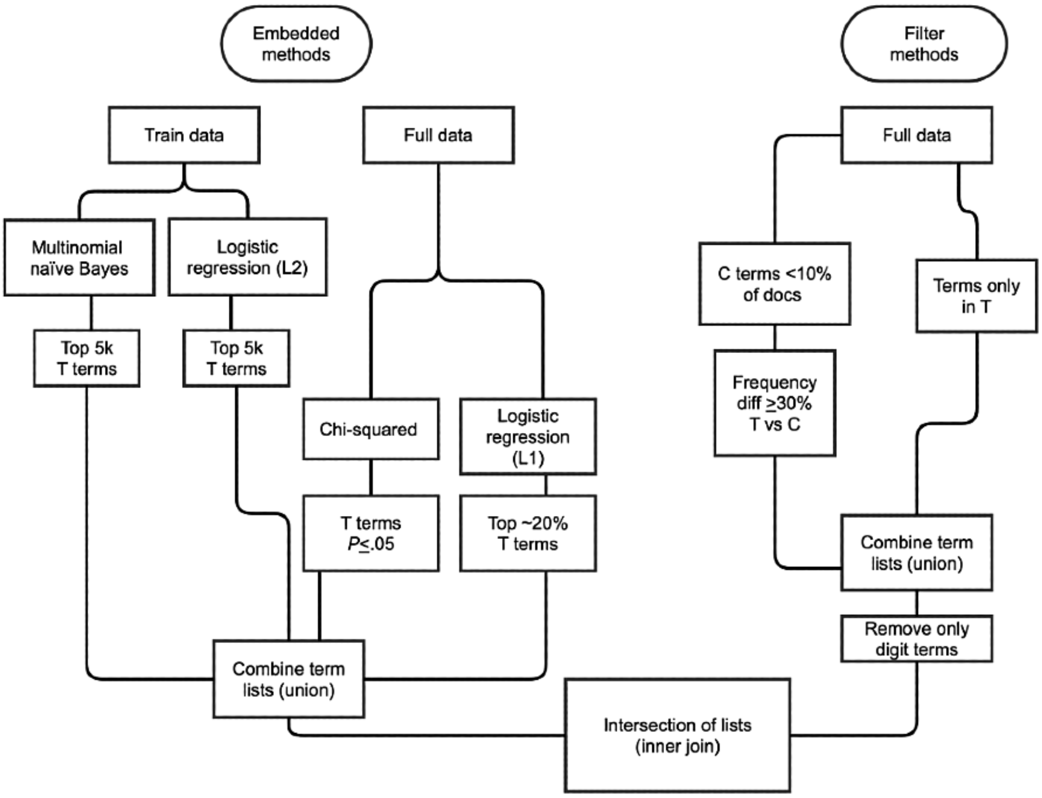
Transfusion Case Step 2: Create Groups

We used the blood transfusion (n=21,443 admissions) and comparison (n=25,468 admissions) groups described in prior work [57] (Figure 1C).

Transfusion Case Step 3: Extract Significant Target Terms

Our goal for steps 3 and 4 was to filter document vectors to only include terms that were significant to the transfused group and then model the topics within those terms in the transfused group to identify experiences emblematic of transfusion. We formalized the process of extracting these terms by looking at term coefficients associated with a classifier that learns to differentiate the two groups. We underwent an iterative process of trying multiple hyperparameters and classification models to identify these terms. We observed that an ensemble of two classification methods (naïve Bayes [NB] and logistic regression [LR]) and filtering [58-62] was useful for capturing common, infrequent, and rare terms that were significant for T. This term selection resulted in 41,664 terms (Figure 2). We reduced the T document vectors to include only the 41,664 terms (see Figure 1E for a truncated example).

Figure 2. Flowchart of the embedded-based and filter-based term selection processes for the transfusion case. T: transfusion, C: comparison.



Transfusion Case Step 4: Model Topics

Topic modeling is an unsupervised method commonly used in NLP to extract the most relevant terms for each topic (cluster) of similar documents [63,64]. We chose latent Dirichlet allocation (LDA) [65] to accomplish topic modeling of the T documents. LDA is a generative probabilistic model that results in interpretable dimensionality reduction, which means that we reduced 41,664 terms to 45 topics for our data. A topic is a multimodal distribution of terms over an entire vocabulary (in our case, all the filtered terms). A topic consists of co-occurring terms in this corpus of T documents. Each document can have a mixture of these topics. Each topic contribution in a document is a probability (we refer to this as a document topic score); thus, the scores of all topics for a document sum to 1 (Figure 3D).

We performed topic modeling (Figure 1F,G) by applying the LDA model to the filtered document word vectors (Figure 1E) to find co-occurring terms and group them into topics.

Topic modeling resulted in a matrix of scores for each term by each topic, which we refer to as term scores (Figure 1F). An additional matrix shows the probability of fit for each topic (Figure 1G).

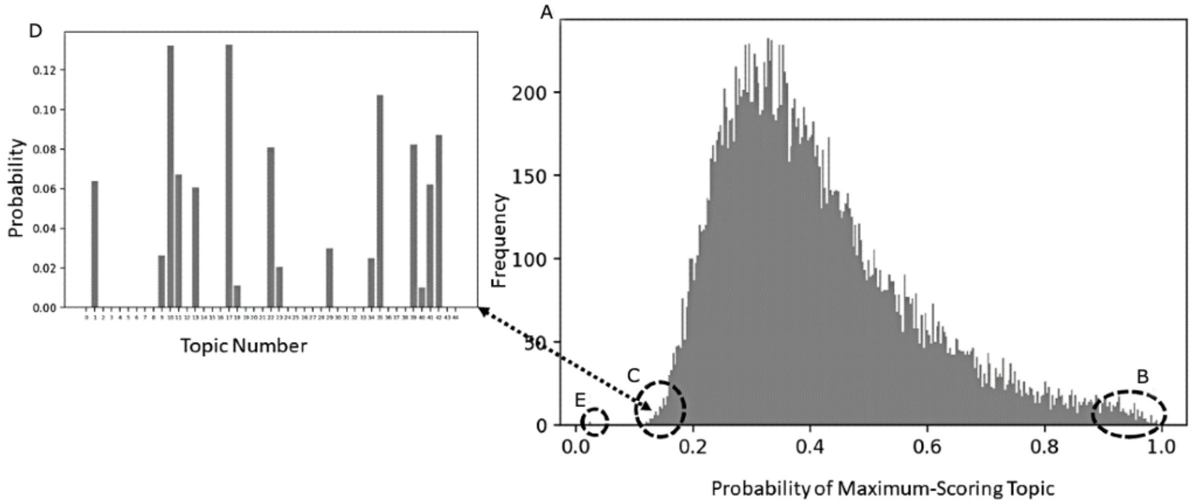
Figure 1G shows the topic document scores, and the maximum topic for each document is circled. This maximum topic is the topic that is the strongest for a document. When the maximum topic score is low, we can infer that the document fits many topics, which in critical care could mean that the patient has many clinical issues, some of which might be PTAEs and should be reviewed.

The maximum document topic scores distribution was plotted in the maximum topic histogram shown in Figure 3A. There were few documents in this corpus with a high maximum topic probability score (Figure 3B, right tail). Most of the documents were comprised of two or more topics (6.1 was the mean number of topics with a minimum score of ≥0.03).

A small number of documents in the left tail of Figure 3C had a low (<20%) maximum topic probability score, meaning that these documents were comprised of many topics. This was further illustrated in the inset (Figure 3D) displaying the topic distribution of a single document from this left tail, which had multiple topics. These extreme documents in the right and left tails were selected for manual review.

An important consideration for LDA is that the number of topics must be selected a priori. The results of topic modeling change depend on the number of topics assigned to a corpus—this is an iterative (hyperparameter tuning) process that requires human judgment to interpret the topics (based on the top terms in each topic) and determine which number of topics best fits the corpus. With too few topics assigned, topics are not cohesive and do not add any clarity or information to an analysis. With too many topics assigned, "incoherent" topics that do not capture terms common to the member documents proliferate; additionally, useful topics are likely split among smaller, more specific topics, although that does not limit the ability to analyze true clusters in the corpus.

Figure 3. Topic-modeling results for the transfusion case (T): (A) distribution of all maximum document topic scores for all T, (B) documents that have only one strong topic, (C) documents that have many topics, (D) all topic scores for a single document that has multiple topics, and (E) two documents with a score of 0.022 for every topic.



To tune the hyperparameters of the LDA model, we calculated models with the following numbers of topics: 25, 35, 45, 55, 65, 75, and 85. We observed (data not shown):

- As the number of topics rose, at first, clinically meaningful topics were added. Still, at higher numbers, the additional topics were incoherent, and the large, meaningful topics tended to split in ways that were not meaningful.
- The top words in topics were generally consistent for topics that were alike across multiple topics. For example, a mechanical ventilation topic was present whether the topic number was 9, 10, or 26.
- Although particular documents changed, the documents with high top topic scores had the top topic terms.
- Topics that had high document topic scores had overlapping concepts in the highest-scoring terms.
- Several topics were difficult to interpret and had low maximum values for both word scores and document topic scores.
- There were 1 to 2 dozen known TAEs [66,67].
- Many documents had several topics, reflecting the clinical complexity of patients in the critical care unit [68].

Transfusion Case Step 5: Review Topics

To evaluate whether topics described PTAEs, we selected the following records for manual document review: the three top-scoring documents for each of the 45 topics (Figures 1H and 3A,B), the 7 documents with the most topics with significant scores (≥0.03) (such as in Figure 3C), and 24 randomly selected documents from the T group. We abstracted events, observations, clinicians' attributions of causality, and clinicians' diagnoses, as well as their dates (where offered). We used further abstractions and tabulations to protect patients' confidentiality.

We tested comparisons with the Fisher exact test [69].

Results

Despite the inclusion of n-grams with a length of 1 to 5 in the vectorization, the terms that we extracted during classification were unigrams.

Distribution of Transfusion Topic Document Scores

A histogram of maximum topic scores (Figure 3A) showed the distribution of each document's maximum (strongest) topic. There were few documents in this corpus with a high maximum topic probability score (Figure 3B, right tail). The left tail of Figure 3C shows a small number of documents with a maximum topic probability score that is low, or less than 20%, suggesting these documents comprised many topics. Figure 3D illustrates this with the topic distribution of a single document from this left tail. The lowest maximum topic document score was 0.022. Two documents had topic document scores of 0.022 for every topic (Figure 3E). They each had only one short record: a brief electrocardiogram report.

There was no strict relationship between top word score and the frequency distribution of document topic scores (Figure 4). Table 1 shows the categories of maximum document topic scores per number of topics. It shows that if there is one topic, the score is over 0.50. As the number of topics increases, the maximum topic score declines. The average number of topics with a topic document score >0.03 was 6.1. The maximum topic document score was 0.994.

Figure 4. Distribution of topic document scores and top term scores for the transfusion case.

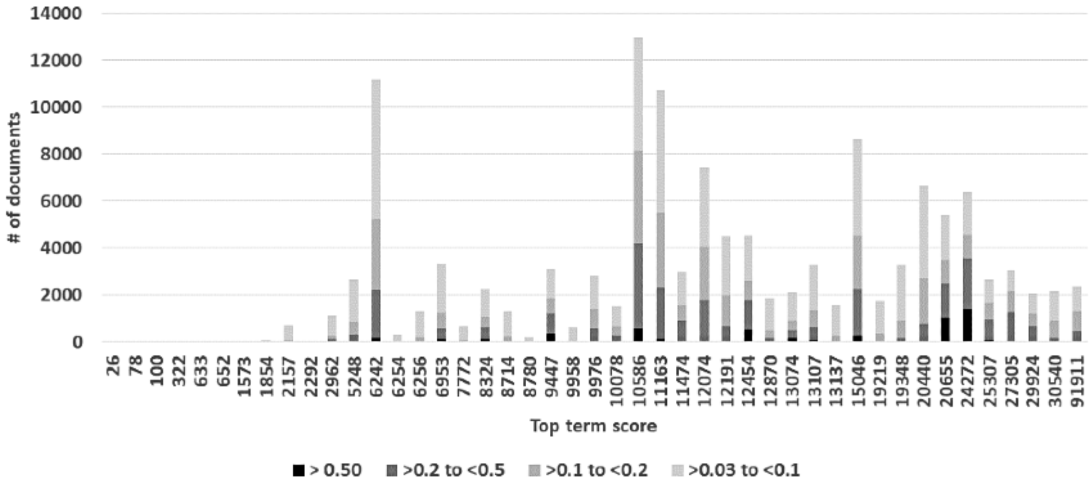


Table 1. Maximum document topic score in the transfusion case for documents in relation to number of topics in a document.

Number of document topic scores ≥0.03	Maximum document topic score, n		
	Score≥0.5	0.2≤score<0.5	0.1≤score<0.2
0	0	0	0
1	132	0	0
2	484	13	0
3	1121	326	0
4	1462	1138	0
5	1179	2582	0
6	610	3509	13
7	209	3595	85
8	55	2427	191
9	13	1183	265
10	0	414	173
11	0	113	91
12	0	25	25
13	0	2	5
14	0	0	1

Top-Scoring Documents for Each Transfusion Topic

Table S1 (Multimedia Appendix 1) shows, for each topic, the score for the top term, the top 20 terms, the top document score, and the distribution of documents by document score range. The rows are sorted by top document score. The maximum word score ranged from 26 to 91,911. The terms with the top 20 scores included plain English words, clinical words, acronyms, shortened words, and misspellings. The maximum document score for a topic went as high as 0.994. The document scores were widely distributed.

Table S2 (Multimedia Appendix 1) presents the summaries of 135 documents. As is expected when hyperparameters of the model are optimal, most topics (n=35) were "coherent," meaning the top documents had clear common themes within topics consistent with the lists of the top 20 terms in the topic. The coherent topics had higher top document scores and tended to be the maximum-scoring topics. Among the least coherent topics, the tendency for documents was to have some other topic as the maximum-scoring topic. This is expected with LDA, as the words that do not fit into a coherent topic will be allocated to separate "junk" topics.

The tabulation of the presence or absence of the notes expected to have the most clinical information showed that 122 had a discharge summary, 66 had a nursing note, and 21 had a physician progress note. None of the documents attributed an AE to transfusion in the billing codes.

New or worsening PTAEs occurring within 1 to 2 days in the T group were:

- In the heart category: atrial fibrillation, tachycardia, bradycardia, other heart rhythm abnormalities, hypotension;
- In the lung category: hypoxia, mechanical ventilation, bilateral pleural effusions, pulmonary edema;
- In the volume category: edema, diuresis therapy, acute kidney failure;
- In the absence of evidence for other infections: fever or chills.

Many documents (n=40) could not be evaluated for TAEs because either the transfusion dates were missing or there was no identified treatment when transfusion could be presumed. For others, there was a clear alternate reason for heart or lung problems: advanced cancer (n=7), thrombotic thrombocytopenic purpura present at admission (n=1), liver failure (n=1), and lung infection (n=1).

Out of the remaining 85 documents with transfusion data, 52 had evidence of PTAEs; the most common were heart PTAEs (n=35) and lung PTAEs (n=33), while non–infection-related fever or chills (n=12) and fluid overload (n=12) were less common. A few documents explicitly considered transfusion as the cause of AEs: in topic 30 (blood disease), one attributed disseminated intravascular coagulation to transfusion and another listed but discarded the possibility of TRALI or TACO, a document in topic 3 (bone trauma from motor vehicle accident) proposed PTAEs, and a document in topic 40 attributed a drop in platelets to transfusion. In 2 documents, the PTAEs were attributed to contrast (topic 37, kidney failure), a brand name for metronidazole (topic 38, colon problem), and surgery (3 cases of bone trauma from a motor vehicle accident).

Documents with transfusion timing but no apparent TAE were in the following topics: 10 (one of the mechanical ventilation topics), 2 (esophageal varices banding), 7 (spine surgery), 18 (gastrointestinal bleeding), 31, and 8. For 10 documents, separate transfusion and PTAE codes were present but were not conceptually linked.

We read 24 randomly selected documents to obtain 20 that did not have advanced cancer, cirrhosis, or severe lung trauma. They are summarized at the bottom of Table S2 (Multimedia Appendix 1).

The documents in the cardiovascular topic group were more likely than the random group to have any of the heart PTAEs (proportion difference=0.47; *P*=.02). The analogous analysis for 14 documents in the lung failure topic group showed a higher rate of any lung PTAEs (proportion difference=0.37; *P*=.049).

Table S3 (Multimedia Appendix 1) depicts the characteristics of the 8 documents that had 13 or 14 topics. Their document topic scores were distributed across many topics, and the notes described a large number of medical challenges to the patients. All of these documents had both discharge summaries and nurse progress notes. One physician wrote that the patient developed alloantibodies and had a delayed transfusion reaction. None of the billing codes linked transfusion to an AE, and in 2 records, the codes included an outcome code. All 8 documents provided dates of transfusion, including 3 for which cancer was the more likely cause of the AE. Of the remaining 5 documents, 3 had pulmonary PTAEs:

- The document with all three types of PTAEs had only one topic with a score above 0.1 (topic 42, heart attack), and the notes, but not codes, indicated the patient had a delayed transfusion reaction.
- The document with pulmonary and volume PTAEs had the following topics with scores ≥0.1: topic 42 (heart attack), topic 24 (tPA [tissue plasminogen activator] to lyse thrombus), topic 10 (cirrhosis), and topic 1 (x-ray confirmation of device placement). The notes attributed worsening acute kidney failure to an antibiotic.
- The document with only pulmonary PTAEs had the following topics with scores ≥0.1: topic 24 (tPA to lyse thrombus), topic 10 (mechanical ventilation), and topic 37 (kidney failure).

Discussion

The Shakespeare method successfully identified PTAEs. The three top-scoring documents in cardiovascular topics (topic 17, heart valve repair; topic 33, tapped pericardial effusion; topic 35, coronary artery bypass graft; topic 42, heart attack; and topic 11, vascular repair) were associated with cardiovascular PTAEs: atrial fibrillation, tachycardia, bradycardia, other heart rhythm abnormality, or hypotension, which are features of TAEs [66,67].

Mechanical ventilation and nitric oxide therapy (topics 9, 10, 16, and 26) were used to treat lung failure [70], which was also a topic (topic 29, acute respiratory distress syndrome). The associated breathing PTAE (hypoxia, mechanical ventilation, bilateral pleural effusion, and pulmonary edema) are components of TRALI and TACO [66,67].

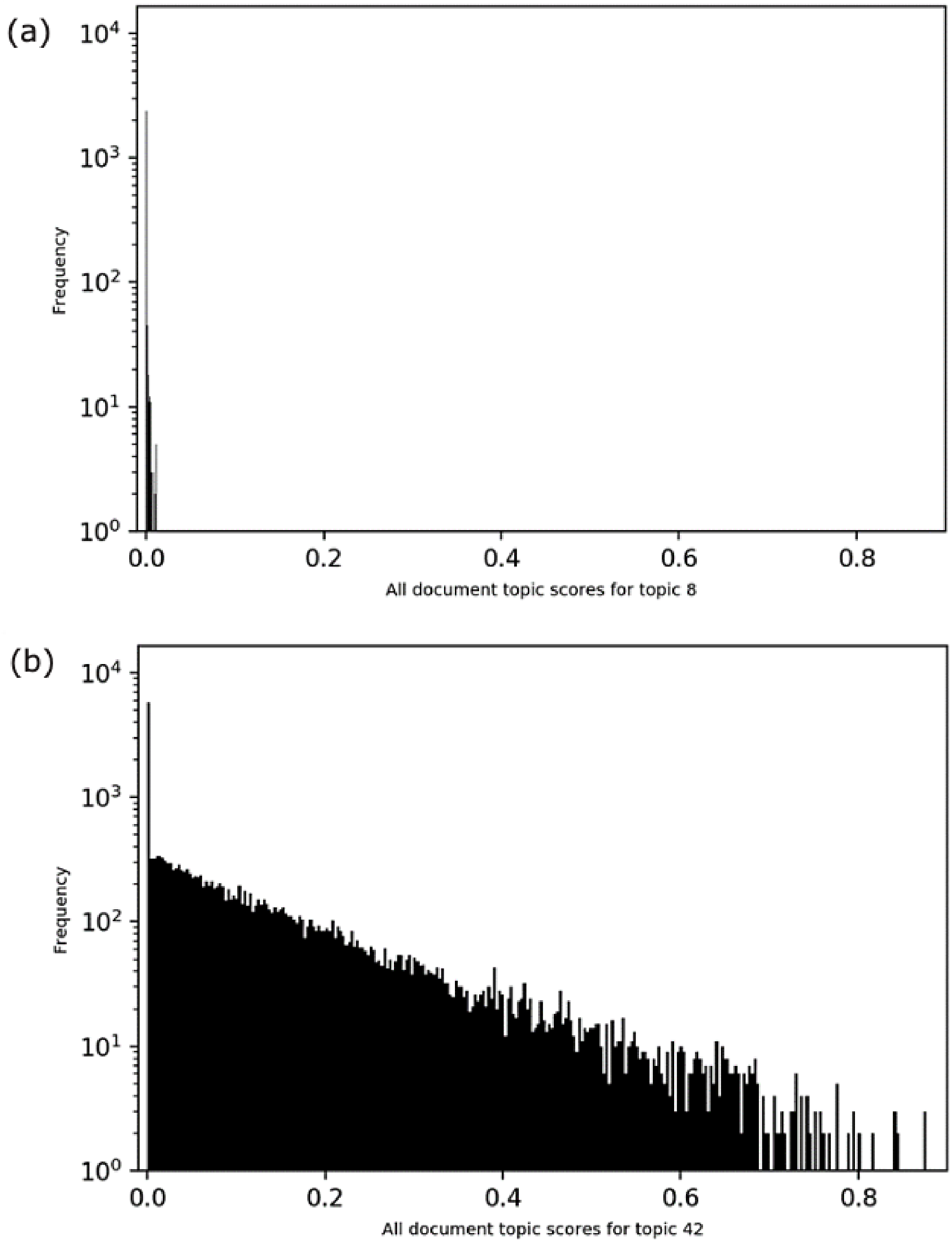
Other PTAEs that correspond with known TAEs were also observed in the top three documents of topics:

- Features of the volume overload component of TACO (edema, acute renal failure, and diuresis) [67];
- A feature of hemolytic transfusion reaction and febrile nonhemolytic transfusion reaction (fever without other signs of infection) [67].

Distribution of Transfusion Topic Document Scores

Incoherent topics had few or no documents with high topic document scores; most documents scored at or close to zero (see example in Figure 5A). A coherent topic follows a similar distribution, but the range is much greater, as seen in the x-axis of Figure 5B when compared to Figure 5A. The coherent topics received higher scores in many documents.

Figure 5. Distribution of document topic scores for two topics in the transfusion case: (a) topic 8, a noncoherent topic, and (b) topic 42, a coherent topic.



Top-Scoring Documents for Each Transfusion Topic

Many topics were conditions that can be reasons for transfusion: anemia [68]; heart attack [71]; blood disease (including blood cancers, chemotherapy, bone marrow transplant, neutropenia, thrombocytopenia, and pancytopenia) [68,72]; major surgery, vascular occlusion or repair, and gastrointestinal problems or bleeding [73]; and tPA to lyse thrombus, because antithrombotic treatment can cause bleeding [74].

Some topics could be consequences of the reasons for transfusion. Tapped pericardial effusion is a candidate because pericardial effusions can result from cancers, heart disease, aortic dissection, and other conditions [75] that prompt transfusion [76]. Past sternotomy, a consequence of heart surgery [77], is often a reason for transfusion [78]. Pneumomediastinum could be caused by surgery, or tearing of the esophagus or trachea [79], which in turn could be a reason to transfuse [73]. Skin breakdown can be a consequence of long-term bed rest [76,80], which is generally associated with critical illness and anemia [68], which in turn prompts transfusion [68].

Some could be alternate reasons for a PTAE: advanced cancer [81], liver disease [82], and infection [83].

Others could be a PTAE or sequelae of PTAEs: mechanical ventilation, which is a known consequence of TAEs [84,85]; pneumomediastinum, which could be caused by mechanical ventilation [79]; a tracheostomy tube, which is placed when long-term mechanical ventilation is anticipated [86]; acute respiratory distress syndrome, which shares features (noncardiogenic pulmonary edema and hypoxia) with TRALI [84] and is also known as acute lung injury and is treated with noninvasive or invasive ventilation [87]; and permanent hemodialysis indicating permanent kidney injury [88], which can result from hemolytic transfusion reactions [89] and is associated with volume overload [90], which is part of TACO [66].

Documents With Multiple Transfusion Topics

The high number of topics per document reflects the complexity of patients in the critical care unit. Multiple topics covering illnesses and procedures were expected for critically ill patients and were the norm for the vast majority of documents. The documents with 13 and 14 significant topics described many complex clinical problems consistent with the need for critical care. Several of the documents had a variety of PTAEs in more than one category, suggesting the importance of checking the documents with multiple nontrivial topics for PTAEs.

The Time-Based Case

Introduction and Study Objective

We wanted to simulate real-time analysis to find new or increasing events in the most recent time period. We examined whether the Shakespeare method would overcome the challenges of EHR texts to detect not only clinical and administrative changes but also trending PAEs, including those related to heparin contamination, which were first reported early in 2008 [91]. Heparin is an anticoagulant used in surgeries [91].

Methods

The MIMIC-III EHRs for critical care admissions used one medical record system from 2001 to 2008 and another system post-2008. We received the real dates, within several weeks, for the earlier data. We followed the same step 1 (create n-gram vectors) as described in *The Shakespeare Method* subsection of the *General Methods* section.

Time-Based Case Step 2: Create Groups

We then divided the study population into three cohorts: admissions starting between July 1, 2001, and June 30, 2006 (period 1; 14,410 documents); July 1, 2006, to June 30, 2007 (period 2; 3581 documents), and July 1, 2007, to June 30, 2008 (period 3; 3296 documents).

Time-Based Case Step 3: Extract Significant Target Terms

To focus on new or increasing AEs, we reduced the number of words to analyze by filtering by whether they were unusual and increasing (or new) in period 3 compared to period 2 (Figures 1C,D and 6A). We adopted two parallel approaches, as shown in Figure 6: (1) binary classification of the notes and (2) analysis of term frequency between periods 3 and 2.

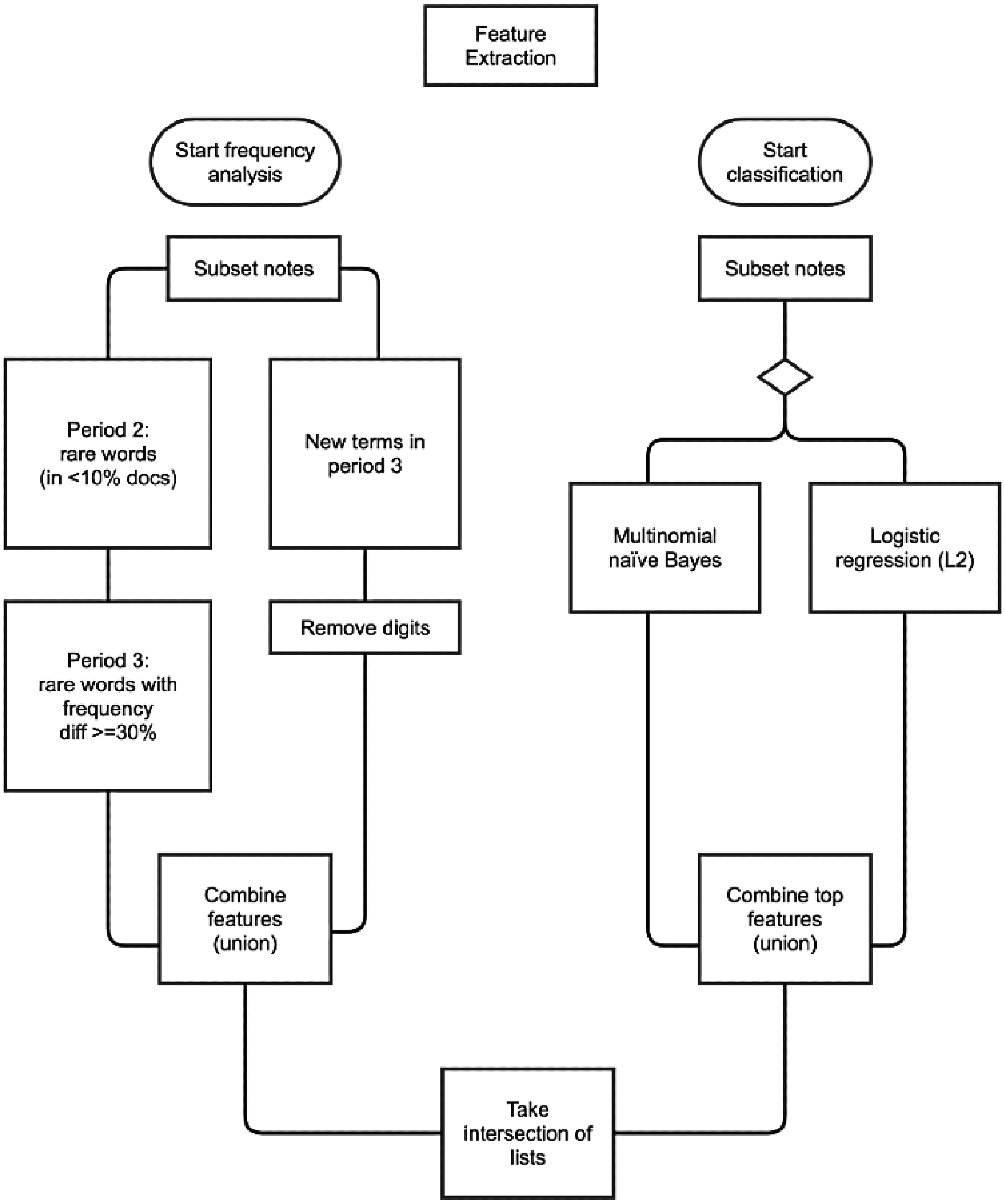
For the binary classification, we fit two classification models: LR with L2/ridge regularization [61] and multinomial NB [59,60]. Model evaluation found LR outperformed NB (with a weighted average F1 score of 0.76 compared to NB's weighted average F1 of 0.69), but that NB more effectively identified completely new terms in the target time period.

After evaluating the models, we refit both models without a train-test split on the entire 24-month data set and combined the top 5000 features from LR (those with the highest positive coefficient associated with the positive target class) and the top 5000 features from NB (those with the lowest log probability ratio). Combining the lists resulted in a set of 9896 terms.

We used frequency analysis to find emerging rare clinical events. We identified two groups of terms: (1) those which appeared in fewer than 10% of documents in period 2 and saw a 30% increase in raw frequency in period 3, and (2) any terms that never appeared in period 2 and did appear in period 3. For those new terms appearing in period 3, we filtered out digit-only terms (a large number of terms in this group).

For the final feature set, we took the intersection of terms identified from the binary classification and frequency analysis processes. This resulted in 6122 significant terms identified from the initial 117,049 unique terms in the documents from period 3 (5.2% of terms). We revectorized (Figure 1E) the 12-month corpus from period 3 using the combined feature list as our vocabulary (which has the effect of filtering the notes to only include terms in the vocabulary).

Figure 6. Feature extraction flowchart for the time-based case. This demonstrates the two parallel processes for extracting relevant features prior to topic modeling on the notes: term frequency analysis and binary classification of notes.



Time-Based Case Step 4: Model Topics

The co-occurrence of words in documents in the last time period was analyzed with LDA topic analysis [65]. We chose the final number of topics (n=20) based on a balance of large and small topics and at least one topic with no substantive words. We used the words with the highest scores of their relationship to topics (Figure 1F), as well as the topic document scores that indicate the probability of the topic fit for a document (Figure 1G), to explore topic meanings. We manually read the three top-scoring documents for each topic (Figure 1H).

Time-Based Case Step 5: Review Topics

Documents from selected individual admissions, as well as summary data from July 2001 to June 2008, were used to evaluate whether any topics formed around AEs. Most topics inspired time plots of selected words, diagnosis codes, or procedure codes (see criteria in Table S4, Multimedia Appendix 1) through periods 1, 2, and 3. Slopes were analyzed for changes [92,93].

For this report, out of concern for patient privacy, we substituted generic words (such as "condition01," "condition02," etc) for rare conditions, drugs, events, and languages since the year of admission is being presented. Related substitute words (eg, "condition09a," "condition09b") were used as synonyms.

Results

Table 2 shows the statistics for each topic. The strength of the maximum word score in a topic roughly corresponded with the number of admissions that had strong matches with the topic. The words in many of the topics seem to readily suggest interpretations, for example, long complex stay (topic 18), heart problem (topic 3), trauma (topic 19), cardiac catheterization (topic 7), brain (topic 1), cardiac catheterization (topic 17), abdomen (topic 12), uterus (topic 16), and a foreign language (topic 2). The other topics were deemed broad.

Table 2. The score for the top term, top 20 substantive terms, top document score, and distribution of documents by document score range for each topic in the time-based case. “Substantive” terms had topic scores above the minimum topic score.

Topic #	Top term score	Top 20 substantive terms	Top document score	Documents in topic score range, n				
				≥0.03	≥0.5	≥0.2 to <0.5	≥0.1 to <0.2	≥0.03 to <0.1
18	75,372	for, hr, plan, vent, intubated, cont, today, skin, are, family, per, support, increased, off, goal, iv, placed, trach, foley, pain	0.99	1793	505	623	326	339
3	42,070	for, hr, pain, bp, are, you, iv, family, time, ccu, per, sats, note, heart, micu, received, skin, if, acute, plan	1.0	2224	912	697	328	287
19	39,731	for, are, pain, you, comparison, acute, upper, evaluate, iv, trauma, hospital, if, note, time, large, level, pleural, wbc, read, throughout	1.0	2089	355	880	468	386
7	30,722	for, are, pain, pleural, cabg, hr, plan, per, comparison, off, bp, pericardial, time, neo, iv, heart, md, mm, mr, catheter	1.0	1686	589	321	319	457
1	12,352	for, are, family, subarachnoid, mm, comparison, pain, iv, occipital, sdh, large, evaluate, plan, cont, acute, craniotomy, per, hr, note, goal	1.0	749	181	235	118	215
4	3523	catheter, pleural, for, pain, jp, [pain-reliever], placed, large, into, pigtail, hr, cont, french, increased, are, pseudoaneurysm, upper, skin, iv, comparison	0.54	683	1	75	180	427
17	3462	for, are, mca, into, time, catheter, arteriogram, occlusion, mm, acute, french, ica, iv, placed, territory, large, cont, comparison, goal, family	0.77	534	39	99	127	269
12	216	[condition01], section, gynecology, [condition02], dystrophy, cesarean, [anti-thyroid], transabdominal, [event01], lmp, wk, [procedure01], [progesterone], prenatal, [condition03], [condition04], [antispasmodic], enteropathy, [condition05], [condition06]	0.22	31	0	1	7	23
11	75	pentobarb, pentobarbital, cmv, encasement, prison, [condition07], satellite, hematologic, rent, [condition08], [condition09a], [condition09b], [antibiotic], federal, bleach, [device01], allergic, [rare-word01], cluster, [rare-word02]	0.11	26	0	0	1	25
5	63	[rare words, misspelled words]	0.05	1	0	0	0	1
15	36	[rare words, misspelled words]	0.13	2	0	0	2	0
16	15	[rare words, misspelled words]	0.11	2	0	0	1	1
6	14	[rare words, misspelled words]	0.02	0	0	0	0	0
10	11	[rare words, misspelled words]	0.06	2	0	0	0	2
0	10	[rare word]	0.04	1	0	0	0	1
2	9	[rare words, foreign language words, misspelled words]	0.12	3	0	0	1	2
14	8	[rare words, misspelled words]	0.03	1	0	0	0	1
9	7	[rare words, misspelled words]	0.07	2	0	0	0	2
13	6	[rare words, misspelled words]	0.06	3	0	0	0	3
8	0	—[a]	0	0	0	0	0	0

[a]Not applicable.

Common Topics for the Time-Based Case

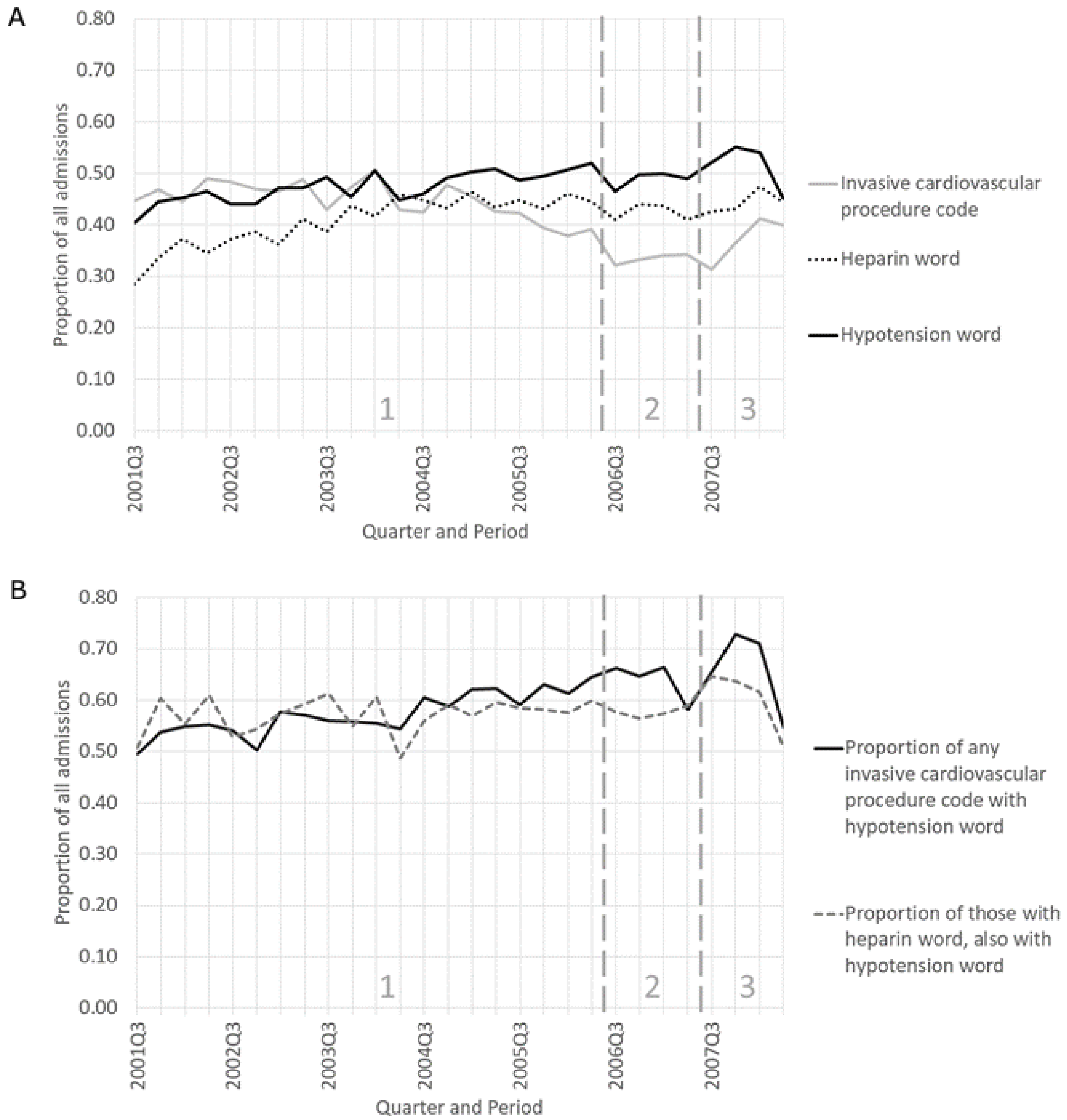
For the most common topics, the admissions with the top three topic match scores are summarized in Table S5 (Multimedia Appendix 1). For the topics with words that suggested an interpretation, the records supported the interpretations. For the other topics, the records suggested interpretations that were consistent with the top words. Each of the three top-scoring admissions within a topic were quite similar to each other (an indication that the topics were coherent and the model was working correctly, with the exception of the third admission in topic 3).

The three top-scoring documents for topic 18 described long complex stays, which included large numbers of notes. The general words in the topic ("for," "hr," "plan," "cont," "today," "skin," and "are") were nearly ubiquitous in periods 2 and 3. The words indicating mechanical ventilation ("vent," "intubated," and "trach") were present in between 51% and 58% of the admissions per quarter in periods 2 and 3, with a slight, clinically insignificant increase for period 3. The lengths of stay and numbers of notes also did not vary between periods 2 and 3.

We noticed that among the five records in Table S5 (Multimedia Appendix 1) that mentioned cardiac catheterization, all mentioned explicit or implied dosing with heparin followed the same day with hypotension that required treatment (heparin is generally part of cardiovascular procedures) [94].

Topics 3 and 7 both have cardiac catheterization for heart problems in common; for 5 out of 6 instances, the procedure or heparin administration was followed by hypotension (4 instances) that needed to be treated or heart rhythm deterioration (1 instance). To investigate whether these potential heparin AEs were increasing between July 2001 and June 2008, we plotted two measures of exposure (an invasive cardiac procedure code and "heparin") and a measure of AE ("hypotension"). The proportion of admissions that had invasive cardiovascular procedure codes (Figure 7A,B) declined overall (Figure 7A), but had a local increase in period 3 compared to period 2. In contrast to the procedures, the words "heparin" and "hypotension" showed an overall rough increase over the entire time frame. We also noticed that the proportion of admissions with invasive cardiology codes that had the word "hypotension" increased gradually over time (Figures 7A,B), followed by a drop in the last quarter; the pattern was similar and weaker for the proportion of admissions with "heparin" that also had "hypotension." There was a decrease in "hypotension" in the last quarter, both as a proportion of all admissions, and as a proportion of either indicator of having been exposed to heparin.

Figure 7. Heparin and hypotension for the time-based case (see Table S4 [Multimedia Appendix 1] for search criteria details). (A) Invasive cardiology-, heparin-, and hypotension-related criteria as a proportion of all admissions. Invasive cardiology is presumed to involve heparin treatment. For invasive cardiovascular procedure code, slope=–0.0053 (95% CI –0.0069 to –0.0037), *P*<.001; for heparin word, slope=0.0039 (95% CI 0.0025-0.0054), *P*<.001; and for hypotension word, slope=0.0029 (95% CI 0.0017-0.0040), *P*<.001. (B) The word "hypotension" as a proportion of presumed heparin exposure. For the proportion of any invasive cardiovascular procedure code (presumed to involve heparin), slope=0.0055 (95% CI 0.0038-0.0072), *P*<.001. For the proportion of those with "heparin," slope=0.0013 (95% CI –0.00036 to 0.0030), *P*=.12.



Other Common Topics for the Time-Based Case

Topic 19 (and 13) corresponded with trauma. Figure 8 shows that trauma diagnosis and procedure codes increased steadily over time through periods 1 to 3.

The brain topic (1 and 17, combined) was centered around admissions for brain injury (ie, bleeding, ischemia, or trauma). Figure 9A-C shows that there were local increases in codes for bleeding and ischemia for period 3 compared to period 2. There were slight increases in the codes for all three types of brain injuries overall. The text words indicating these conditions showed similar trends.

Topic 4 describes prolonged drainage after abdominal surgery. The index surgeries were performed before admission for 2 instances and during hospitalization for the third. Figure 10 shows that codes for wounds were quite infrequent. However, long patient stays with words for leaky surgical wound or catheter were more common, rose gradually over time, and had a local increase in period 3, compared to period 2.

Condition01 was the subject of the three admissions with the top match scores for topic 12. The codes and words were generally rare for the three periods and showed a local increase between periods 2 and 3.

Figure 8. Trauma code, word, or both as a proportion of all admissions by quarter for the time-based case (see Table S4 [Multimedia Appendix 1] for search criteria details). For the proportion of trauma code, slope=0.0022 (95% CI 0.0014-0.0030), *P*<.001. For the proportion of the word "trauma," slope=0.0057 (95% CI 0.0047-0.0067), *P*<.001. For the proportion with both trauma code and word, slope=0.0019 (95% CI 0.0012-0.0027), *P*<.001.

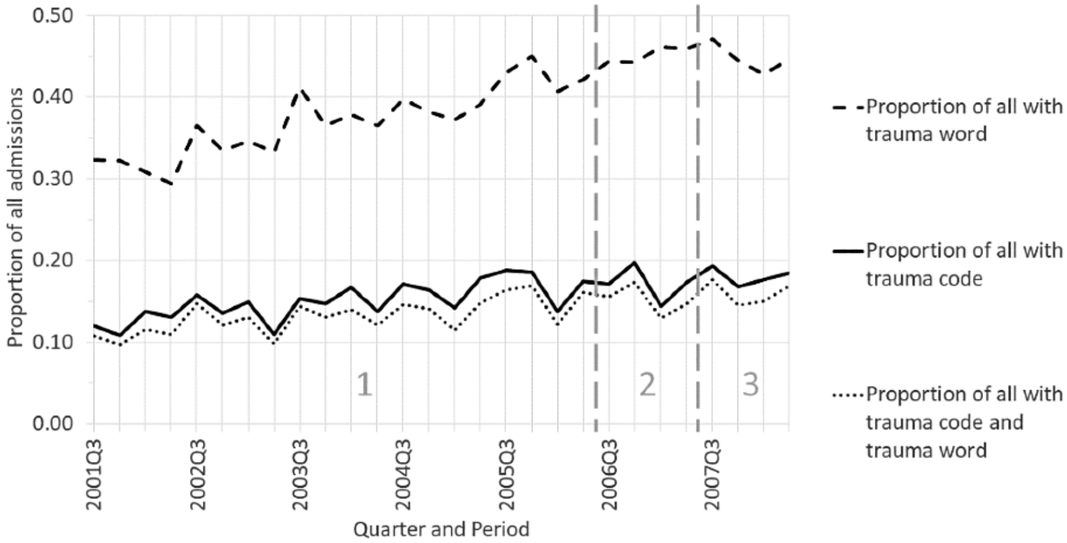


Figure 9. Brain ischemia codes or text words for (A) bleeding, (B) ischemia, and (C) trauma, as a proportion of all admissions by quarter for the time-based case (see Table S4 [Multimedia Appendix 1] for search criteria details). For brain bleed code, slope=0.00022 (95% CI –0.0006 to 0.0010), *P*=.61. For brain word and brain bleed word, slope=0.00039 (95% CI 0-0.00085), *P*=.10. For brain ischemia code, slope=0.00019 (95% CI 0.00051-0.0013), *P*<.001. For brain word and "occlusion*," slope=0 (95% CI –0.00064 to 0.00080), *P*=.84. For brain trauma code, slope=0.0013 (95% CI 0.00073-0.0018), *P*<.001. For brain word and "trauma," slope=0.0021 (95% CI 0.0014-0.0028), *P*<.001.

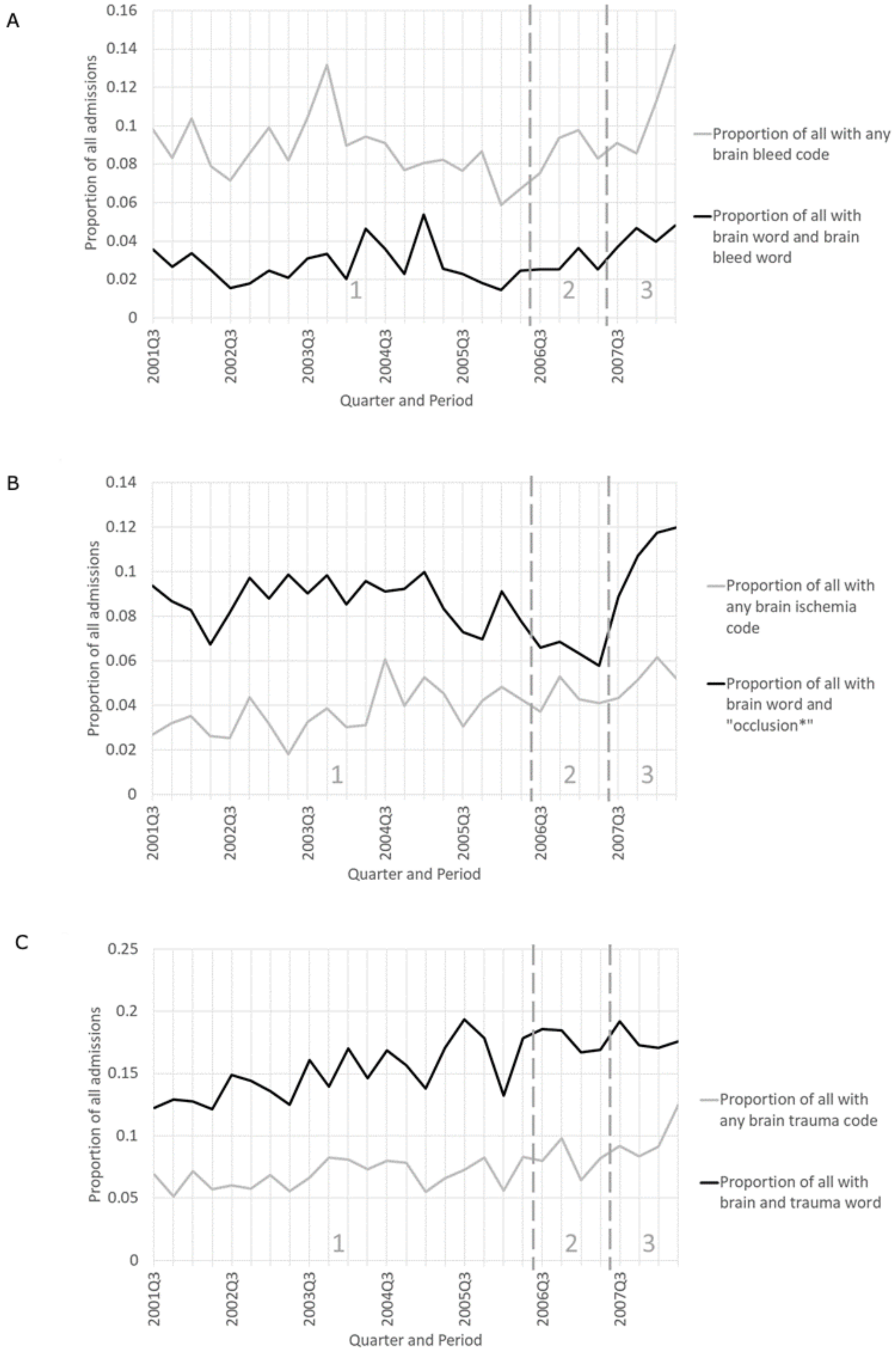
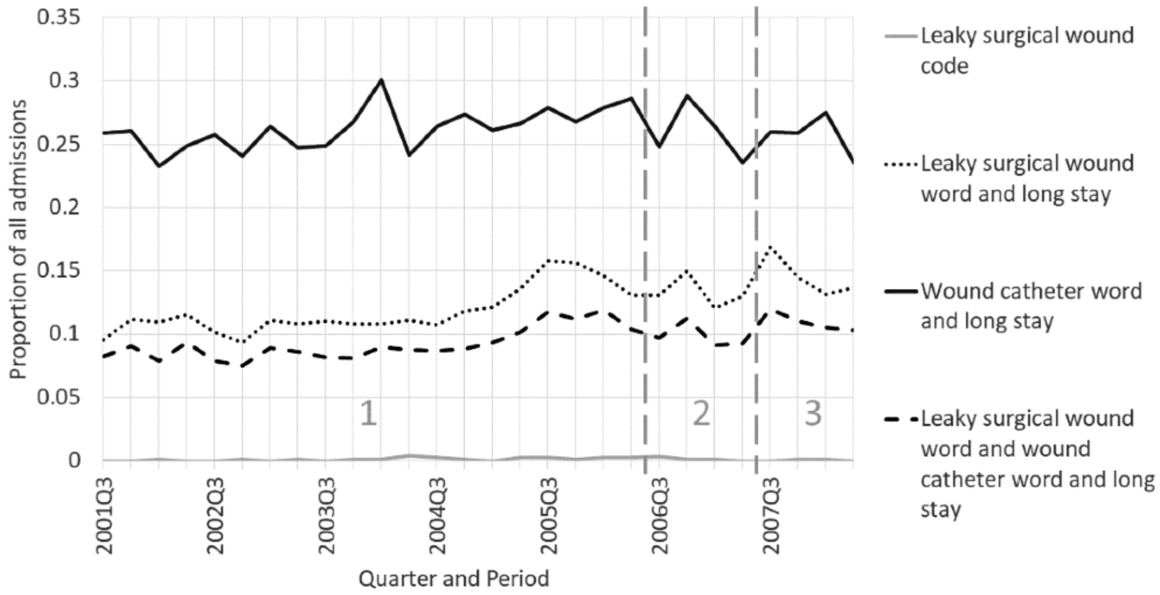


Figure 10. Excess draining from postsurgical wounds as a proportion of all admissions by quarter for the time-based case (see Table S4 [Multimedia Appendix 1] for search criteria details). For leaky surgical wound code, slope=0.000027 (95% CI –0.000028 to 0.000082), *P*=.34. For leaky surgical wound word and long stay, slope=0.0018 (95% CI 0.0012-0.0024), *P*<.001. For wound catheter word and long stay, slope=0.00038 (95% CI –0.00039 to 0.0012), *P*=.34. For leaky surgical wound word and wound catheter word and long stay, slope=0.0011 (95% CI 0.00071-0.0016), *P*<.001.



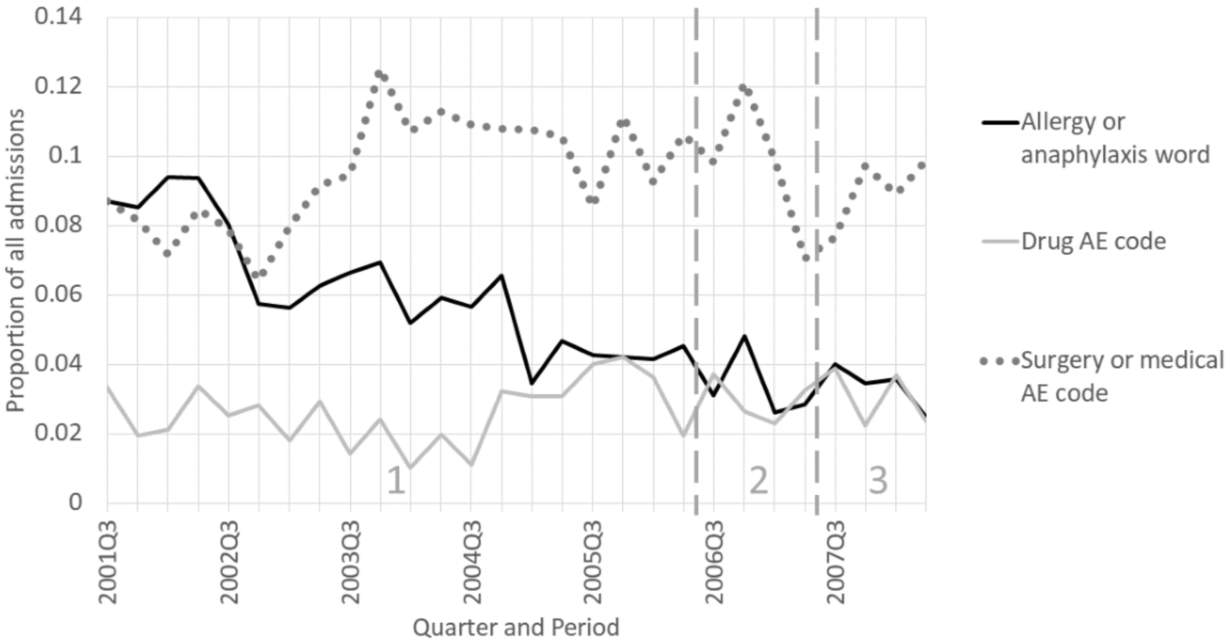
Less Common Topics for the Time-Based Case

Summaries of admissions with topic matching scores for the less common topics are shown in Table S6 (Multimedia Appendix 1). We examined the top-scoring admissions matched to topic 11 and all admissions matched to the others. All admissions in this table had topic match scores for the index topic of <0.15 (column 2). Despite each admission in Table S6 (Multimedia Appendix 1) having at least one strong topic match score for at least one of the strong topics in Table S5 (Multimedia Appendix 1), the topics in Table S6 are distinct from those in Table S5. Some of the topics have admissions that have common aspects (topics 11, 10, 2, 9).

A total of 14 PAEs evident in the notes were distributed among the less common topics: 13 related to medical therapy (6 medications, 3 medical devices, 2 procedures, and 2 combinations) and 2 were nonmedical. Five drug and all of the medical device PAEs were published in the product labels and/or in the medical literature. Of the PAEs, 9 occurred outside the hospital and were related to the reason for admission. The diagnosis and procedure codes generally did not give enough information to understand the specific cause and associated PAE. Figure 11 shows that while the proportions over the 7 years of admissions with allergy and anaphylaxis words steadily decreased, the diagnosis codes for drug AEs and for surgical or procedure-related AEs increased slightly over time.

The other rare and infrequent terms, related diagnosis or procedure codes, and foreign language sentences were rare throughout all three time periods and increased during period 3.

Figure 11. Allergy, anaphylaxis, and adverse effect (AE) as a proportion of admissions by quarter for the time-based case (see Table S4 [Multimedia Appendix 1] for search criteria details). For allergy or anaphylaxis word, slope=–0.0022 (95% CI –0.0027 to –0.0018), *P*<.001. For drug AE code, slope=0.00031 (95% CI –0.000079 to 0.00070), *P*=.12. For surgery or medical AE code, slope=0.00049 (95% CI –0.00022 to 0.0012), *P*=.18.



Discussion

We succeeded in our expectation of finding increases in clinical events and our hope of finding increases in PAEs, especially PAEs that were not attributed and thus likely not reported. We found increases in hypotension following heparin or presumed heparin exposure. Hypotension occurring in the cardiac catheterization lab could be a vasovagal reaction [95]. However, vasovagal reaction generally does not respond to fluids and drugs for raising blood pressure, and hypotension in all our observed patients did respond to treatment. Hypotension can occur as anaphylaxis begins and, alone, may reflect mild anaphylaxis. We note that the nurses and physicians that described the sequence of events did not link sudden hypotension to heparin and the diagnosis codes did not reflect any awareness of a link. The warnings from the FDA and the Centers for Disease Control and Prevention about heparin in the winter of 2007-2008 were for anaphylaxis due to contaminated heparin [96,97]. Knowledge of the extent of the distribution of contaminated heparin products was not specific, so it may have been in the hospital's stock at the time. We had expected to see increases starting in 2006 because a few articles indicate heparin may have been adulterated before 2007 [98-100], but were surprised that the increases had started before 2006. The reduction in the last quarter coincided with recalls of contaminated heparin products and lend credibility to the idea that contaminated heparin was in slowly increasing use at this hospital for many years. It is surprising that such a high proportion of the invasive cardiac catheter patients in the last 2 years experienced hypotension following heparin exposure (either as explicitly documented administration or implicitly in the catheter coating).

Other types of clinical event changes we detected from periods 2 to 3 were increases in patients with common conditions (heart disease, brain injuries, trauma, and complex conditions associated with long hospital stays), increases in rare conditions, change in administration (foreign language portion), and PAEs of concern. The increases in common conditions may have reflected hospital marketing [101]. The increases in rare conditions could have reflected chance, or marketing as a referral center.

Nine of the PAEs happened outside the hospital and illustrate the utility of hospital records for monitoring severe reactions that occur in other health facilities or outside the health care system. Our method was useful for detecting words that are rare in hospital records, partly reflecting events that normally occur outside the hospital.

The topic with the highest document score exhibited behavior typical of a topic containing words that are common to most documents. The filter that was removing words comprised of only digits also removed digits from some words. This resulted in some high-frequency words entering the vocabulary. When topic modeling, this resulted in high scores for these common words in the topics where they were correlated (as expected, this happened in several topics) and created a common word topic (topic 18). This topic is a noise topic; the LDA model will put words that are low scoring and not correlated with other topics into their own noise topic in order to deal with noise and frequent words. Because this topic included words that were frequent in almost all documents, the document topic scores for this topic were high as expected [102]. This was dealt with by looking at the other more coherent topics that were assigned to each document (essentially ignoring this common-noise topic), capturing what most documents had in common. The top-scoring words in this topic that were general survived the ensemble filtering method as an artifact of the digit-removal step. For future work, we recommend removing this step from the filtering process and relying on the classification terms to filter out irrelevant variations of terms.

Our method worked despite:

- The known challenges posed by clinical text notes;
- Restriction to one major hospital;
- Lack of all surgical and non–critical care unit nursing notes, and variable lack of physician, nursing, or discharge summary notes, probably reflecting the hospital policy of gradually converting types of notes to EHRs [103];
- Errors up to several weeks in dates.

Different, and hopefully improved, results may be derived from EHR databases that are more complete and have actual dates.

Discussion of the Shakespeare Method

Comparison of the Shakespeare Method to Other Applications of LDA Topic Modeling

LDA topic modeling has been used for a variety of NLP tasks [63,64] (although it can also be used on other high-dimension data) such as text classification and filtering [65]. LDA topic modeling has been applied to the unstructured notes of EHRs to describe clinical groups [104-108] and predicting outcomes [109-116]. We were unable to find published instances of LDA topic-modeling applications for AE detection. Furthermore, we found none that apply LDA topic modeling to words or phrases in documents in the group of interest that are filtered to terms that most significantly distinguished a patient group of interest from a comparison group. This filtering process was essential for identifying topics describing the unique qualities of target versus comparison groups. Additionally, to our knowledge, we were the first to check the interpretation of documents with large numbers of topics with nontrivial scores.

The chosen number of topics was effective for identifying a range of PAEs. Evaluation of the overlap of topics and contents of documents identified for the varying numbers of topics has not been reported in the literature. Our iterative approach to evaluating different hyperparameters demonstrated, to our satisfaction, the relative stability of PAEs indicated by topics.

We determined the number of topics based on our experience of tuning the hyperparameters, the number of AEs reported in the literature, and the complexities of critical care patients. We were satisfied with the number because there was both overlap of topics that simultaneously had high word and document scores and some incoherent topics with low scores. As the number of topics becomes too large, additional topics are uninterpretable, and that as data set size increases, more robust topics are generated [117]. A systematic evaluation of the number of topics and other hyperparameters is always necessary for LDA topic modeling in a new setting.

LDA topic modeling has enabled identifying records for specific patients [118] who are or were clinically similar to an index patient. Identification of specific admissions is crucial to investigate PAEs. As reported in other studies [104], the topics with high scores tended to have good overlap of documents with similar clinical course and PAEs. Minor adjustments to the number of topics would still result in identifying the same PAE, even if different documents receive the top scores.

In the setting of using EHR notes with topic modeling to predict an outcome, studies noted that bigrams, trigrams, and unusual words added predictive ability [104,109]. Only unigrams survived our filtering process; however, different use cases or hyperparameter settings could yield useful multiword n-grams.

Use of Classification to Filter Document Vectors

As noted before in the transfusion case, we were initially surprised that primarily unigrams (and not the longer sequences) appeared to play a significant role in distinguishing transfusion from comparison texts. We believe it is possible that enough unigrams that were part of meaningful phrases were also in other phrases or were significant on their own to result in relatively higher scores. For example, although "mechanical ventilation" conveys more meaning than just "mechanical" or "ventilation," each word occurs singly or in phrases other than "mechanical ventilation." We observed in the time-based case that similarly only unigrams survived classification.

Because bigrams and phrases were important in other LDA studies [104,109], we do not conclude that our unigram finding is necessarily applicable to other study settings. In this data set and blood transfusion and time-based cases, including only unigrams would not be expected to have changed the particular unigrams selected during the ensemble classification step. In other studies, it might be important to include n-grams where n>1.

Filtering the vectors to only terms that were important for focusing the topics on clinical conditions specific to the index condition, including reasons for and consequences of the condition, was important for identifying PAEs.

Unsupervised Methods for the Surveillance of AEs in EHRs

We observed that the notes contained much more AE data than explicit discussion. We also found more AE data in the notes than in the diagnosis and procedure codes. Our prior analysis of diagnosis codes [57] demonstrated that in transfused versus nontransfused patients, there were some explicit TAEs, as well as more frequent diagnoses that were similar to TAEs (TRALI vs breathing difficulty, TACO vs acute kidney failure, etc). None of the documents we manually reviewed for this transfusion study bore any explicit TAE diagnosis code. Our prior and current analyses demonstrate that effective surveillance could benefit from using unstructured text as well as codes.

Our method was successful despite the limitations of this data set. The extent of records for each admission grew during the time that the data were collected because of the hospital's policy of gradually adding more types of records to EHRs [103]. There was variation in the presence of nursing and physician progress notes in the examined records, which would not be present in the EHRs in systems that have long since become completely electronic. The presence of different types of records would logically have influenced the generated topics; for example, the topic on x-ray confirmation of device placement depends on the presence of radiology reports.

Much of our manual work to evaluate topics could be reduced with a combination of NLP and dictionaries of clinical terms. Dictionaries should include standard acronyms and common abbreviations, and should try to account for context when the meaning of a term could be ambiguous. The ability to decipher ongoing care notes will be important for noticing unrecognized signals of AEs.

Conclusions

Topic analysis of statistically significant words in target documents found records indicative of PAEs, even if the clinician did not explicitly state an outcome was a suspected AE.

Among the PTAEs were unattributed evidence of TACO and TRALI. Some of the mid-2007 to mid-2008 PAEs were increased unattributed events consistent with heparin contamination–related AEs. Our results suggest that heparin contamination may have started before it was officially recognized in the winter of 2007-2008.

This method succeeded despite a wide variety of vocabulary (discipline-specific, context dependence, misspellings, multiple-word expressions, acronyms, personal abbreviations, etc) and formats (sentences, phrases, free lists, formatted lists, etc) used in the text. The Shakespeare method would likely generalize to other EHR notes and other types of medical texts. The computing tools are accessible and openly available. Their application to EHRs broadens the number of types of entities that could independently conduct surveillance of AEs.

It will be useful to adapt NLP methods to automate the abstraction of the notes; the tools will need to be tailored to the various formats used in the notes by different disciplines and individual clinicians. The expansion of vocabulary and acronym lists will also be useful. Automation tools will help to understand how PAEs are distributed within and among topics.

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Authors' Contributions

All authors had access to the data. All authors were responsible for the study design, interpretation of results, and writing of the paper. RAB, SJB, and LAMP conceived the study and selected the use cases. RAB, SKR, KD, and SVB were responsible for methods development, data processing, and analysis.

Conflicts of Interest

The research was done with FDA support and under contract HHSF223201510027B between the FDA and Booz Allen Hamilton Inc. None of the authors have other relevant financial interests. The opinions presented in this paper are those of the authors and do not represent official policy of either the FDA or Booz Allen Hamilton.

Multimedia Appendix 1
Supplementary tables.
[DOCX File , 83 KB - xmed_v2i3e27017_app1.docx]

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Abbreviations

AE: adverse event
C: comparison group
EHR: electronic health care record
FDA: Food and Drug Administration
LDA: latent Dirichlet allocation

LR: logistic regression
MIMIC-III: Medical Information Mart for Intensive Care III
NB: naïve Bayes
NLP: natural language processing
PAE: potential adverse event
PTAE: potential transfusion adverse event
T: transfusion group
TACO: transfusion-associated circulatory overload
TAE: transfusion adverse event
tPA: tissue plasminogen activator
TRALI: transfusion-related acute lung injury

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Original Paper

Early Experience With Neutralizing Monoclonal Antibody Therapy for COVID-19: Retrospective Cohort Survival Analysis and Descriptive Study

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Abstract

Background: Neutralizing monoclonal antibody (MAB) therapies may benefit patients with mild to moderate COVID-19 at high risk for progressing to severe COVID-19 or hospitalization. Studies documenting approaches to deliver MAB infusions and demonstrating their efficacy are lacking.

Objective: We describe our experience and the outcomes of almost 3000 patients who received MAB infusion therapy at Northwell Health, a large integrated health care system in New York.

Methods: This is a descriptive study of adult patients who received MAB therapy between November 20, 2020, to January 31, 2021, and a retrospective cohort survival analysis comparing patients who received MAB therapy prior to admission versus those who did not. A multivariable Cox model with inverse probability weighting according to the propensity score including covariates (sociodemographic, comorbidities, and presenting vital signs) was used. The primary outcome was in-hospital mortality; additional evaluations included emergency department use and hospitalization within 28 days of a positive COVID-19 test for patients who received MAB therapy.

Results: During the study period, 2818 adult patients received MAB infusion. Following therapy and within 28 days of a COVID-19 test, 123 (4.4%) patients presented to the emergency department and were released, and 145 (5.1%) patients were hospitalized. These 145 patients were compared with 200 controls who were eligible for but did not receive MAB therapy and were hospitalized. In the MAB group, 16 (11%) patients met the primary outcome of in-hospital mortality, versus 21 (10.5%) in the control group. In an unadjusted Cox model, the hazard ratio (HR) for time to in-hospital mortality for the MAB group was 1.38 (95% CI 0.696-2.719). Models adjusting for demographics (HR 1.1, 95% CI 0.53-2.23), demographics and Charlson Comorbidity Index (HR 1.22, 95% CI 0.573-2.59), and with inverse probability weighting according to propensity scores (HR

1.19, 95% CI 0.619-2.29) did not demonstrate significance. The hospitalization rate was 4.4% for patients who received MAB therapy within 0 to 4 days, 5% within 5 to 7 days, and 6.1% in ≥8 days of symptom onset (*P*=.15).

Conclusions: Establishing the capability to provide neutralizing MAB infusion therapy requires substantial planning and coordination. Although this therapy may be an important treatment option for early mild to moderate COVID-19 in patients who are at high risk, further investigations are needed to define the optimal timing of MAB treatment to reduce hospitalization and mortality.

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KEYWORDS

infectious disease; monoclonal antibody therapy; COVID-19; experience; therapy; drug; patient outcome; risk; efficacy; approach; treatment; pandemic; antibody; immunotherapy; immune therapy

Introduction

In November 2020, the Federal Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the neutralizing monoclonal antibody (MAB) infusions bamlanivimab and casirivimab/imdevimab for treatment of early mild to moderate SARS-CoV-2 infection in patients at high risk for progressing to severe COVID-19 or hospitalization [1]. Bamlanivimab has been found to decrease viral load at 11 days, and exploratory analysis of COVID-19–related hospitalization suggested a decrease in hospitalization rate from 6.3% to 1.6% [2]. Additional studies of bamlanivimab in combination with etesevimab also found reductions in viral load and similarly found a reduction in hospitalization, although the latter was not the primary outcome [3]. Most recently, bamlanivimab coadministered with remdesivir did not demonstrate efficacy among patients who were hospitalized with COVID-19 without end organ failure [4]. To date, published data on the effectiveness of these therapies is mixed, and the National Institutes of Health correspondingly notes that data are insufficient to recommend for or against the use of MAB therapy for ambulatory patients [5].

Given the operational complexity and uncertain clinical effectiveness of setting up a MAB infusion program, widespread use has been slow across the United States [6]. Potential barriers to implementation include staffing challenges during disease resurgence, the necessity to provide infusions in a COVID-19 contained environment, transportation of underserved and older patients to infusion centers, and the need to obtain timely referrals from providers [7]. Mobile units have shown to be successful in a small study [8], although the ability to scale this solution appears limited. The Mayo Clinic recently reported their implementation of a program across multiple facilities in different states, culminating in over 4000 doses delivered [9].

Northwell Health, a 23-hospital integrated health care system in metropolitan New York, established outpatient infusion centers based on their experience with the spring 2020 surge [10], which stretched inpatient capacity. At the peak of the early surge, Northwell had more than 3400 COVID-19 inpatients, with over 800 receiving invasive mechanical ventilation. With the goal of reducing hospitalizations, intensive care unit admissions, and deaths during the fall and winter 2020 rise in cases, Northwell rapidly scaled a MAB infusion program. We reviewed our initial experience in using MAB therapy and describe the outcomes of almost 3000 patients who received this outpatient infusion therapy, the largest cohort with outcomes published to date.

Methods

This was a retrospective study of a large integrated health care system, with 23 hospitals and over 800 ambulatory locations. Data for this study were obtained from the enterprise inpatient and outpatient electronic health record (Sunrise Clinical Manager and Touchworks, respectively; Allscripts), our health information exchange (Healthshare; Intersystems), and our locally developed population health management tool (CareTool Listapp; Northwell Health).

Monoclonal Antibody Infusion Eligibility Criteria

Eligibility to receive MAB therapy as directed by the FDA EUA is limited to patients with a positive direct viral test for SARS-CoV-2 within 10 days of symptom onset. Patients must be ≥12 years of age, weigh at least 40 kg, and be at high risk for progressing to severe COVID-19 or hospitalization. High risk is defined as having one of the following conditions: age ≥65 years, obesity (BMI≥35 kg/m^2), diabetes mellitus (DM), chronic kidney disease (CKD), immunosuppressive disease, or currently receiving immunosuppressive treatment. Patients 55-64 years of age who have cardiovascular disease, hypertension, chronic obstructive pulmonary disease (COPD), or chronic respiratory disease also are eligible. Pediatric patients aged 12-17 years with one of the following conditions were also eligible: BMI≥85th percentile for age and gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders, a medical-related technological dependence, asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control.

Two MAB therapies were offered at Northwell, based upon availability: bamlanivimab (Eli Lilly and Company) and casirivimab/imdevimab (Regeneron Pharmaceuticals, Inc).

Monoclonal Antibody Infusion Operations

Northwell established a taskforce of clinicians paired with an operational team to develop a four-phase strategy and operational plan for MAB infusion. The initial phase established five outpatient infusion sites, all located on hospital campuses in freestanding buildings or in mobile hospital tents previously erected to accommodate the spring 2020 COVID-19 surge.

In recognition that the emergency department (ED) is often the health care access point in underserved areas, phase 2 established MAB infusions directly for treat-and-release ED patients meeting EUA criteria, who otherwise lacked resources to travel to an infusion center. Phase 3 included administration of MAB therapy to eligible inpatients who developed COVID-19 while hospitalized for another cause and were COVID-19 negative on admission (all patients were tested upon hospital admission). The final phase included MAB therapy administration to patients in skilled nursing facilities, although with the rapid vaccine deployment supporting these facilities, this phase contributed only a small group of patients.

Information technology systems were configured to support patient referral, registration, and throughput in the infusion centers. Information about MAB therapy, the EUA, and referral instructions were disseminated widely to all Northwell's New York metropolitan area–affiliated providers. A dedicated call center and secure internal webpage were deployed to facilitate easy referral. The information collected included patient demographics and location, referring provider information, presence and details of COVID-19 symptoms and onset date, and screening of eligible comorbidities. The dedicated call center handled referrals, questions from providers and patients, and scheduling.

All patients were screened based on the EUA criteria at the time of referral. Infusion center staff training was created and deployed, including nursing competencies in biologic infusions and preparation with appropriate advanced cardiovascular life support protocols and equipment in the event of an infusion reaction. Specific patient protocols were developed to treat patient reactions to the infusion, including rapid response team evaluation and transfer to the local ED most proximate to the infusion center if necessary. To accommodate the EUA mandate for infusion within 10 days of COVID-19 symptom onset, the infusion centers were staffed 7 days a week.

Study Population

All adult patients (age ≥18 years) who received MAB therapy in an ambulatory or ED location between November 20, 2020, and January 31, 2021, were included. Pediatric patients, inpatients, and skilled nursing facility patients that received MAB therapy in this date range were excluded from the analysis. Data collected include demographics, comorbidities, symptoms and their date of onset, date of COVID-19 test, and outcomes (including ED presentation, hospital admission, and mortality).

We further identified all patients aged ≥18 years with a positive COVID-19 test between November 20, 2020, and January 31, 2021, who did not receive MAB therapy but were eligible based upon EUA criteria. We excluded patients with a COVID-19 positive test or hospitalization prior to the study period. The outpatient outcomes of these patients are described but not directly compared to the treatment group, as we did not have symptoms (presence, timing, type, or severity) for the nontreatment group.

Outcomes

We examined ED use and hospitalization within 28 days of a positive COVID-19 test for patients who received MAB therapy. A total of 9 patients were missing a COVID-19 test date; for these patients, we used the date of MAB therapy subtracted by the cohort median number of days from test to MAB therapy (4 days). The hospitalization rate by timing of MAB therapy relative to symptoms was also assessed.

For patients who were hospitalized, we performed a retrospective cohort study with a time-to-event survival analysis and a primary outcome of in-hospital mortality. The control group was selected from the population of patients who met eligibility for MAB therapy but did not receive it during the evaluation period.

Covariates

We included sociodemographic and clinical features, including patient age, sex, race or ethnicity, number of hospital visits in the prior year, comorbidities, and presenting vital signs. Race or ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other or multiracial, and unknown or declined. The comorbidities included DM, obesity, chronic respiratory conditions, COPD, CKD, hypertension, and immuno-compromising conditions (including the use of immunosuppressive medications). Presenting vital signs for patients hospitalized include heart rate, oxyhemoglobin saturation, temperature, and systolic and diastolic blood pressure.

Statistical Analysis

We reported descriptive statistics including median and IQR for skewed continuous measures and proportions for categorical measures. We compared baseline clinical characteristics between patients who were and were not hospitalized using Fisher exact tests for categorical variables and nonparametric Kruskal-Wallis tests for continuous variables. Patients were categorized into 3 groups based on timing of MAB therapy relative to symptom onset date (0-4 days, 5-7 days, and ≥8 days) to assess the difference in hospitalization rate.

For a univariable time-to-event analysis comparing mortality risk, we used the Kaplan-Meier survival curve to estimate in-hospital mortality to 28 days. Cox proportional hazards regression models were used to estimate the association between MAB therapy and in-hospital mortality. We initially evaluated an unadjusted model; a model adjusted for age, sex, and race or ethnicity; and a model that added the Charlson Comorbidity Index (CCI) to the prior model. The primary analysis used inverse probability weighting (IPW), whereby the predicted probabilities from a propensity score model were used to calculate the stabilized IPW weight. The covariates included in the propensity model were age, sex, race or ethnicity, number of hospitalizations in prior year, and comorbidities and presenting vital signs (listed in the Covariates section).

All analyses were performed using the R programming language, version 4.0.3 (R Foundation for Statistical Computing). A *P* value <.05 was considered significant. The Institutional Review Board of Northwell Health approved the study protocol before the commencement of the study. Individual-level informed consent was not obtained given the retrospective nature of the analysis of a large electronic medical record.

Results

Overview

From November 20, 2020, to January 31, 2021, 2818 adult patients with symptomatic COVID-19 received MAB infusion at Northwell Health: 2745 (97%) ambulatory and 73 (3%) ED (Table 1). An additional 21 pediatric patients and 59 hospitalized patients received MAB therapy and were not included in the analysis. The median patient age was 67 (IQR 58-74) years, and 59% (1648/2818) were 65 years or older. The gender distribution was split evenly between males (n=1412, 50.1%) and females (n=1406, 49.9%). Most patients were non-Hispanic White (n=2061, 73%), 104 (3.7%) were non-Hispanic Black, and 168 (6%) were Hispanic. Hypertension was the most common comorbidity (n=1011, 36%), followed by obesity (n=401, 23%). The most common symptom was cough (n=1954, 70% of patients), followed by malaise (n=1471, 53%), fever (n=1422, 51%), and headache (n=820, 30%). Although cough as the sole documented symptom was most common, many patients had multiple presenting symptoms (Figure S1 in Multimedia Appendix 1).

Most patients developed symptoms prior to a COVID-19 test (median 2, IQR 1-3 days; Figure S2 in Multimedia Appendix 1). Among the patients with known symptom onset date, the median time from symptom onset to MAB therapy was 6 days (IQR 4-8; Figure S3 in Multimedia Appendix 1). MAB referral to infusion scheduling occurred in under half a day (median 0.05, IQR 0.01-0.54 days), and the MAB infusion occurred a median 1.75 (IQR 0.85-1.88) days after referral. Most patients received bamlanivimab (n=2501, 89%), with the remainder receiving casirivimab/imdevimab (n=317, 11%).

Following MAB therapy and within 28 days of a COVID-19 test, 123 (4.4%) patients presented to the ED and were released a median of 7 (IQR 5-11) days from a COVID-19 test. In a similar time frame, 145 (5.1%) patients who received MAB therapy were hospitalized a median of 7 (IQR 5-11) days after a COVID-19 test. The median time from MAB therapy to ED presentation therapy was 3 (IQR 0-6) days, and the median time from MAB therapy to hospitalization was 3 (IQR 1-8) days. A greater proportion of patients who were hospitalized following MAB therapy had comorbidities, including diabetes, hypertension, chronic kidney disease, respiratory disease, and immunosuppressive disease (see Table 1).

In the subgroup of patients where symptom onset date was known (n=2721, 96.6%), the hospitalization rate within 28 days of COVID-19 test was 4.4% (95% CI 2.9%-5.9%) for patients who received MAB therapy early (within 0-4 days of symptom onset), 5% (95% CI 3.6%-6.2%) for those within 5 to 7 days, and 6.1% (95% CI 4.6%-7.4%) for those who received it ≥8 days, although this was not statistically significant (*P* value for trend .15; Figure 1).

Among 2713 COVID-19–positive patients meeting eligibility criteria based on age or comorbidities but not receiving MAB therapy, the median age was 66 (IQR 55-73) years and 55% (n=1497) were female. Non-Hispanic White patients were most common (n=1596, 59%), and there were 183 (6.7%) non-Hispanic Black and 334 (12.3%) Hispanic patients. Symptoms were not ascertained for this group, but similar to the MAB therapy group, hypertension was the most common comorbidity (n=1119, 41%). A total of 142 (5.2%) patients and 200 (7.4%) patients in this group had an ED visit and inpatient hospitalization, respectively, within 28 days of a COVID-19 test. Patients hospitalized had a higher burden of comorbid conditions (Table S1 in Multimedia Appendix 1).

Table 1. Characteristics of 2818 patients with COVID-19 who received monoclonal antibody therapy in ambulatory or emergency department setting.

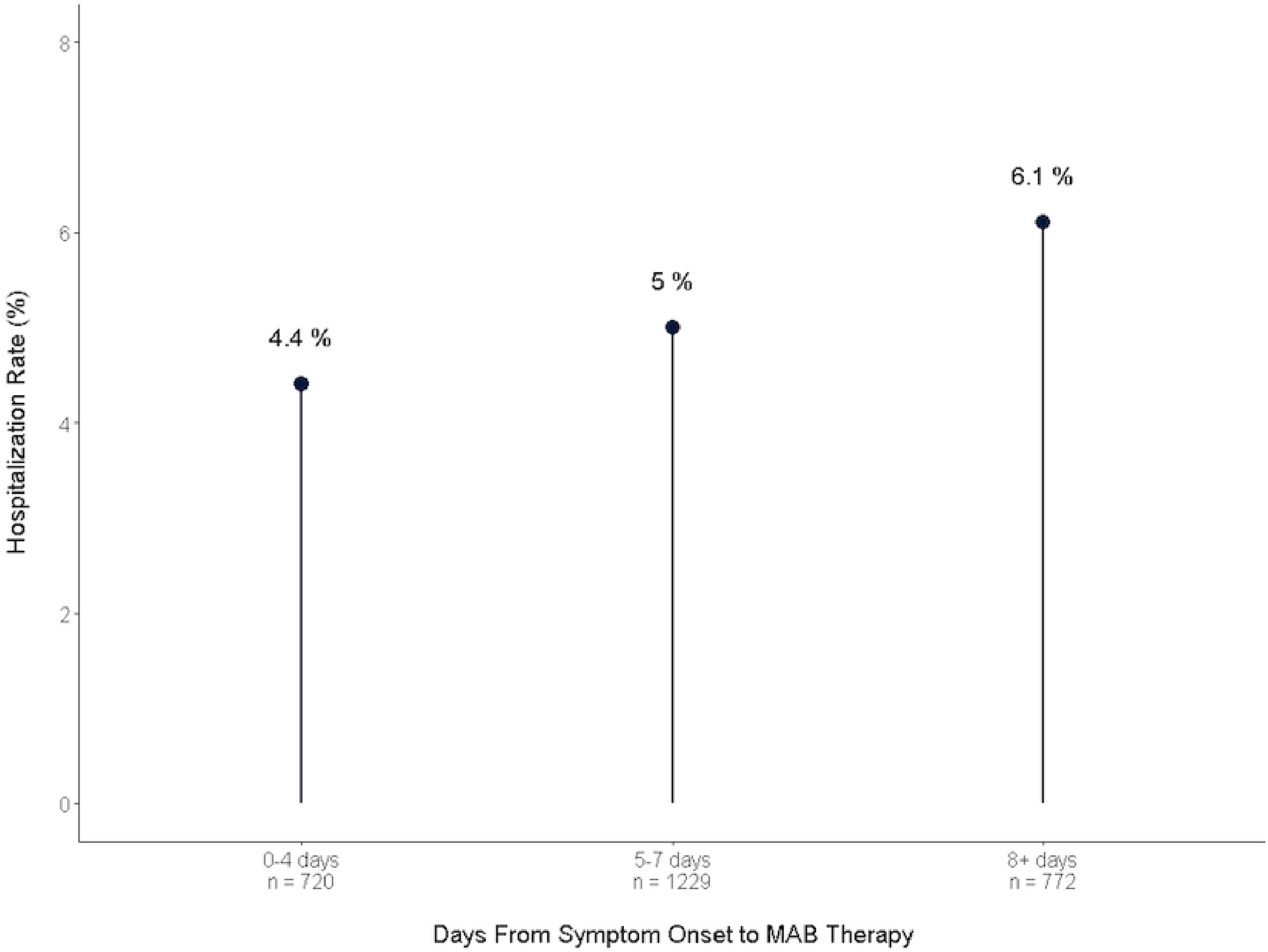
Variables	Overall (N=2818)	No inpatient visit (n=2673)	Inpatient visit (n=145)	*P* value
Age (years), median (IQR)	67.00 (58.00-74.00)	66.00 (58.00-74.00)	75.00 (64.00-82.00)	<.001
Age categories (years), n (%)				<.001
<55	460 (16.3)	450 (16.8)	10 (6.9)	
55-64	710 (25.2)	683 (25.6)	27 (18.6)	
65-74	964 (34.2)	930 (34.8)	34 (23.4)	
≥75	684 (24.3)	610 (22.8)	74 (51.0)	
Female sex, n (%)	1406 (49.9)	1343 (50.2)	63 (43.4)	.13
Race/ethnicity, n (%)				.39
Hispanic	168 (6.0)	160 (6.0)	8 (5.5)	
Non-Hispanic Black	104 (3.7)	99 (3.7)	5 (3.4)	
Asian	110 (3.9)	103 (3.9)	7 (4.8)	
Non-Hispanic White	2061 (73.1)	1948 (72.9)	113 (77.9)	
Other/multiracial	332 (11.8)	323 (12.1)	9 (6.2)	
Unknown/declined	43 (1.5)	40 (1.5)	3 (2.1)	
Comorbidities, n (%)				
Obesity	401 (23.3)	377 (23.4)	24 (21.4)	.71
Diabetes mellitus	484 (17.2)	421 (15.8)	63 (43.4)	<.001
Hypertension	1011 (35.9)	901 (33.7)	110 (75.9)	<.001
Chronic kidney disease	113 (4.0)	85 (3.2)	28 (19.3)	<.001
Chronic obstructive pulmonary disease	434 (15.4)	394 (14.7)	40 (27.6)	<.001
Chronic respiratory disease	463 (16.4)	418 (15.6)	45 (31.0)	<.001
Immunosuppressed	179 (6.4)	161 (6.0)	18 (12.4)	.004
COVID-19 symptoms, n (%)				
Cough	1954 (70.4)	1847 (70.2)	107 (74.3)	.34
Malaise	1471 (53.0)	1398 (53.1)	73 (50.7)	.63
Fever	1422 (51.2)	1350 (51.3)	72 (50.0)	.83
Headache	820 (29.5)	788 (30.0)	32 (22.2)	.06
Sore throat	555 (20.0)	532 (20.2)	23 (16.0)	.26
Gastrointestinal	371 (13.4)	351 (13.3)	20 (13.9)	.95
Loss taste/smell	309 (11.1)	296 (11.3)	13 (9.0)	.49
Muscle pain	256 (9.2)	240 (9.1)	16 (11.1)	.51
Shortness of breath	143 (5.2)	131 (5.0)	12 (8.3)	.11
Monoclonal antibody type, n (%)				.30
Casirivimab/imdevimab	317 (11.2)	305 (11.4)	12 (8.3)	
Bamlanivimab	2501 (88.8)	2368 (88.6)	133 (91.7)	
Monoclonal antibody timing, median (IQR)				
Days from symptom onset to therapy	6.00 (4.00-8.00)	6.00 (4.00-8.00)	6.00 (5.00-8.00)	.39
Days from symptom onset to COVID-19 test	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-3.25)	.03
ED[a] and hospital use				
ED visit within 28 days, n (%)	123 (4.4)	112 (4.2)	11 (7.6)	.08
Days from COVID-19 test to ED visit, median (IQR)	7.00 (5.00-11.00)	7.00 (5.00-11.00)	6.00 (3.00-10.50)	.49
Days from therapy to ED visit, median (IQR)	3.00 (0.00-6.00)	3.00 (0.00-6.00)	2.00 (0.50-4.50)	.56

Variables	Overall (N=2818)	No inpatient visit (n=2673)	Inpatient visit (n=145)	*P* value
Days from COVID-19 test to hospitalization, median (IQR)	N/A[b]	N/A	7.00 (5.00-11.00)	N/A
Days from therapy to hospitalization, median (IQR)	N/A	N/A	3.00 (1.00-8.00)	N/A

[a]ED: emergency department.

[b]N/A: not applicable.

Figure 1. Timing of MAB therapy and hospitalization rate. MAB: monoclonal antibody.



Hospital Outcomes

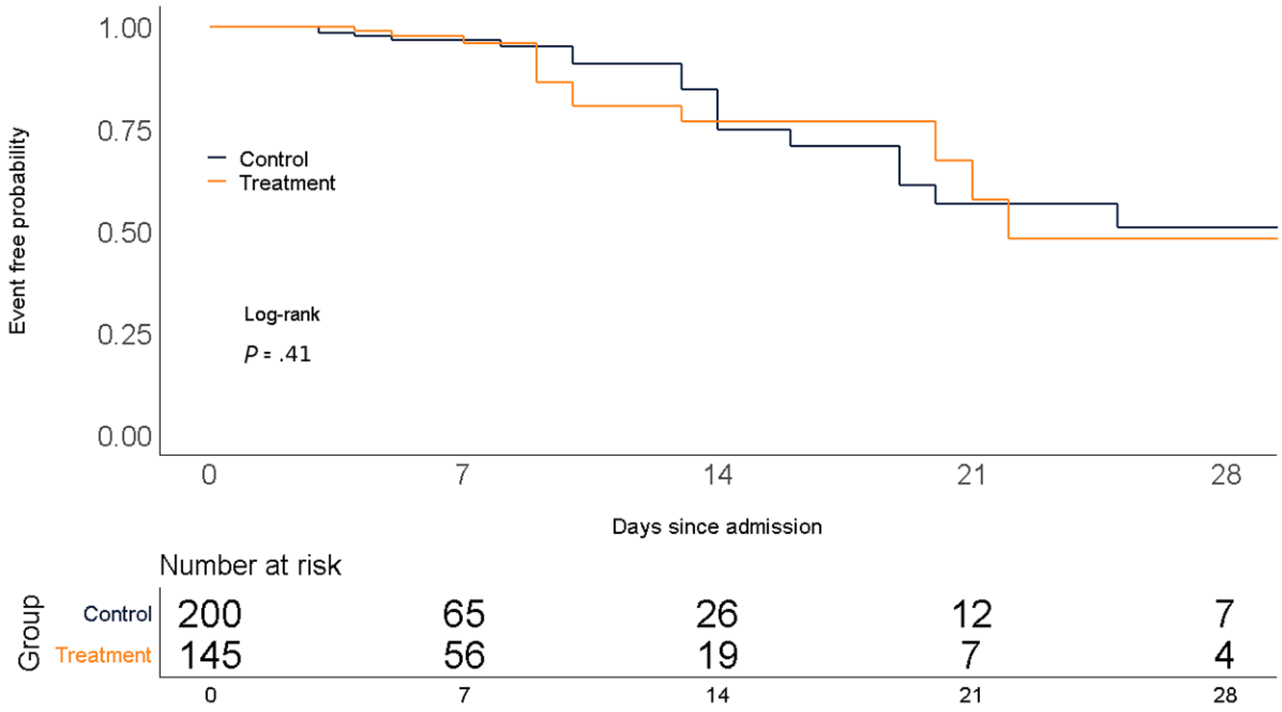
A total of 145 MAB patients were hospitalized and were compared with 200 controls who otherwise met MAB therapy eligibility criteria and were hospitalized (Table 2). The MAB group was slightly older (median age 75, IQR 64-82 years vs median age 69, IQR 57-78 years), with a lower proportion of women (63/145, 43% vs 106/200, 53%) and a higher proportion of non-Hispanic White race (113/145, 78% vs 118/200, 59%). There was no significant difference in the presence of comorbidities between the groups.

In the MAB group, 16 (11%) patients met the primary outcome of in-hospital mortality, versus 21 (10.5%) in the control group. Kaplan-Meier survival curve showed no difference between the two groups for event-free probability (log-rank *P*=.41; Figure 2). In an unadjusted Cox proportional hazards model, the hazard ratio (HR) for time to inpatient mortality for the MAB group was 1.38 (95% CI 0.696-2.719). There was no significant association between prehospitalization MAB use and the primary end point in both a model adjusted for demographics (HR 1.1, 95% CI 0.53-2.23), a model adjusted for demographics and CCI (HR 1.22, 95% CI 0.573-2.59), and a model with IPW according to the propensity score (HR 1.19, 95% CI 0.619-2.29).

Table 2. Characteristics of patients who received and did not receive prehospital monoclonal antibody therapy and were hospitalized within 28 days of a COVID-19 test.

Variables	All hospitalized patients (n=345)	Control group (n=200)	Monoclonal antibody treatment group (n=145)	*P* value
Age (years), median (IQR)	72.00 (61.00-80.00)	69.00 (57.00-78.00)	75.00 (64.00-82.00)	.001
Age categories (years), n (%)				.001
<55	52 (15.1)	42 (21.0)	10 (6.9)	
55-64	62 (18.0)	35 (17.5)	27 (18.6)	
65-74	89 (25.8)	55 (27.5)	34 (23.4)	
≥75	142 (41.2)	68 (34.0)	74 (51.0)	
Female sex, n (%)	169 (49.0)	106 (53.0)	63 (43.4)	.10
Race/ethnicity, n (%)				.02
Hispanic	32 (9.3)	24 (12.0)	8 (5.5)	
Non-Hispanic Black	25 (7.2)	20 (10.0)	5 (3.4)	
Asian	19 (5.5)	12 (6.0)	7 (4.8)	
Non-Hispanic White	231 (67.0)	118 (59.0)	113 (77.9)	
Other/multiracial	29 (8.4)	20 (10.0)	9 (6.2)	
Unknown/declined	9 (2.6)	6 (3.0)	3 (2.1)	
Comorbidities, n (%)				
Obesity	73 (23.4)	49 (24.5)	24 (21.4)	.64
Diabetes mellitus	149 (43.2)	86 (43.0)	63 (43.4)	>.99
Hypertension	259 (75.1)	149 (74.5)	110 (75.9)	.87
Chronic kidney disease	50 (14.5)	25 (12.5)	25 (17.2)	.28
Chronic obstructive pulmonary disease	95 (27.5)	55 (27.5)	40 (27.6)	>.99
Chronic respiratory disease	113 (32.8)	68 (34.0)	45 (31.0)	.64
Immunosuppressed	38 (11.0)	20 (10.0)	18 (12.4)	.59
Charlson Comorbidity Index, median (IQR)	6.00 (4.00-8.00)	5.00 (3.00-8.00)	6.00 (4.00-8.00)	.22
Presentation vital signs, median (IQR)				
Heart rate (beats per minute)	89.00 (78.00-102.00)	89.50 (77.00-103.00)	89.00 (79.00-100.00)	.58
Systolic blood pressure (mmHg)	131.00 (119.00-147.00)	131.50 (118.75-146.25)	130.00 (121.00-147.00)	.98
Diastolic blood pressure (mmHg)	74.00 (67.00-83.00)	74.00 (67.00-83.00)	75.00 (66.00-82.00)	.44
Temperature (°C)	37.00 (36.70-37.60)	36.90 (36.70-37.42)	37.10 (36.70-37.70)	.04
Oxygen saturation (%)	96.00 (92.00-98.00)	96.00 (92.00-98.00)	96.00 (93.00-97.00)	.48

Figure 2. Freedom from the end point of in-hospital mortality.



Discussion

Principal Findings

Despite the issuance of an FDA EUA for two MAB therapies in late 2020 to treat mild to moderate COVID-19 in high-risk outpatients, adoption and use nationally has been slow [5]. Hesitancy may be related to questions of treatment effectiveness, logistical challenges, and staffing requirements during the pandemic [9]. In the 2.5-month period following the EUA, Northwell scaled up an ambulatory MAB infusion operation and successfully administered therapy to over 2800 eligible patients, with most patients receiving therapy within 1.8 days of referral. The operational success required close collaboration and coordination of clinical, operation, informatics, information technology, ambulatory, and population health leadership to ensure the appropriate requirements were in place.

Among the patients who received MAB therapy, a majority received bamlanivimab due to availability. A total of 145 (5.1%) patients were hospitalized within 28 days of a COVID-19 test, and 16 died (0.6% of total population and 11% of patients who were hospitalized). We did find a trend toward a lower rate of hospitalization for patients receiving therapy more proximate to symptom onset date, although this finding was not statistically significant. Inasmuch as the effect of MAB therapy is to reduce SARS-CoV-2 viral load [11], receiving these therapies earlier in the disease course should be beneficial; the low numbers of hospitalized patients in our treatment group may contribute to the lack of statistical significance. Among the 2713 patients who tested positive for COVID-19 during the same time period in our health system, and who met age or comorbidity eligibility criteria for MAB yet did not receive it, 200 (7.4%) were hospitalized within 28 days. A direct comparison to our MAB cohort, however, is not feasible given the lack of symptom data for these non-MAB patients.

Compared to a matched control group, there was no significant difference in the hospital outcome of in-hospital mortality. Although our sample size of patients who were hospitalized was small, this finding may be more related to COVID-19 disease burden; once a patient meets clinical requirements for hospitalization, prior MAB therapy likely does not alter the clinical trajectory. Indeed, randomized trials of MAB in patients who were hospitalized did not demonstrate efficacy [4].

Although the published randomized control trials to date presented promising efficacy data, the primary endpoint was focused on viral load rather than clinically meaningful outcomes such as hospitalization or death [2,3]. A case series suggesting benefit has been described but had a small sample size and lack of control [12]. We were able to describe the outcomes in 2818 patients receiving MAB therapy and further compared in-hospital mortality with an appropriately matched control group. Our study did not demonstrate effectiveness of MAB therapy on preventing in-hospital mortality, and we did not have a control group to examine the effectiveness of MAB therapy on preventing hospitalization. Nonetheless, the trend toward reduced hospitalization seen in the early treatment cohort is intriguing; timely referral and operational efficiency to administer MAB therapy early in the course of disease would benefit hospital operations by reducing the burden on capacity issues. Although we invested resources to specifically staff the MAB infusion facilities, such a derived benefit may outweigh the MAB resource use. Certainly, preventing mortality is the most critical outcome, however, a reduced burden of patients who are critically ill would allow the hospital staff to focus on non–COVID-19 patients as well. In addition, the administration of MAB therapy in the ED helped facilitate health equity, since many underserved communities, challenged by the lack of primary care and a high prevalence of comorbid conditions, were disproportionately affected by severe COVID-19. Interestingly, this phase of our MAB program did not result in ED overcrowding.

Future efforts for MAB therapy may include home infusion or mobile treatment options. Although these were considered in our original MAB strategy, staffing burden for the number of patients that could be treated was high and operational considerations such as preparation and transportation of the mixed MAB infusion were considerable. It is hoped that alternate routes (eg, intramuscular or subcutaneous) of administering MAB therapies can be developed to offset these operational and staffing challenges.

As many health systems continue to deal with COVID-19 surges, we recommend establishing a national database to analyze MAB treatment in larger cohorts. Although randomized placebo-controlled trials may not be logistically feasible, further meta-analyses of centers leveraging these therapies may be in order.

Limitations

Limitations of our study include the observational and retrospective study design. In addition, our health system is based in New York and may not be generalizable to other regions. Due to the lack of symptom documentation for our control group of patients, we were unable to assess the impact of MAB therapy on hospitalization rate. Given the small number of patients and low event rate, our analysis of inpatient mortality may be underpowered to detect a difference.

Conclusions

The EUA for the MAB infusions provides a foundation for treatment of early mild to moderate COVID-19 in patients who are at high risk. This study describes the rapid development of a MAB infusion program to provide such treatment for over 2800 patients. Establishing the capability to perform MAB infusion therapy requires close collaboration and coordination of numerous stakeholders and can support hospital operations in the setting of a pandemic surge. Further investigation is required to define the optimal timing of MAB therapy and the potential attendant reduction in hospitalization and mortality.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary material.
[DOCX File , 48 KB - xmed_v2i3e29638_app1.docx]

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Abbreviations

CCI: Charlson Comorbidity Index
CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease
DM: diabetes mellitus
ED: emergency department
EUA: Emergency Use Authorization
FDA: Federal Drug Administration
HR: hazard ratio
IPW: inverse probability weighting
MAB: monoclonal antibody

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Original Paper

Initial SARS-CoV-2 Vaccination Uptake in a Correctional Setting: Cross-sectional Study

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Abstract

Background: The largest outbreaks of COVID-19 in the United States have occurred in correctional facilities, and little is known about the feasibility and acceptability of SARS-CoV-2 vaccine campaigns among incarcerated people.

Objective: The aim of this study was to describe a statewide vaccination program among incarcerated people and staff working in a prison setting.

Methods: Between December 2020 and February 2021, the Rhode Island Department of Corrections (RIDOC) offered the opportunity for SARS-CoV-2 vaccination to all correctional staff and sentenced individuals. Two RIDOC public health educators provided education on the vaccine, answered questions, and obtained consent before the vaccine clinic day for the incarcerated group. All staff received information on signing up for vaccines and watched an educational video that was created by the medical director. Additional information regarding vaccine education and resources was sent via email to the entire RIDOC department.

Results: During this initial campaign, 76.4% (1106/1447) of sentenced individuals and 68.4% (1008/1474) of correctional staff accepted and received the vaccine. Four months after the first vaccine was offered, 77.7% (1124/1447) of the sentenced population and 69.6% (1026/1474) of staff were fully vaccinated.

Conclusions: This study demonstrates the feasibility and efficiency of vaccine implementation in a carceral setting. Education and communication likely played an important role in mitigating vaccine refusals.

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KEYWORDS

vaccination; COVID-19; incarcerated individuals; correctional facility; public health; pandemic; vaccine; carceral setting; vaccine implementation; correctional staff

Introduction

The largest outbreaks of COVID-19 in the United States have occurred in correctional facilities [1]. Correctional outbreaks have been shown to contribute to community and statewide spread of infection [2]. The rate of COVID-19 in correctional settings is 5 times that of the general population, and the age-adjusted mortality rate is nearly 4 times higher [3]. Thus, vaccinating individuals who live and work in correctional facilities should be a high priority and is recommended by multiple organizations [4,5]. Despite these recommendations, few states initially prioritized vaccination in correctional settings [6]. Furthermore, vaccine uptake among correctional staff and incarcerated individuals is unknown.

Since the beginning of the pandemic, the Rhode Island Department of Corrections (RIDOC) has collaborated closely with the Rhode Island Department of Health to address COVID-19 with clear testing and isolation procedures, mask wearing, surface sanitation, and ongoing education of staff and incarcerated individuals. Vaccinations were initiated in December 2020.

Methods

The RIDOC is a unified (combined prison and jail) statewide correctional facility that currently houses approximately 1500 sentenced and 500 awaiting-trial individuals across 6 facilities among a spectrum of security levels, including Minimum Security, Medium Security, Maximum Security, and High Security facilities. The final 2 facilities, Intake facility and Women's Facility, are jail-like facilities that comprise mostly individuals awaiting trial. The vaccine program initially focused on sentenced individuals (ie, individuals typically housed in a prison). Staff (eg, correctional officers) were concurrently vaccinated at the RIDOC through a parallel vaccine program.

SARS-CoV-2 vaccines were initially offered starting on December 22, 2020, to the sentenced population. By February 5, 2021, the entire sentenced population had received at least one opportunity for vaccination. Second-dose vaccinations for this population were completed by March 5, 2021.

Among incarcerated people, RIDOC leadership prioritized vaccine allocation based on risk factors (as outlined by the Centers for Disease Control and Prevention [CDC] and local Department of Health) and/or security facility. RIDOC nurses administered the vaccine. Two RIDOC public health educators provided education on the vaccine, answered questions, and obtained consent before the vaccine clinic day. All eligible individuals were offered vaccination in this way with the option to accept or defer. Second doses were provided at appropriate time intervals.

Vaccines arrived each week and were distributed in "phases" based on risk factors and logistics. In phase 1, individuals at the highest risk (aged >65 years or >55 years with specific comorbidities) were offered the vaccine. In phase 2, smaller facilities (ie, facilities with a smaller average daily population: Women's Facility; Minimum, Maximum, and High Security facilities) were offered the vaccine in an attempt to achieve herd immunity in those communities. Phase 3 included the largest remaining security facility—Medium Security as well as sentenced individuals at the Intake facility who were awaiting transfer to one of the sentenced facilities. Phase 4 included all individuals who had previously tested positive for COVID-19 within 90 days and individuals who had initially declined but subsequently accepted. After completion of the four phases, vaccines continued to be offered upon request. A portion of individuals in phase 1 received the Pfizer vaccine, and the rest received the Moderna vaccine.

Among corrections staff, individuals were vaccinated with an opt-in system (signing up via email), prioritizing self-identified high-risk correctional officers (by age and comorbidity) and individuals with direct contact with incarcerated people. During morning "roll call," all staff received information on signing up for vaccines and watched an educational video that was created by the medical director and made available on the intranet [7]. Additional information regarding vaccine education and resources was sent via email to the entire RIDOC department (Multimedia Appendix 1).

Results

During the 6-week campaign, a total of 1106 out of 1447 (76.4%) incarcerated individuals and 1008 out of 1474 (68.4%) staff received the vaccine. Among staff, a total of 466 of 1474 individuals (31%) did not opt in for a vaccine during the initial vaccine offering. Table 1 describes the four phases of first-dose vaccination.

Table 1. First-dose SARS-CoV-2 vaccination of incarcerated people and correctional staff.

Group	Dates	Offered, N	Vaccinated, n (%)	Declined, n (%)
Incarcerated people		1447	1106 (76.4)	341 (23.6)
Phase 1: Age >65 years, immunocompromised, or age >55 years with comorbidities	Dec 26-29, 2020	143	130 (90.9)	13 (9.1)
Phase 2: Small facilities (Minimum, Maximum, High, Women's)	Dec 31, 2020, to Jan 5, 2021	222	143 (64.4)	79 (35.6)
Phase 3: Medium facility and sentenced individuals awaiting transfer	Jan 13-27, 2021	730	605 (82.9)	125 (17.1)
Phase 4: All remaining sentenced individuals, including those who had COVID-19 within 90 days	Jan 29 to Feb 5, 2021	352	228 (64.8)	124 (35.2)
Correctional officers and other staff				
Priority to self-reported high-risk individuals and those with direct contact with incarcerated individuals	Dec 22, 2020, to Feb 10, 2021	1474	1008 (68.4)	466 (31.6)

A total of 3 incarcerated individuals and 6 staff members who received their first dose of vaccine opted to not receive their second dose. During this time, "overpulls" (ie, a common 11th dose of vaccine could be pulled from a 10-dose vial) and additional vaccine clinics were offered to incarcerated individuals and staff who ultimately did opt in to receive the vaccine on a rolling basis based on vaccine availability.

Four months after the first vaccine was offered on December 22, 2020, 77.7% (n=1124) of the sentenced population and 69.6% (n=1026) of staff were fully vaccinated. There were no significant vaccine adverse events.

Discussion

Vaccination was acceptable to individuals in a correctional setting with an acceptance rate of 70% to 75% among both staff and incarcerated people (for comparison, the rate of influenza vaccination uptake at the RIDOC last year was 50.6%). This aligns with necessary immunization rates modeled to achieve herd immunity [8]. More importantly, this is a departure from some concerns of high vaccine hesitancy rates, including a recent CDC publication estimating only a 45% willingness to receive vaccination among incarcerated people [9]. Education and communication likely played an important role in mitigating refusals. Rhode Island, like most other state correctional facilities [10], had COVID-19 outbreaks with fatalities. This may have increased the willingness to get vaccinated. Efforts to increase vaccine uptake have continued.

The high acceptance rate in a correctional setting is particularly relevant given the increased risk of COVID-19–related transmission, disease, and death in this population [3]. The pandemic has substantially affected correctional settings, and the spread of disease in these facilities can catalyze transmission to their surrounding communities [2]. Additionally, both COVID-19 and mass incarceration have disproportionately impacted communities of color [1]. Thus, by vaccinating incarcerated people, policymakers can target a high-risk and marginalized group, decrease community spread, improve equitable allocation to a marginalized group, and potentially reduce the health system costs of neighboring health systems. The successful vaccination of incarcerated individuals and staff in the state of Rhode Island demonstrates the feasibility and efficiency of widespread vaccine programming among those at high risk.

Vaccination of incarcerated people does have unique challenges. Rhode Island was able to coordinate the administration of second doses among the sentenced population without loss to follow-up, but this was in part due to the small size of the state's population. Additionally, the jail setting offers a greater challenge given the high turnover of the population, often with individuals being released to the community before their second dose is due. While Rhode Island was successful in implementing 2-dose vaccines, strategic implementation of a single-dose vaccine may better align with this unique environment in other larger states, especially for the short-term jailed population.

This vaccine campaign exemplified adherence to public health principles: vaccinate where spread and disease can best be prevented [11]. Correctional settings should remain a priority in vaccination strategies during a pandemic and indeed offer an opportunity to target a high-risk and marginalized population.

Conflicts of Interest

None declared.

Multimedia Appendix 1
RIDOC educational email to staff regarding COVID-19 vaccination.
[PDF File (Adobe PDF File), 52 KB - xmed_v2i3e30176_app1.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
RIDOC: Rhode Island Department of Corrections

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Original Paper

Selection of the Optimal L-asparaginase II Against Acute Lymphoblastic Leukemia: An In Silico Approach

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Abstract

Background: L-asparaginase II (asnB), a periplasmic protein commercially extracted from *E coli* and *Erwinia*, is often used to treat acute lymphoblastic leukemia. L-asparaginase is an enzyme that converts L-asparagine to aspartic acid and ammonia. Cancer cells are dependent on asparagine from other sources for growth, and when these cells are deprived of asparagine by the action of the enzyme, the cancer cells selectively die.

Objective: Questions remain as to whether asnB from *E coli* and *Erwinia* is the best asparaginase as they have many side effects. asnBs with the lowest Michaelis constant (Km; most potent) and lowest immunogenicity are considered the most optimal enzymes. In this paper, we have attempted the development of a method to screen for optimal enzymes that are better than commercially available enzymes.

Methods: In this paper, the asnB sequence of *E coli* was used to search for homologous proteins in different bacterial and archaeal phyla, and a maximum likelihood phylogenetic tree was constructed. The sequences that are most distant from *E coli* and *Erwinia* were considered the best candidates in terms of immunogenicity and were chosen for further processing. The structures of these proteins were built by homology modeling, and asparagine was docked with these proteins to calculate the binding energy.

Results: asnBs from *Streptomyces griseus*, *Streptomyces venezuelae*, and *Streptomyces collinus* were found to have the highest binding energy (–5.3 kcal/mol, –5.2 kcal/mol, and –5.3 kcal/mol, respectively; higher than the *E coli* and *Erwinia* asnBs) and were predicted to have the lowest Kms, as we found that there is an inverse relationship between binding energy and Km. Besides predicting the most optimal asparaginase, this technique can also be used to predict the most optimal enzymes where the substrate is known and the structure of one of the homologs is solved.

Conclusions: We have devised an in silico method to predict the enzyme kinetics from a sequence of an enzyme along with being able to screen for optimal alternative asnBs against acute lymphoblastic leukemia.

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KEYWORDS

L-asparaginase II; acute lymphoblastic leukemia; leukemia; cancer; enzyme kinetics; binding affinity; homology modeling; docking; molecular biology; structural biology; protein chemistry; biochemistry

Introduction

Acute lymphoblastic leukemia is a malignant cancer of the white blood cells characterized by uncontrolled overproduction and accumulation of lymphoid progenitor cells [1]. It is most common among children, which compromise 80% of the worldwide acute lymphoblastic leukemia occurrences, although some cases in adults are also seen. It is equally life-threatening in both cases. In the United States, acute lymphoblastic leukemia is estimated to have a frequency of 1.7 cases per 100,000 people [2]. In 2015 alone, 111,000 deaths were reported out of 876,000 cases worldwide [3]. Thus, a substantial potential market exists for new and improved therapies to acute lymphoblastic leukemia.

Experiments in the 1950s with guinea pig serum have shown that it could inhibit the growth of transplantable lymphoblastic tumors in mice and rats along with radiation-induced leukemia in mice [4]. Research linked this effect to guinea pig serum being rich in L-asparaginase [5], a nonhuman enzyme of often bacterial origin, belonging to the amidase group that hydrolyses the amide bond in L-asparagine to form L-aspartic acid and ammonia [6]. It has since been shown to be an effective antineoplastic agent and is often used in conjugation with chemotherapy for acute lymphoblastic leukemia treatment.

Normal cells require L-asparagine as an amino acid for the synthesis of proteins. A natural diet like vegetables is one of the sources of L-asparagine for the body. It is not classified as an essential amino acid as it is naturally synthesized by the body through a pathway involving the enzyme L-asparagine synthase, which coverts aspartic acid and glutamic acid into L-asparagine [7]. Neoplastic cells like acute lymphoblastic leukemia cells lack this enzyme and therefore are not able to produce L-asparagine on their own [8]. This leaves them dependent on L-asparagine from outside sources like the serum where it is pooled from diet and from normal cells. This provides the basis for the use of L-asparaginase as a therapeutic agent against acute lymphoblastic leukemia, the intent being to deplete the local circulating pools of L-asparagine in the blood serum thus starving the cancer cells of the amino acid and causing cell death.

L-asparaginase is produced by a wide variety of organisms and can be classified into several families. The ones of therapeutic interest can consist of two enzymes called L-asparaginase of two closely related families named L-asparaginase I and L-asparaginase II. L-asparaginase I, referred to also as asnA, is a low-affinity enzyme found in the cytoplasm and is constitutively produced by the organism. L-asparaginase II, referred to as asnB, on the other hand, is a high-affinity periplasmic enzyme expressed during anaerobiosis. Its expression is dependent on aeration, carbon source, and amino acid availability [9].

Extracellular L-asparaginase accumulates in the culture broth and thus is most favorable for extraction and downstream processing for commercial production [10]. The most commercial form of therapeutic L-asparaginase is extracted from *E coli* and *Erwinia* species. They secrete the enzyme into the periplasmic space between the plasma membrane and the cell envelope [11]. The enzyme is extracted by lysis of the cells, which brings the enzyme along with inner cell contents into the culture medium. It is usually purified using fractionation with ammonia sulfate.

However, the commercially available L-asparaginase has several drawbacks. L-asparaginase from *E coli* and *Erwinia* is known to show immunogenic and allergic reactions. Most therapeutic use of L-asparaginase has shown toxicity [12]. Toxicity of L-asparaginase can be attributed to lower activity of the enzyme to L-asparagine and higher activity to glutamine. Thus, the decrease in glutamine levels in the normal cells causes an allergic reaction [13]. Another problem with the currently available L-asparaginase is the immunological response. The body recognizes the enzyme as being foreign and thus mounts an immune response against the enzyme, which can range from a mild allergic reaction to anaphylactic shock [14].

The Michaelis constant (Km) is a value for the substrate concentration at which the reaction rate is half of the maximum reaction rate. A lower Km suggests that the enzyme can reach half the maximum reaction rate at lower substrate concentrations. One can interpret this to mean that enzymes with lower Km have greater activity toward that substrate. An enzyme with greater activity toward L-asparagine can be expected to show fewer undesirable effects, as it will have a lower activity to unintended substrates [15]. Another useful metric for the measurement of enzyme activity is k_{cat} or the turnover number. It gives the number of substrates converted to a product by a single molecule of enzyme per unit time. The turnover number signifies the rate at which a substrate is catalyzed by the enzyme [16].

Catalysis is based on binding energy that lowers the activation energy and overcomes the unfavorable entropic requirements needed for the correct orientation of the catalyst and reactants brought together for reaction [17]. Binding energy is the energy released when a substrate forms weak bonds with the enzyme active site. Binding energy is measured as the free energy (Delta G). Gibbs free energy, defined as “a thermodynamic potential that measures the capacity of a thermodynamic system to do maximum or reversible work at a constant temperature and pressure (isothermal, isobaric), is one of the most important thermodynamic quantities for the characterization of the driving forces" [18].

Experimental calculation of this energy is difficult and cumbersome. Thus, experimental screening techniques for a lead compound for drug candidates are still expensive and slow despite several advances in automation and parallelization of the process. A more efficient method would be to screen a large library of small molecules in silico before short-listing a small group for experimental verification. The availability of large volumes of experimental data on the 3D structure of the enzymes and their substrates allows us to analyze their interaction. Docking is one of these in silico methods where rigid body interaction of contact surfaces of the ligand or small molecules and the target protein is determined using computational methods. Combinatorial methods are used to account for the ligand conformational flexibility, and various energy functions are used to calculate energetics of the interaction. Docking is typically used to screen for potential lead compound candidates from a large library of small molecules based on their binding energy and other parameters to the target protein. Those compounds with greater binding energy to the protein are seen as potential inhibitors and thus considered to lead for developing drugs of therapeutic value [19]. However, in L-asparaginase–based therapy of acute lymphoblastic leukemia, the enzyme itself is used as a therapeutic agent, while the substrate, L-asparagine, is the target compound. Our goal in this research is to find a better enzyme candidate with more favorable interaction with our target compound. Thus, our use of docking in this research is different from the standard use of the docking method. We used docking to screen a collection of L-asparaginase enzyme from different organisms and select a suitable enzyme based on its binding energy to L-asparagine.

The *E coli* L-asparaginase II has a functional form in a homotetramer having the molecular mass from 140 to 160 kDa. The monomers are 330 amino acid long and have two distinct domains. One is the larger N-terminal domain and the other is the smaller C-terminal domain. The two domains are connected by a 20-residue linker. The functional form of the enzyme is thought to contain five active sites [20].

Homology modeling is a technique used to generate a model from an amino acid sequence based on a template of a 3D structure of a closely related protein obtained via experimental data. It uses comparative protein structure modeling where the template and the query sequences are aligned and the query's structure is predicted. According to Eswar et al [21], it has the following four major steps: fold assignment, which identifies similarity between the target and at least one known template structure; alignment of the target sequence and the template or templates; building a model based on the alignment with the chosen template or templates; and predicting model errors. We have used MODELLER 9.22 to model L-asparaginase sequence from the organisms that were selected, using the *E coli* L-asparaginase II (PDB ID: 1nns) as a template for generating all of them.

E coli and *Erwinia* L-asparaginases, the two commercially available forms of the therapeutic enzymes, have deficiencies in the aforementioned parameters. Thus, they show unsatisfactory results and side effects. In this research, we hope to find a better L-asparaginase from a different host organism for the commercial production of this therapeutic enzyme. We hypothesize that a host whose L-asparaginase amino acid sequence is distinct from that of the currently used organisms can be assumed to have markedly different properties. We can screen such a family or genus of host organisms and hope to find L-asparaginase that displays kinetic and binding properties that decrease the chances of immunogenic and allergic reactions making it more favorable for therapeutic use. We have used a phylogenetic tree-based approach to find such host organisms. A phylogenetic tree is an important bioinformatics tool that allows us to analyze the sequences of proteins, DNA, and RNA to find the historical and evolutionary relationship between the sequences. The nodes of a tree can be given values as support values for its reliability. These are called bootstrap values that give the expectation of that particular node in the many alternate trees generated by reruns of the same sequence data set [22]. Many algorithms for tree construction exist. Here, we have used the maximum likelihood (ML) algorithm in the MEGA bioinformatics tool to construct, bootstrap, and analyze our tree. The tree was used to look for hosts with evolutionarily distant L-asparaginase sequences, which can be screened for desired properties using docking tools.

Methods

Phylogenetic Tree Construction

To construct a phylogenetic tree, we retrieved the L-asparaginase B (asnB) protein sequence of *Escherichia coli k12* strain from the Uniprot [23] (UniProtKB-P00805 ASPG2_ECOLI). Microorganisms that are capable of producing the asnB based on the previous literature [24-27] were searched by doing blastp in the National Center for Biotechnology Information (NCBI) database [28]. Basic Local Alignment Search Tool (BLAST) is a sequence analysis tool that searches a database for sequences that are similar to a query sequence. Blastp is a variation of standard blast that searches a database of nonredundant and nonpatented sequences based on a query sequence. Blastp can be used to search a database for organisms that produce sequences that are the same or similar to our query sequence, helping us in compiling a list of known asnB-producing organisms that can be used for construction of our phylogenetic tree. The protein sequence of *E coli k12* asnB was used as the query sequence for blastp on a nr database resulting in a list of organisms that produced proteins of a similar sequence. The organisms with percentage identity greater than or equal to 30% were selected. The genomes of two types of organisms were searched for the presence of asnB. The first group of organisms were already characterized for the production of asnB protein. The other group of organisms included bacteria and archaea from various phyla [29] that represented the entire tree of life. A total of 101 sequences were retrieved after searching for asnB sequence in organisms given by the literature. Organisms with more than one asnB sequences were also retrieved and labeled as genus species 1, 2, or 3. The phylogenetic tree was then constructed in Mega-X software (Pennsylvania State University) [30], in which the alignment was done by Muscle. The following criteria were used to run a tree: statistical method: ML; test of phylogeny: bootstrap method; substitution type: amino acid; model or method: WAG model; rates among sites: gamma distributed with invariant sites, number of discrete gamma categories: 5; gaps or missing data treatment: partial deletion; site coverage cutoff: 95%; ML heuristic method: nearest neighbor interchange; initial tree for ML: make initial tree automatically (Default-NJ/BioNJ); branch swap filter: None; and number of threads: 3 [31]. In our method, we have used a sequence based on genetic or evolutionary distance for the construction of our tree.

Homology Modeling

The organisms that were distantly placed in the phylogenetic tree with respect to *E coli* and *Erwinia* were chosen, and organisms whose enzymes were characterized in the literature were also chosen. To carry out homology modeling, the MODELLER 9.22 was used. The selected organism's asnB sequence was used as the query while *E coli k12* asnB ("1nns") [32] with a resolution of 1.95 Å was used as the reference template. Discrete optimization protein energy (DOPE) is an atomic distance–based scoring function used to access the quality of models produced from homology modeling, derived from a sample of native protein structures in PDB. Statistically optimized atomic potentials (SOAP) is another scoring function based on data from native protein structures used in the assessment of homology modeling results. For each organism, the structure with the lowest DOPE or SOAP assessment score and with the highest GA341 assessment score was selected [33]. Each protein's model was then checked for protein structure stereochemistry including Ramachandran plot and Psi/Phi angles using PROCHECK. Further verification was done using WHATCHECK and ProSA-web [34].

Active Site Prediction

After the validation of the model, active sites for each protein were determined using PyMol (Schrödinger, Inc) software [35]. The models built were superimposed to the 1nns structure, and then by aligning both model and 1nns sequences, the active site with reference to the 1nns active site was predicted. The active site of 1nns for L-asparagine is T(12), S(58), Q(59), T(89), and D(90) [36].

Molecular Docking Studies

Docking of ligands, L-asparagine (derived from the PubChem website) with enzymes L-asparaginases (distant proteins from E coli and Erwinia and enzymes with measured Km value) was performed by using AutoDock Vina [37] conjugated with PyRx software (Sarkis Dallakian) [38]. The AutoDock tool's graphic interface was used for the preparation of all the proteins (enzymes). Proteins were prepared by removing water, adding polar hydrogen, merging nonpolar, and adding Kollman charge. In the case of ligand, L-asparagine was retrieved from PubChem (Compound CID: 6267; molecular formula: C4H8N2O3; molecular weight: 132.12 g/mol) [39]. Energy minimization was done by the Universal Force Field using Open Babel (Open Babel Development Team) software [40] conjugated with PyRx. The grid parameter file and docking parameter file were set, and the grid points for auto grid calculations were set as 25 × 25 × 25 Å, with the active site residues in the middle of the grid box. The algorithm used in the overall process was the Lamarckian genetic algorithm, which was used to calculate protein-fixed ligand-flexible calculations [41].

Interacting Atoms With Active Sites

Distant organisms' asnBs with the best binding energies were selected. The docked protein and ligand files were run on ligPlot+ (European Bioinformatics Institute) software [42] for viewing the interacting atoms between ligands and proteins.

Relation Between Km, k_{cat}, and Binding Energy

To evaluate if the binding energy could predict the relative efficacy of the enzymes, Km and k_{cat} values from the literature were tabulated alongside binding energy. A total of 10 Km and 5 k_{cat} values were obtained from the literature for asnBs of different species. The line fitted plot was drawn using minitab [43], plotting binding energy on the x-axis and Km on the y-axis.

Pairwise Sequence Alignment

Pairwise sequence alignment and comparison of three predicted optimal asnB enzyme sequences was done against the *E coli* asnB enzyme sequence using blastp (protein-protein blast) on Blast+ [28]. Scoring parameters used were BLOSUM62 matrix, gap penalties of 11 for existence, and 1 for extension.

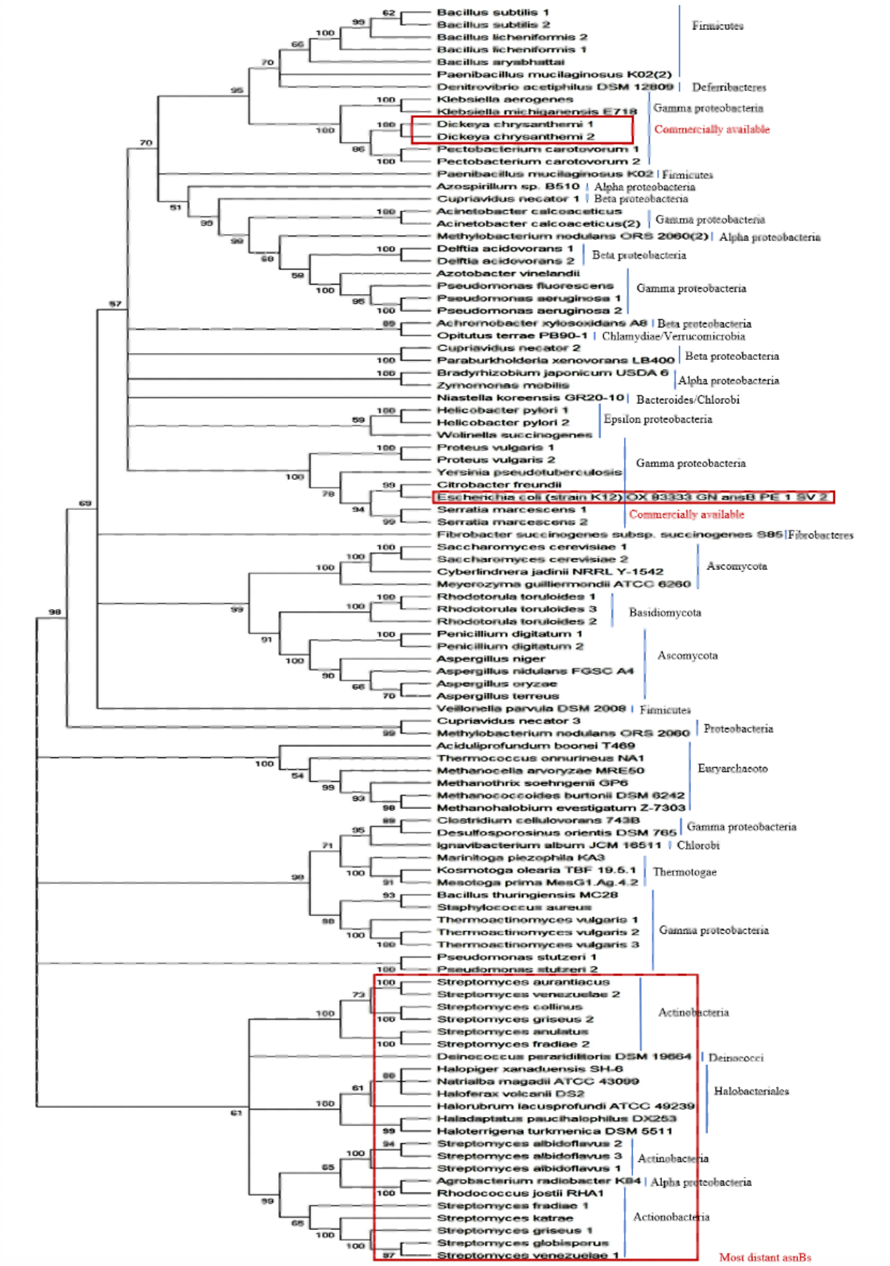
Results

Deductions From the Phylogenetic Tree

A list of asparaginase-producing organisms were compiled from the literature. Asparaginase II (asnB) homologs of these organisms were searched by protein blasting asnB from *E coli* against the nonredundant protein database of these organisms in NCBI. The organisms whose genomes are not sequenced were not used in this study. Additionally, the protein database of a wide variety of bacteria and archaea from different phylum were searched for the presence of asnB. The two lists were compiled to make up our list of a wide range of asnBs. A ML phylogenetic tree of 101 asnBs was drawn for these proteins using Mega X software using the parameters described in the Methods section. The resulting tree is shown in Figure 1. The phylum of bacteria, archaea, and fungi to which the proteins belong to is labeled on the right. Unlike most other proteins for which similar trees were drawn, there were minimal proteins from the same phylum that lay next to each other in the tree. When a similar tree was drawn for Ku protein in bacteria and beta clamp for bacteria, proteins from the same phylum tended to cluster together in the tree (unpublished data). Although some clustering is found for asnB tree, proteins from the same phylum are distributed throughout the tree, indicating extensive horizontal gene transfer. Among the list of asnBs that we have collected, the largest number of proteins comes from proteobacteria (alpha, beta, gamma, delta, and epsilon).

Besides predicting the origin and history of asparaginases, the tree is also useful in predicting which of the asnBs are closely related by evaluating which lie close together and which lie further apart. From the tree, the most common commercially used asnB from *E coli* lies somewhere in the center. The other commercially used asnB from *Erwinia* (nowadays called *Dickeya chrysanthami*) lies at the top of the tree. The asnBs that are most distant from these two commercially available asparaginases, and hence least likely to give an immunogenic reaction when these two give an immunogenic reaction, lie at the bottom of the tree. Of the 101 asnBs used in construction of the phylogenetic tree, 23 asnBs were selected as candidates for better enzyme activity due to them being the most evolutionarily distant from the commercially available asnBs. These have been labeled in Figure 1. Most of them lie in the *Streptomyces* genus and some are from archaea. Since most of the candidates in this group were *Streptomyces*, we decided to limit our list of potential asnB candidates to the 13 *Streptomyces* species in the list. Thus, we screened 13 potential species out of the 101 asnB-producing organisms we had found via blastp due to them being most evolutionarily distant from the organisms that produce commercially available asnBs.

Figure 1. Phylogenetic tree of the total 101 sequences of asnBs using the maximum likelihood method. The top and middle portion of the tree under the red rectangle shows organisms that are currently used for the commercial production of asnBs for the treatment of acute lymphocytic leukemia. The bottom portion of the tree shows organisms that are most distant to E coli (mostly Actinobacteria), and their enzyme activity is yet to be discovered.

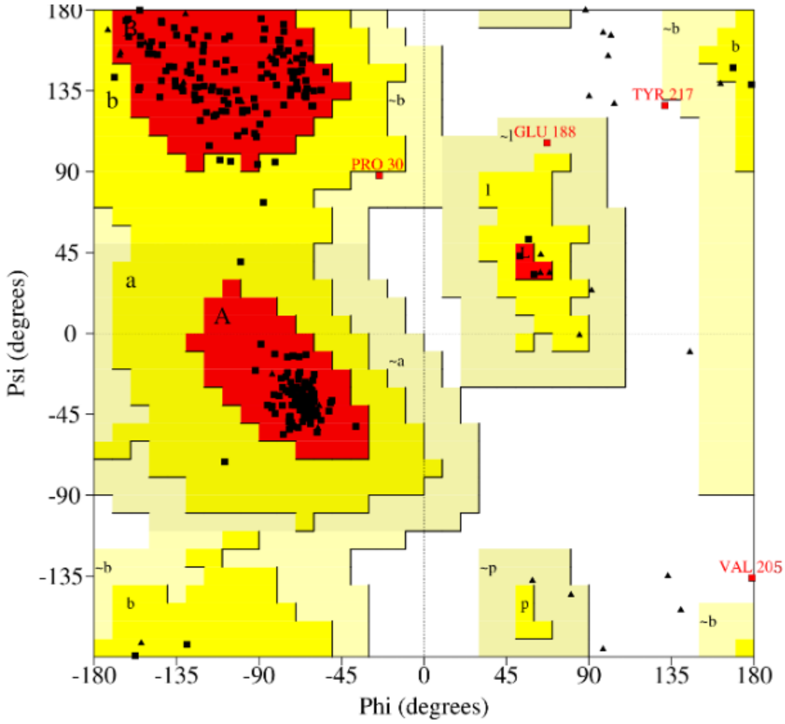


Use of a phylogenetic tree is perfectly adequate for identifying organisms that produce asnBs that can be expected to have better activity and lower immunogenicity than commercially available asnBs. This is because there is a direct relationship between a protein's sequence, structure, function, and immunogenicity. Therefore, asnBs that are evolutionarily distant to commercially available asnBs can be expected to have markedly different structure and can be expected to have potentially better activity than commercial variants. We can also expect evolutionarily distant asnBs to show different immunogenicity when compared to their commercial counterparts. The severity of immunogenic reaction from an antigen on an organism depends on the measure of its novelty. Immune response to a biological macromolecule is complex and dependent on many factors, a significant one being structure, which is dependent on sequence [44]. Two proteins that are evolutionarily different will also be structurally different and thus have different levels of immune responses. An example is that commonly used experimental antigen bovine serum albumin does not show immunogenic reaction when injected in cows but is actively immunogenic when injected into rabbits. Sidewise it would show enhanced reaction in chickens than in goats, for the reason that the latter is closely related to bovines. These analyses endorse that the greater the phylogenetic distances between two species, the greater the structural (and therefore the antigenic) divergence that can be found between them [45].

Homology Modeling and Verification

For homology modeling, MODELLER 9.22 (University of California, San Francisco) software was used, and five models were built for each protein, among which the model with the lowest DOPE was selected. This software uses an inbuilt DOPE function to access the quality of all the models that were made. The model that was selected according to the lowest DOPE scores was validated using Ramachandran plot. A Ramachandran plot of the three best organisms that lie distant to the *E coli* and have a better binding affinity toward L-asparagine than *E coli* and *Dickeya chrysanthami* are shown in Figures 2-4. The plot shows 94.5% (256/271) of residues in most favored regions, 4.4% (12/271) in additional allowed regions, 0.4% (1/271) residues in generously allowed regions, and 0.7% (2/271) residues in disallowed regions for *Streptomyces collinus* (Figure 2); 86% (263/304) of residues in most favored regions, 10.5% (32/304) in additional allowed regions, 2.3% (7/304) residues in generously allowed regions, 0.7% (2/304) residues in disallowed regions for *Streptomyces griseus* 1 (Figure 3); and 90.7% (244/269) of residues in most favored regions, 7.8% (21/269) in additional allowed regions, 0.7% (2/269) residues in generously allowed regions, and 0.7% (2/269) residues in disallowed regions for *Streptomyces venezuelae 2* (Figure 4). More than 99% of residues in the allowed region given by the Ramachandran plot indicate a very good model. Furthermore, the Ramachandran *z* scores calculated by WHATCHECK (–0.245, –1.024, and –0.830 for *S collinus*, *S griseus* 1, *S venezuelae* 2, respectively) fall on the accepted region [46] and were allowed by the WHATCHECK. The structures were finally validated using ProSA-web server. This server gives the *z* score, which indicates the overall model quality and measures the deviation of the total energy of the structure with respect to an energy distribution derived from random conformations [47]. The *z* scores given by the server (–9.44, –7.88, and –9.07 for *S collinus*, *S griseus 1*, and *S venezuelae 2*, respectively) fall inside the range of the plot (black dot) that contains the *z* scores of all the experimentally determined protein in the PDB (X-ray, nuclear magnetic resonance; part a of Figures 5-7). The energy plot (part b of Figures 5-7) indicates the local model quality by plotting energy as the function of the amino acid sequence. Generally, the portion in the positive region of the plot indicates the erroneous part of the structure. We can conclude from the plot that the structure is feasible or accepted as overall residue energies fall under the negative part of the plot. The colored 3D structure of the proteins (part c of Figures 5-7) shows that the portion in red color is of high energy and the portions with the blue color are of low energy [34]. Validation of all other structures used in the experiment is in Multimedia Appendix 1. Most of the active site residues are conserved in every model made by MODELLER 9.22 in reference to the 1nns structure, which also signifies that good models were made during the process and can proceed toward the docking (Table 1).

Figure 2. Ramachandran plot of *Streptomyces collinus*. The Ramachandran plot shows the phi-psi torsion angles for all residues (black cubes) in the structure (except those at the chain termini). Glycine residues are separately identified by triangles, as these are not restricted to the regions of the plot appropriate to the other sidechain types. The darkest red area indicates "core" regions representing the most favorable combinations of phi-psi values. The regions are labeled as follows: A (core alpha), L (core left-handed alpha), a (allowed alpha), l (allowed left-handed alpha), ~a (generous alpha), ~l (generous left-handed alpha), B (core beta), p (allowed epsilon), b (allowed beta), ~p (generous epsilon), and ~b (generous beta).



Plot statistics

Residues in most favoured regions [A,B,L]	256	94.5%
Residues in additional allowed regions [a,b,l,p]	12	4.4%
Residues in generously allowed regions [~a,~b,~l,~p]	1	0.4%
Residues in disallowed regions	2	0.7%
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Number of non-glycine and non-proline residues	271	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	41	
Number of proline residues	19	

Total number of residues	333	

Figure 3. Ramachandran plot of *Streptomyces griseus* 1. The Ramachandran plot shows the phi-psi torsion angles for all residues (black cubes) in the structure (except those at the chain termini). Glycine residues are separately identified by triangles, as these are not restricted to the regions of the plot appropriate to the other side chain types. The darkest red area indicates the "core" regions representing the most favorable combinations of phi-psi values. The regions are labeled as follows: A (core alpha), L (core left-handed alpha), a (allowed alpha), l (allowed left-handed alpha), ~a (generous alpha), ~l (generous left-handed alpha), B (core beta), p (allowed epsilon), b (allowed beta), ~p (generous epsilon), and ~b (generous beta).

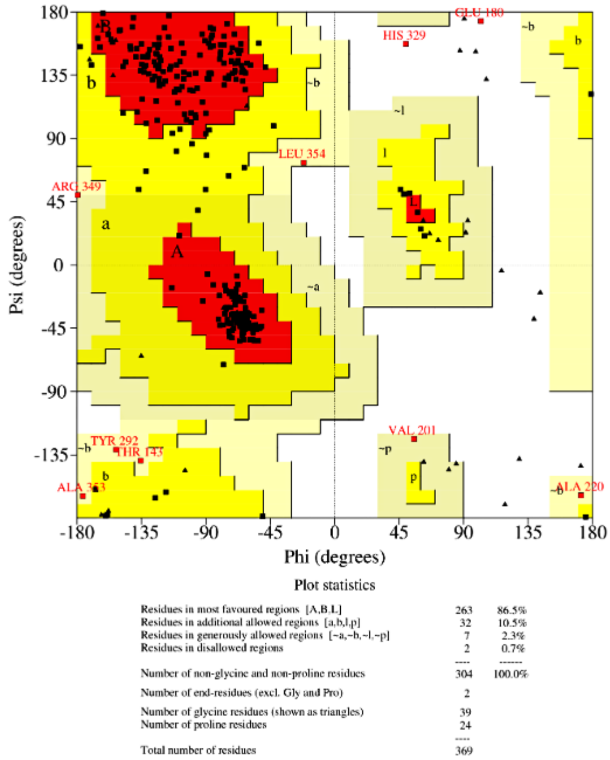


Figure 4. Ramachandran plot: *Streptomyces venezuelae* 2. The Ramachandran plot shows the phi-psi torsion angles for all residues (black cubes) in the structure (except those at the chain termini). Glycine residues are separately identified by triangles, as these are not restricted to the regions of the plot appropriate to the other sidechain types. The darkest red area indicates the "core" regions representing the most favorable combinations of phi-psi values. The regions are labeled as follows: A (core alpha), L (core left-handed alpha), a (allowed alpha), l (allowed left-handed alpha), ~a (generous alpha), ~l (generous left-handed alpha), B (core beta), p (allowed epsilon), b (allowed beta), ~p (generous epsilon), ~b (generous beta).

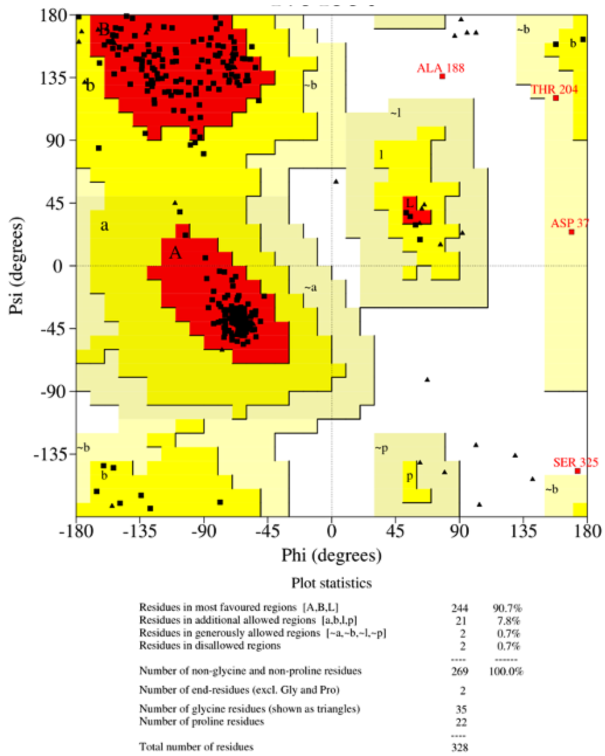


Figure 5. Validation of model *Streptomyces collinus*. (a) ProSA-web z scores of all protein chains in the Protein Data Bank determined by X-ray crystallography (light blue) or NMR (dark blue) with respect to their length. The black dot in the plot indicates that the model protein structure falls inside the range of the plot that contains the z score of all the experimentally determined proteins in the Protein Data Bank. The plot shows only chains with less than 1000 residues and a z score 10. The z scores of model proteins are highlighted as large dots. (b) Energy plot of model protein that indicates the local model quality by plotting energy as the function of the amino acid sequence. Generally, the portion in the positive region of the plot indicates the erroneous part of the structure. (c) Residues are colored from blue to red in the order of increasing residue energy. NMR: nuclear magnetic resonance.

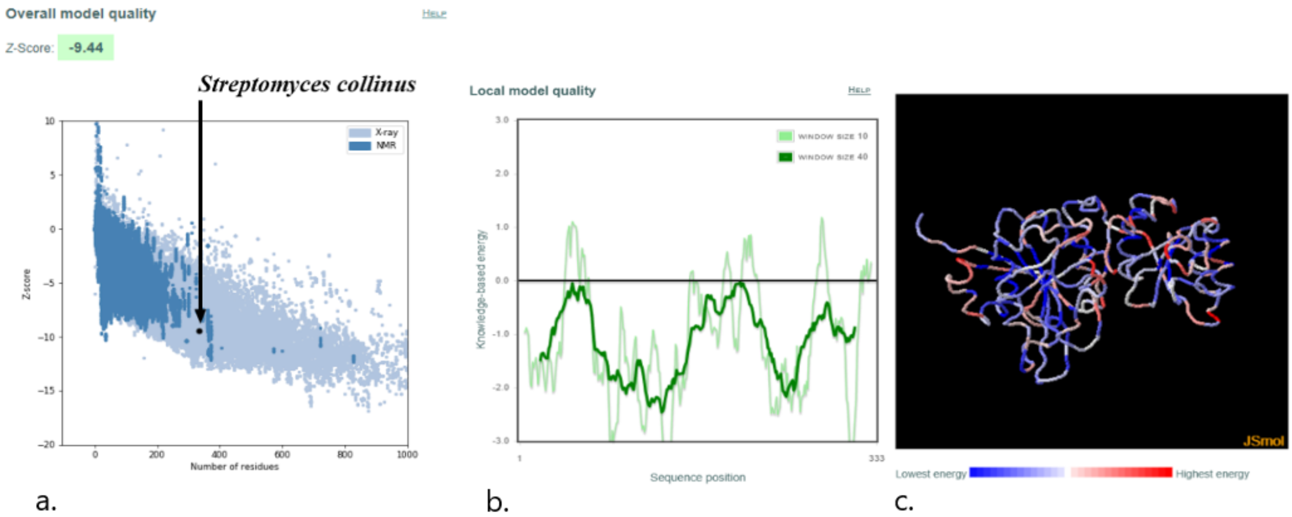


Figure 6. Validation of model: *Streptomyces griseus* 1. (a) ProSA-web z scores of all protein chains in the Protein Data Bank determined by X-ray crystallography (light blue) or NMR spectroscopy (dark blue) with respect to their length. The black dot in the plot indicates that the model protein structure falls inside the range of the plot that contains the z score of all the experimentally determined proteins in the Protein Data Bank. The plot shows only chains with less than 1000 residues and a z score of 10. The z scores of model proteins are highlighted as large dots. (b) Energy plot of model protein that indicates the local model quality by plotting energy as the function of the amino acid sequence. Generally, the portion in the positive region of the plot indicates the erroneous part of the structure. (c) Residues are colored from blue to red in the order of increasing residue energy. NMR: nuclear magnetic resonance.

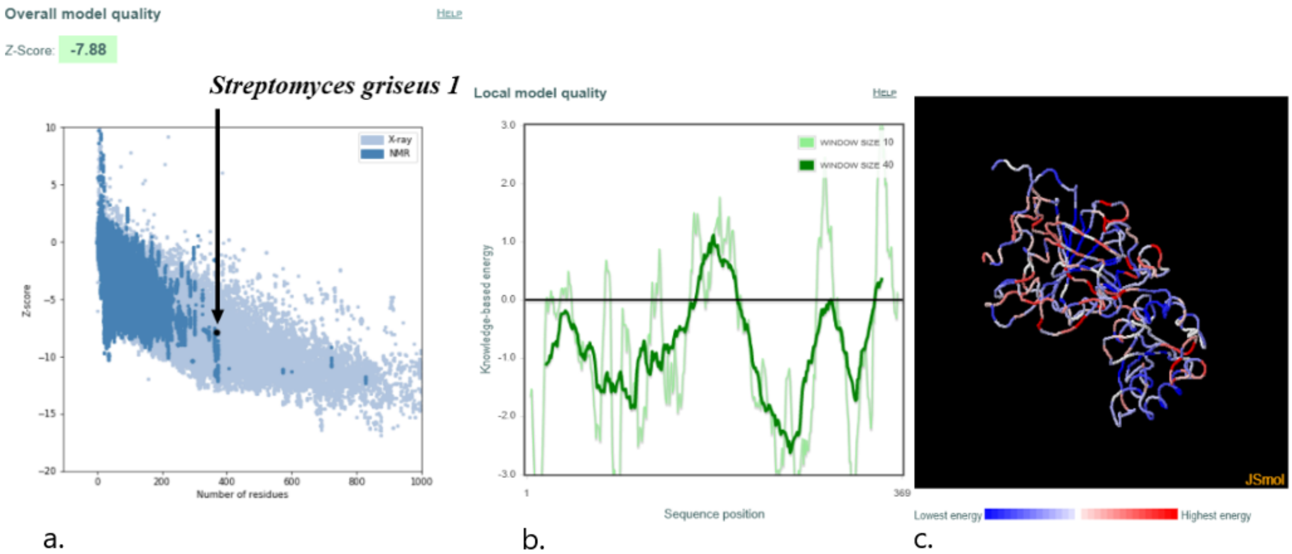


Figure 7. Validation of model: *Streptomyces venezuelae* 2. (a) ProSA-web z scores of all protein chains in the Protein Data Bank determined by X-ray crystallography (light blue) or NMR spectroscopy (dark blue) with respect to their length. The black dot in the plot indicates that the model protein structure falls inside the range of the plot that contains the z score of all the experimentally determined proteins in the Protein Data Bank. The plot shows only chains with less than 1000 residues and a z score 10. The z scores of model proteins are highlighted as large dots. (b) Energy plot of model protein that indicates the local model quality by plotting energy as the function of the amino acid sequence. Generally, the portion in the positive region of the plot indicates the erroneous part of the structure. (c) Residues are colored from blue to red in the order of increasing residue energy.

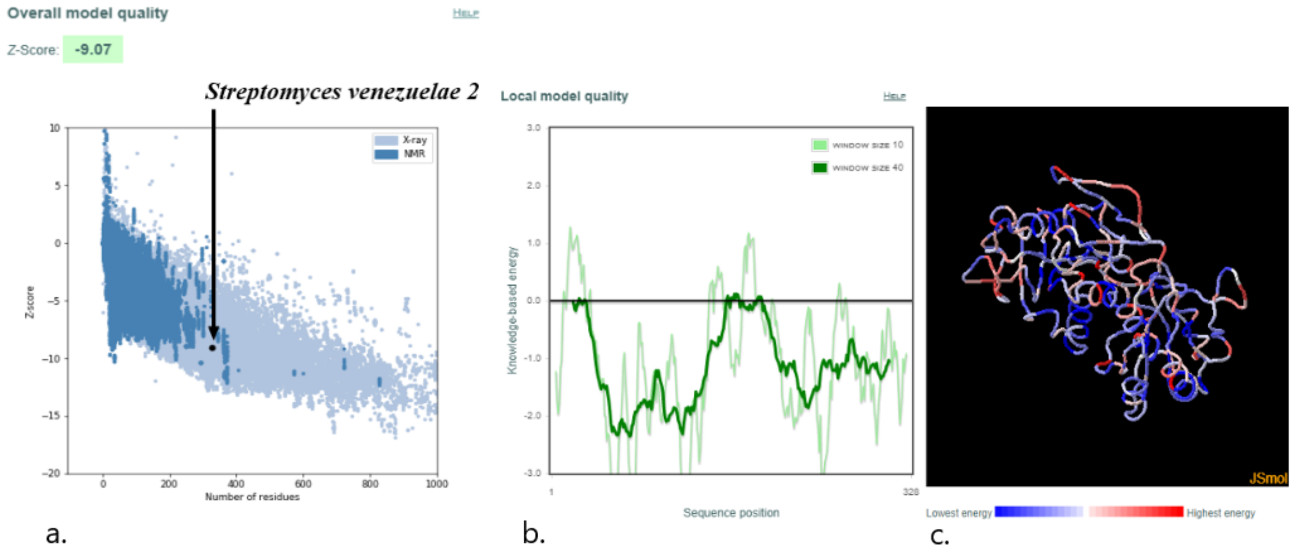


Table 1. Predicted active sites of proteins of organisms that were distant to the *E coli* and organisms whose Km has been determined experimentally (described elsewhere in the paper).[a]

Organisms	Predicted active site residues
Escherichia coli	T(34), S(80), Q(81), T(111), D(112)
Streptomyces globisporus	I(12), S(61), S(62), T(94), D(95)
Streptomyces venezuelae 1	I(12), S(61), S(62), T(94), D(95)
Streptomyces griseus 1	T(20), S(61), S(62), T(94), D(95)
Streptomyces katrae	T(12), S(53), P(54), T(86), D(87)
Streptomyces fradiae	A(12), G(43), A(44), T(75), D(76)
Streptomyces albidoflavus 1	T(12), M(62), R(63), T(94), D(95)
Streptomyces albidoflavus 2	T(12), M(62), R(63), T(94), D(95)
Streptomyces albidoflavus 3	T(12), R(63), L(64), T(94), D(95)
Streptomyces fradiae 2	T(8), S(50), Y(51), T(83), D(84)
Streptomyces collinus	T(16), S(63), L(64), T(94), D(95)
Streptomyces griseus 2	T(16), P(60), G(61), T(94), D(95)
Streptomyces aurontiacus	T(13), S(54), L(55), T(83), D(84)
Streptomyces venezuelae 2	T(12), —, —, T(79), D(80)
Pectobacterium carotovorum 1	T(34), S(81), E(82), T(114), D(115)
Dickeya chrysanthami (Erwinia) 1	T(36), S(83), E(84), T(116), D(117)
Bacilus aryabhattai	T(55), S(102), Q(103), S(135), D(136)
Bacillus Licheniformis 1	T(62), S(109), Q(110), T(142), D(143)
Bacillus subtilis 1	T(61), S(108), T(109), T(141), D(142)
Delftia acidovorans 1	T(62), S(109), E(110), T(142), D(143)
Azotobacter vinelandii	T(45), S(92), E(93), T(125), D(126)
Dickeya chrysanthami (Erwinia) 2	T(36), S(83), E(84), T(116), D(117)
Helicobacter pylori 1	T(34), S(80), Q(81), T(113), D(114)
Pseudomonas stutzeri 1	—, S(80), D(81), T(113), D(114)
Pseudomonas stutzeri 2	—, S(80), D(81), T(113), D(114)
Bacillus subtilis 2	T(61), S(108), T(109), T(141), D(142)
Bacillus licheniformis 2	T(63), S(110), T(111), T(143), D(144)
Delftia acidovorans 2	T(62), S(109), E(110), T(142), D(143)
Helicobacter pylori 2	T(34), S(80), Q(81), T(113), D(114)
Pectobacterium carotovorum 2	T(34), S(81), E(82), T(114), D(115)

[a]Five amino acids were conserved, which has been termed a pentad in this paper. The letter represents the amino acid involved in the active site, the number in parenthesis represents the position of the amino acid. When no amino acid homology was found, the site was left blank with an em dash.

Active Site of asnBs

Along with the 1nns structure of *E coli* asnB, obtained from pdb, comes the description of active site amino acid residues. Using aspartate as a surrogate for asparagine, the active sites have been predicted. For the full-length protein, the active site contains 5 amino acid residues: T(34), S(80), Q(81), T(111), and D(112). These 5 residues can be called a pentad. A table with these pentad residues has been constructed for asnBs of other organisms (Table 1). Four of the five residues—T(34), S(80), T(111), and D(112)—are highly conserved across species (Table 1).

Km, k_{cat}, and Binding Energies of asnBs

To further predict which list of asnBs would be most useful to treat acute lymphoblastic leukemia, binding energies were calculated using docking software. First, using a 1nns structure of *E coli* asnB, structures of unsolved asnBs were predicted using homology modeling These structures were docked to asparagine to calculate binding energy. To evaluate if the binding energy could predict the relative efficacy of the enzymes, Km and k_{cat} values from the literature were tabulated alongside binding energy (Table 2). A total of 10 Km values were obtained from the literature for asnBs of different species.

For the species with only 1 Km value—*Escherichia coli*, *Azobacter vinelandi*, and *Bacillus aryabhattai*—comparison between the relationship of Km and binding energy was easy. When Km value increased, binding energy decreased. Species with the highest binding energy, *E coli*, also had the lowest Km value. Species with the lowest binding energy, *Bacillus aryabhattai*, had the highest Km value.

However, six species contained two asparaginases. From the literature, specific Km values could be assigned to specific asnBs (ie, sequence of protein used to calculate the Km experimentally and sequence of protein used to calculate the binding energy were the same). Those asnBs are marked in the table. *Dickeya chrysanthami* 2, *Heliobacter pylori* 1, and *Bacillus subtilis* 1 had known Km values that were assigned next to them on the table. Similarly, using docking, separate binding energies could be calculated for each asnB protein. In species where two asnBs are available, the Km value measured for the species is assigned to asnB that most closely forms an inverse relationship with the binding energy. For example, *Pseudomonas stutzeri* has two asnBs with binding energies of –5.1 Kcal/mol and –4.9 kcal/mol. Since its Km value is high, the asnB with low binding energy was assigned this Km, although this could not be verified experimentally. When all values were assigned, a clear inverse relationship between Km and binding energy emerged. The binding energies of asnB to asparagine ranged from –5.1 kcal/mol to –4.4 kcal/mol, which are relatively high values of binding in AutoDock Vina software. No relationship could be discerned for k_{cat} value and binding energy. To be able to compare Km value to binding energies, plots were drawn. A smooth curve was fitted (Figure 8).

Table 2. Km value, k_{cat} value (retrieved from the literature), and binding energy (calculated by AutoDock Vina) of the enzyme, asnB, toward L-asparagine.

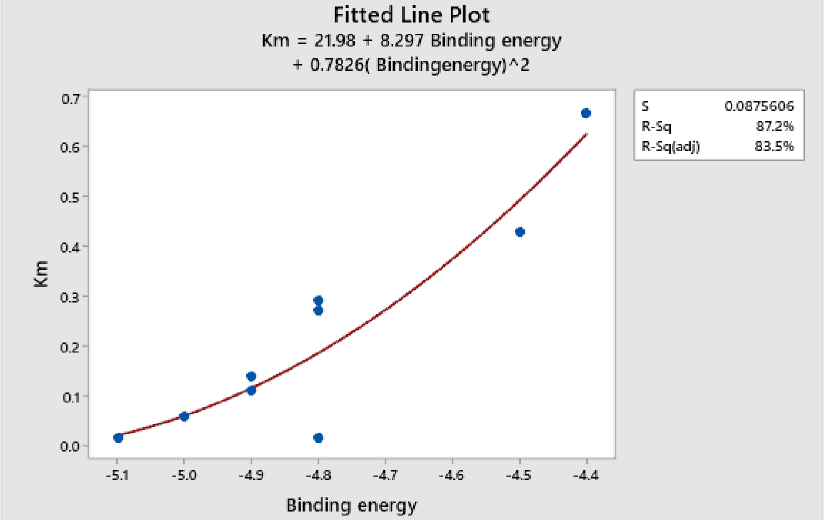
Organism	Michaelis constant value from literature (mM)	Measured k_{cat} values from literature (s^{-1})[a]	Binding affinity calculated from docking (kcal/mol)	References
Bacillus licheniformis 1	0.014	2.68×10^3	–4.8	[48]
Escherichia coli[b]	0.015	2.4×10^1	–5.1	[49]
Deftia acidovorous[b]	0.015	—[c]	–5.1	[50]
Dickeya chrysanthami 2[b]	0.058	23.8×10^3	–5.0	[51]
Azobacter vinelandi[b]	0.11	—	–4.9	[52]
Pseudomonas stutzeri 2	0.14	—	–4.9	[53]
Bacillus aryabhattai[b]	0.257	—	–4.8	[54]
Helicobacter pylori 1[b]	0.29	19.26 +/– 0.56	–4.8	[55]
Bacillus subitilis 1[b]	0.43	—	–4.5	[56]
Pectobacterium carotovorum 1	0.657	2.751×10^3	–4.4	[57]
Dickeya chrysanthami 1	—	—	–4.4	—
Bacillus licheniformis 2	—	—	–4.6	—
Pseudomonas stutzeri 1	—	—	–5.1	—
Deftia acidovorous 2	—	—	–5.0	—
Bacillus subtilis 2	—	—	–5.0	—
Pectobacterium carotovorum 2	—	—	–4.7	—
Heliobacter pylori 2	—	—	–5.1	—

[a]k_{cat} values demonstrate no relationship to the binding energy.

[b]For 6 species, corresponding Km values and binding energies are known (ie, the sequence of protein used to calculate the Km experimentally and the sequence of protein used to calculate the binding energy were the same). For four other species, the Km value that best fit the binding energy value was randomly assigned. The six Km values are perfectly inversely correlated to binding energies.

[c]Experimental data is not available for these particular organisms in the literature.

Figure 8. Relation between Km and binding energy of enzyme toward L-asparagine. The fitted line plot shows that Km and binding energy are inversely proportional to each other. The more negative the binding energy, the less the Km value is. More negative binding energy and less Km signifies the greater affinity of an enzyme toward the substrate. All the enzymes' Km and Binding energy shows how they are inversely proportional to each other except one, which is the enzyme from Bacillus licheniformis 1 (0.014mM Km at –4.8 kcal/mol). We were also unable to confirm that the sequence of the enzyme that was used to calculate the Km value [48] and the sequence of the enzyme used in this experiment was the same.



Finding an Optimal asnB

For 13 asnBs that are most distant from *E coli* and *Erwinia* asparaginase, binding energies were calculated using docking (Table 3). The proteins for which binding energy were calculated are *Streptomyces albidoflavus* 1, 2, and 3; *Streptomyces aurantiacus*; *Stereptomyces collinus*; *Streptomyces fradiae* 1 and 2; *Streptomyces globisporus*; *Streptomyces griseus* 1 and 2; *Streptomcyces katrae*; and *Streptomyces venezuelae* 1 and 2. Out of these 13 proteins, 3 asnBs—*Stereptomyces collinus*, *Streptomyces griseus* 1, and *Streptomyces venezualae* 2—showed biding energy of –5.3 kcal/mol, –5.3 kcal/mol, and 5.2 kcal/mol, respectively, higher than *E coli* anB. Docked structures are shown in Figures 9-12. These asparaginases can be further cloned and tested for Km and k_{cat} values.

Figure 9. Docked structure of *Escherichia coli* asnB and *L-asparagine*. L-asparagine is seen to be completely impended in the catalytic pocket of the enzymes.

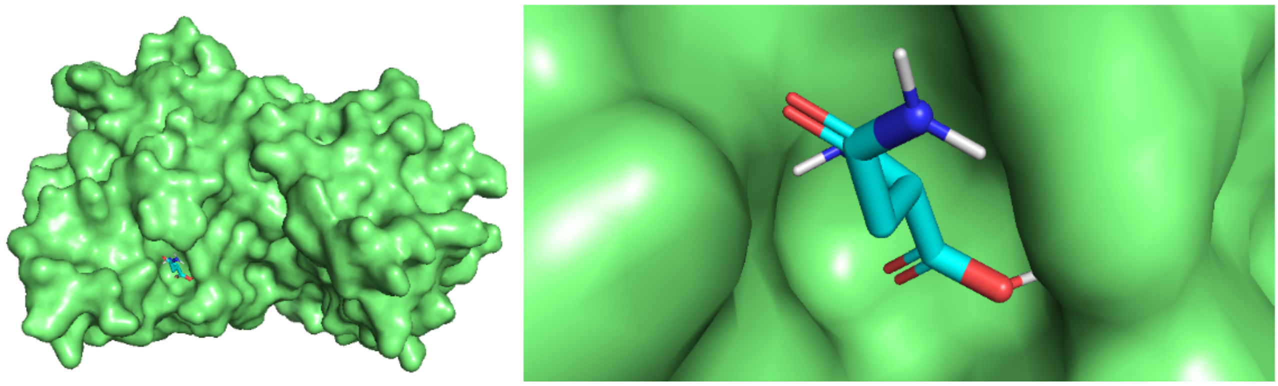


Figure 10. Docked structure of *Streptomyces griseus* 1 asnB and *L-asparagine*. L-asparagine is seen to be completely impended in the catalytic pocket of the enzymes.

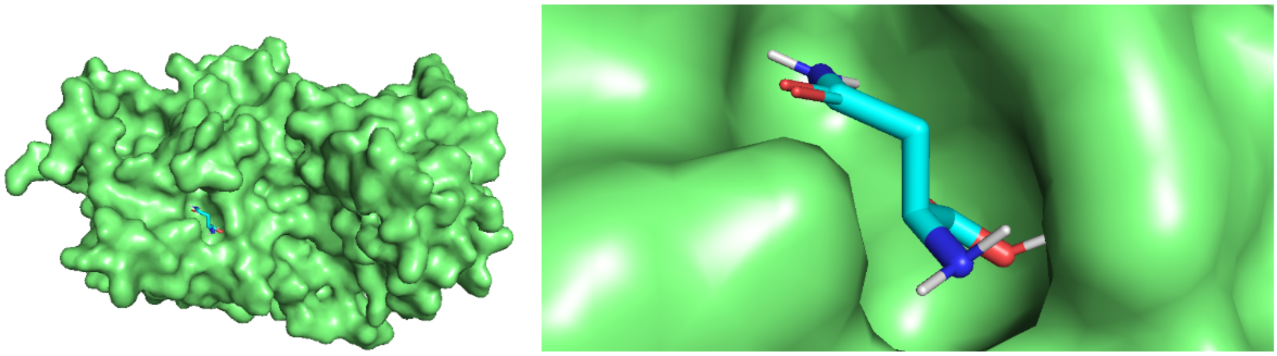


Figure 11. Docked structure of *Streptomyces venezuelae* 1 asnB and *L-asparagine*. L-asparagine is seen to be completely impended in the catalytic pocket of the enzymes.

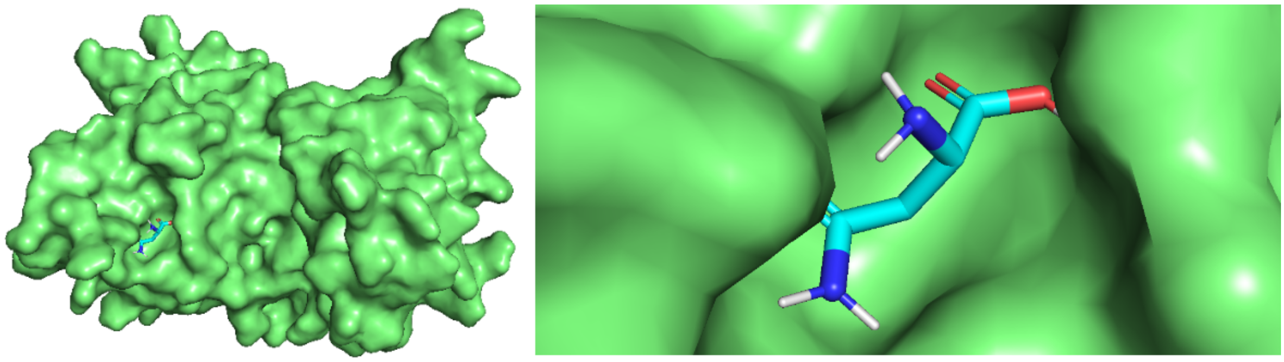


Figure 12. Docked structure of *Streptomyces collinus* asnB and *L-asparagine*. *L-asparagine* is seen to be completely impended in the catalytic pocket of the enzymes.

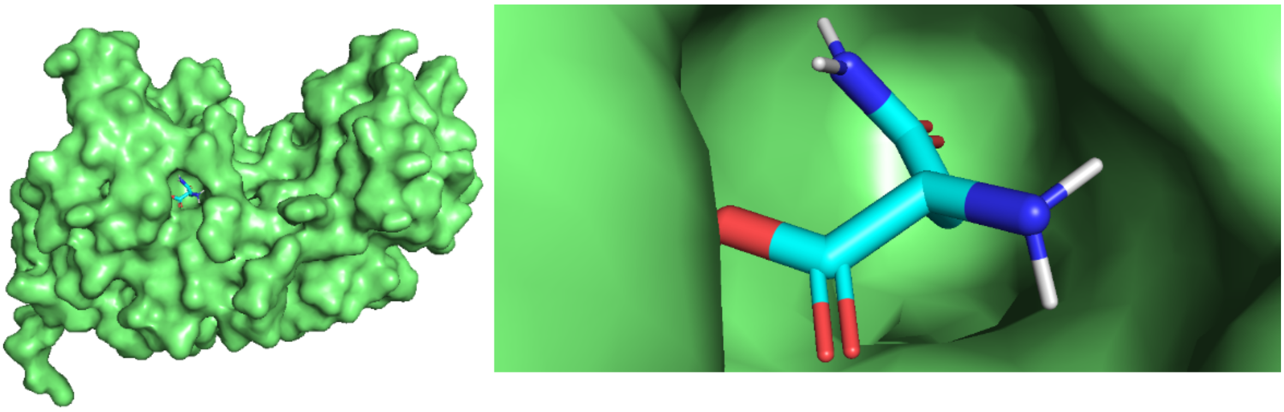


Table 3. Binding energy of distant organism's asnB and L-asparagine.

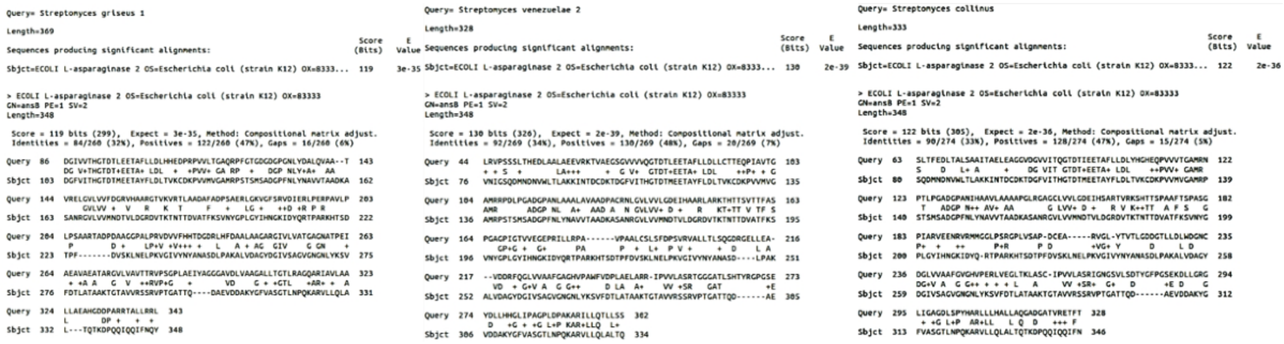
Organisms	Binding affinity calculated from docking (kcal/mol)
Streptomyces albidoflavus 1	–4.8
Streptomyces albidoflavus 2	–4.8
Streptomyces albidoflavus 3	–4.5
Streptomyces aurantiacus	–4.2
Streptomyces collinus [a]	–5.3
Streptomyces fradiae 1	–4.9
Streptomyces fradiae 2	–4.9
Streptomyces globisporus	–4.2
Streptomyces griseus 1[a]	–5.3
Streptomyces griseus 2	–4.6
Streptomyces katrae	–4.9
Streptomyces venezuelae 1	–4.8
Streptomyces venezuelae 2[a]	–5.2

[a]*Streptomyces collinus*, *Streptomyces griseus* 1, and *Streptomyces venezuelae* 2 asnBs have –5.3 kcal/mol, 5.3 kcal/mol, and 5.2 kcal/mol binding energy, respectively, which is greater than the *E coli* and *Dickeya chrysanthami* –5.1 and –5.0 kcal/mol, respectively, which indicate that these organisms' asnB have a greater affinity toward the L-asparagine.

Pairwise Sequence Alignment

We also compared the amino acid sequence of the three optimal asnBs selected with that of *E coli* asnB sequence. *Streptomyces venezuelae* 2 showed the highest alignment score of 130 with 34% sequence identity to *E coli* asnB. *Streptomyces collinus* showed 33% identity with *E coli* and an alignment score of 122. *Streptomyces griseus* 1 had the lowest alignment score of 119 and sequence identity of 32% among the three optimal asnBs selected. Conversely, *Streptomyces griseus* 1 had the lowest E value (3×10^{-35}) compared to *Streptomyces venezuelae* 2 (2×10^{-39}) and *Streptomyces collinus* (2×10^{-36}). All of them had a similar percentage of gaps when aligned with the query sequence shown in Figure 13.

Figure 13. Sequence alignment results for Streptomyces collinus, Streptomyces griseus 1, and Streptomyces venezuelae 2 asnB sequences with the E coli asnB sequence. The query sequence is displayed above the subject. Starting and ending amino acid positions for each row are given for both query and subject. The score, E values, the percentage of positive hits, and the percentage of gaps are given above the alignment diagram.



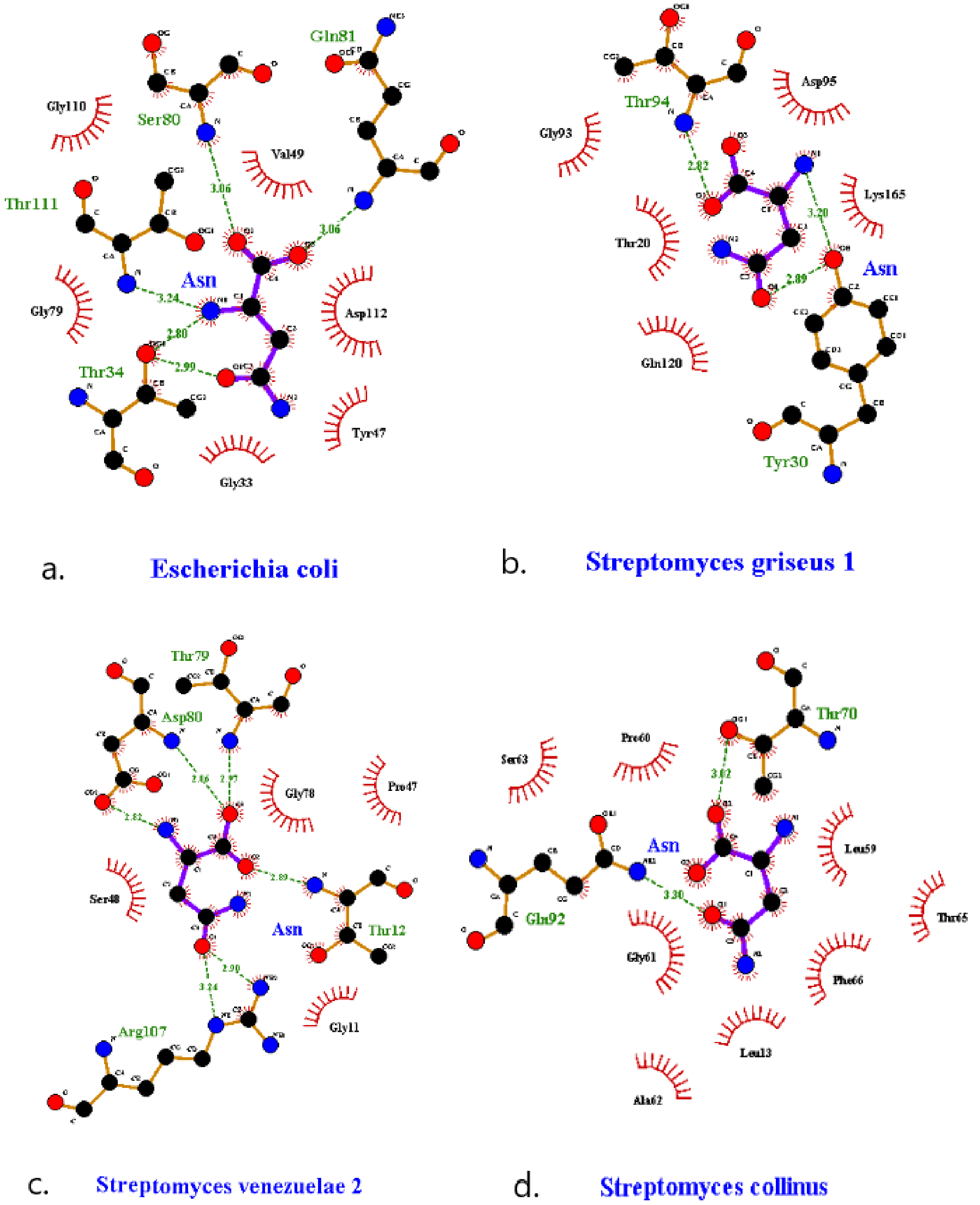
Interaction With Active Sites

A LigPlot showing active site interactions of asnB and asparagine was constructed and is shown in Figure 14. The active site of *E coli* asnB contains all 5 active site residues. Four of those residues—T(34), S(80), Q(81), and T(111)—form direct hydrogen bonding with asparagine. D(112), unlike in the 1nns active site predicted by pdb, does not form a hydrogen bond and only stays in the active site as a hydrophobic interactor in our LigPlot model. As 1nns is the structure complexed with aspartic acid (D), a closer inspection of the active site interactions in the 1nns predicted in the pdb website and our LigPlot model show some similarities and some variations.

LigPlot showing active site interactions of asnB and asparagine was constructed and shown in Figure 14. In *Streptomyces griseus* 1 asnB, 3 amino acid residues—T(20), T(94), and D(95)—of the pentad (out of five predicted residues) interacts with asparagine (Figure 14). Out of three residues, only one residue T(94) is involved in the formation of a hydrogen bond, whereas two other residues form a hydrophobic interaction with asparagine. Y(30) forms another hydrogen bond with asparagine. Only 3 of the pentads were detected in *Streptomyces venezuelae* 2. All three amino acids form an H-bond with asparagine. Additionally, R(107) forms a hydrogen bond with asparagine (Figure 14).

As for *Streptomyces collinus* asnB, 4 of the catalytic pentad residues—T(16), L(64), T(94), and D(95)—are absent at the catalytic site interaction with asparagine. Only S(63) is present in the active site. When the ligand was docked to the *Streptomyces collinus* asnB predicted active site with the grid box size 25 × 25 × 25 Å, AutoDock software automatically detected that there was another catalytical pocket present adjacent to the predicted one with almost the same interacting residues (Figure 14) as predicted but with the different position that gives the binding energy of –5.3 kcal/mol, where T(70) and Q(92) contributes on hydrogen bonding and other residues are involved in hydrophobic interaction. This binding site is shown in Figure 14 and is visibly almost the same but in a different position from all predicted active site residues.

Figure 14. LigPlot of interacting atoms of *E coli* and selected three organisms. (a) *Escherichia coli*, (b) *Streptomyces griseus* 1, (c) *Streptomyces venezuelae* 1, (d) *Streptomyces collinus* enzymes, and *L-asparagine* (Asn).



Discussion

Rapid and cost-effective screening of enzymes is a common undertaking in enzymology. Industrially produced enzymes have a role in a wide range of functions in pharmaceutical, food, biofuel, and chemical industries. Such enzymes are often screened from novel organisms in the soil, water, or other resources. Many of the commercially useful enzymes have been discovered through such screens. The fungus that produces cellulase, *Trichoderma reesei*, was isolated from garments and canvas that was degraded in the Solomon Islands during the Second World War [58]. Similarly, most of the alpha amylases used in the industry find their source in Bacillus [59]. Asparaginase that is used as an anticancer agent is derived from *E coli* and *Erwinia*. Most of these microorganisms have been discovered from simple screens developed for certain enzymes.

This does not necessarily mean that these enzymes have the most optimal sequences for activity. This is because the screen could have easily missed out on better sequences that are not as well expressed in native cells. If these better sequences could be discovered, they would be easily cloned into amenable expression systems, expressed in high numbers, and used for industrial purposes.

In this paper, we have developed a method to in silico screen for the sequence with the best enzymatic activity. Since asnB is one of the most widely screened and studied enzymes, we chose to in silico predict the optimal sequence for its production. The first task was to collect a list of sequences from which optimal sequences could be predicted. This task has been made easier in recent years by an explosion in the number of genomes of organisms sequenced. It has become easy to discover homologous proteins in different phyla and in different domains of life. We collected a total of 101 sequence homologs of asnB from different phyla in bacteria, archaea, and eukarya. Using these 101 sequences, an ML phylogenetic tree was constructed. The tree served two purposes. First, it helped us predict the evolution and history of the asnB protein. Since proteins from the same phylum tend to congregate little in the tree, it can be predicted that there was a lot of horizontal gene transfer during the evolution of asnB. Less than half the species we searched had asnB sequences, indicating the lack of the enzyme's universal presence in different organisms. Second, the tree helped pick sequences that were most distant and hence least likely to cause immunogenicity when both *E coli* and *Erwinia* asnBs showed immunogenicity. *E coli*, being one of the most studied model organisms, was the obvious first choice as a source of asnB. There is no clear indication in the literature as to why *Erwinia* was chosen as the second source of asnB, but the tree we have drawn confirms that *Erwinia* as a source was a wise choice since *Erwinia* asnB lies at one end of the tree distant to *E coli* asnB that lies around the center of the tree. The organisms we have zeroed in on are distant compared to *Erwinia* and *E coli*, and mostly lie in the *Streptomyces* genus.

As we can see, phylogenetic analysis can provide valuable insight about our protein of interest. Phylogenetic methods have been previously used successfully for studying L-asparaginase given its importance in the therapeutic setting. These methods have proven useful in identifying similarities between asnBs from different organisms based on the evolutionary relationship of their sequences, allowing researchers to group together organisms producing asnBs at a molecular level. This has led to discoveries regarding important amino acids and sequences of the L-asparaginase enzyme [60]. Information gleamed from phylogenetic analysis is not only useful in understanding the genetic variation and history of a protein across various organisms but also for identifying organisms that may produce more optimal proteins than those that are currently used, especially for commercially important proteins. Researchers have used them to identify clades with specific amino acid sequences that are also found in *E coli*. This information was then used to short list candidates for in silico screening for alternative L-asparaginase using docking [61].

Molecular modeling and docking have proven adequate for studies involving screening for alternative L-asparaginase candidates and optimization of this enzyme. They have been successfully used in previous studies for identifying alternative organisms for higher production of L-asparaginase candidates. These studies have also been validated using *in vitro* experimental work on the identified candidates [62]. Similarly, docking has been used in screening for L-asparaginase enzymes that have better activity toward asparagine and reduce its glutaminase side activity as well [63]. We used homology modeling and virtual docking in our method to identify enzymes with better binding energy than the commercially available asnBs produced from *E coli* and *Erwinia*. The candidates we zeroed in on using the phylogenetic tree were modeled using homology modeling and their binding energy to our substrate, asparagine, calculated using docking. Of the 13 potential candidates we had identified from the tree, 3 of them, *Streptomyces griseus* 1, *Streptomyces venezuelae* 2, and *Streptomyces collinus*, were deemed to be better than the commercially available option.

Additionally, we wanted to develop an in silico tool to predict the reaction kinetics of individual enzymes. To that end, we relied on molecular modeling and docking approaches. Although reaction kinetics is defined by different parameters like Km, k_{cat}, maximum velocity (Vmax), and specificity constant (k_{cat}/Km), Km is often the most widely measured quantity. This turned out to be the case for asnBs as well. From the literature, 10 Km values corresponding to asnBs from different species were discovered, while only 4 k_{cat} values were discovered. We set out to discover if the sequence of asnB can predict Km value without having to determine it experimentally. Through homology modeling, we predicted the structures of asnBs with known Km. After that, asparagine (the substrate) was docked onto the predicted asnB structures, and the binding energy was calculated. This binding energy was compared to the measured Km values to detect a correlation. Out of 10 species for which Km is known, only in 6 species (*Escherichia coli*, *Deftia acidovorous*, *Dickeya chrysanthami* 2, *Azobacter vinelandi*, *Pseudomonas stutzeri*, *Bacillus aryabhattai*, *Helicobacter pylori* 1, and *Bacillus subitilis* 1) could Km be definitely assigned to a certain sequence. A clear inverse relationship between Km value and binding energy emerged. A higher Km value corresponded to lower binding energy.

This finding makes sense according to a definition of Km. The Michaelis-Menten kinetics is derived using the following equation:

Where E is the enzyme, S is the substrate, ES is the enzyme-substrate complex, P is the product, k_1 is the rate of forward reaction during the formation of ES complex, k_{-1} is the rate of backward reaction during ES dissociation into E and S, and k_2 is the rate of reaction for the dissociation of ES complex into E and P. From this equation, Km is defined as $(k_2 + k_{-1}) / k_1$. When $k_2 << k_{-1}$ under the rapid equilibrium assumption, $K_m = k_{-1} / k_1$. Thus, Km is equal to the dissociation constant. There is also a relationship between the dissociation constant and binding energy—deltaG (binding energy) is proportional to

–lnKm. However, when lnKm is plotted against binding energy, a linear fit graph was not obtained (data not shown). However, the negative relationship between Km and binding energy makes sense from this equation [64].

This result demonstrates that if binding energies can be compared among homologs, the homolog with the highest binding energy will give the lowest Km value. This can be used to predict the enzyme sequence that will give the lowest Km value. In this paper, the binding energies of asnBs from various Streptomyces species were calculated to obtain the one with the highest binding energy. Of the 13 asnBs, 3 give biding energy of –5.3 kcal/mol and –5.2 kcal/mol with asparagine. asnBs from *Streptomyces griseus*, *Streptomyces collinus*, and *Streptomyces venezuelae* gave these values. These values are higher than the binding energy of *E coli* and *Erwinia* asnBs. We can expect the kinetics of the enzyme produced from Streptomyces species to be better than those of commercially available asparaginase, making it a valuable target for cloning.

For the three optimal asnBs and *E coli* asnB, a LigPlot diagram of the active site along with interacting aspargine was drawn. It was demonstrated in *E coli* that the catalytic pentad residues were actively involved in bonding. Four of the five active-site residues formed hydrogen bonds, whereas one stayed in the active site forming hydrophobic interaction. Although the residues interacting are the same in the active site published by pdb site, different amino acid residues form hydrogen bonds with asparagine at different locations from the one given in the LigPlot in this paper. This is in line with the idea that the exact mechanism of asparaginase catalysis is not figured out, though it is predicted that the mechanism for type I and type II asparaginases will be conserved [65]. Two different mechanisms have been proposed for asparaginase catalysis. One mechanism describes double displacement, where the ammonia in asparagine is first displaced by the enzyme before the enzyme attached to asparagine is again displaced by water. The second mechanism describes the single displacement where water directly displaces ammonia from asparagine. There are contrary experimental and theoretical predictions for the validity of the two models [65,66].

From the LigPlot of *Streptomyces griseus* 1 and *Streptomyces venezuelae* 2, it can be demonstrated that three of the pentad residues are present in the active site. This shows that the active site in these distant species is conserved. It has been predicted that one of the two threonines acts as a nucleophile in the double displacement mechanism. Conservation of both threonines suggests that this could indeed be the case. A dynamic simulation modeling rather than the static docking modeling we have carried out might give a clearer answer to the active sites involved, the catalytic mechanism, and the relevant nucleophiles and electrophiles.

Thus, we have devised an in silico method to predict the enzyme kinetics (Km value) from a sequence of an enzyme along with being able to screen for optimal alternative asnBs against acute lymphoblastic leukemia. Our method uses sequence-based phylogenetic analysis to zero in on a small number of candidates on which virtual docking can be used to identify a set of optimal enzymes that may be better than those that are commercially used. In this paper, we have shown the effectiveness of our method for identifying enzymes that are more optimal than a known commercial variant. We have also validated the effectiveness of this method to predict Km values of asparaginase II with a high degree of accuracy. This method is applicable not only to asparaginases but also to a slew of other industrial proteins such as amylases, cellulases, and many others. In the future, it will be worthwhile to apply this technique to the prediction of Km and the selection of industrially valuable sequences of other enzymes. We have predicted three possible highly promising L-asparaginase II enzymes produced by three Streptomyces species. The next step will be to verify using cloning if these sequences give a low Km value.

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Authors' Contributions

HKB conceived and initiated the project. HKB and A Baral designed the experiments. A Baral and RG carried out the phylogenetic analysis. A Baral and A Basnet carried out the homology modeling. A Baral and SK worked on the verification of the protein model. A Baral and RG carried out the docking experiment. HKB, A Baral, and RG wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary file.
[DOCX File , 4400 KB - xmed_v2i3e29844_app1.docx]

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Abbreviations

BLAST: Basic Local Alignment Search Tool
DOPE: discrete optimization protein energy
ML: maximum likelihood
NCBI: National Center for Biotechnology Information
SOAP: statistically optimized atomic potentials

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Original Paper

The Exchange of Informational Support in Online Health Communities at the Onset of the COVID-19 Pandemic: Content Analysis

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Abstract

Background: Online health communities (OHCs) provide social support for ongoing health-related problems. COVID-19, the disease caused by SARS-CoV-2, has been an acute and substantial stressor worldwide. The disease and its impact, especially in the beginning phases, left many people with questions about the nature, treatment, and prevention of COVID-19. Unlike typical chronic ailments discussed on OHCs, which are more established, COVID-19, at least at the onset of the pandemic, is distinct in that it lacks a consensus of clinical diagnosis and an existing community foundation.

Objective: The study aims to investigate a newly formed OHC for COVID-19 to determine the topics and types of information exchange as well as the sources of information this community referenced during the early phases of the COVID-19 pandemic in the United States.

Methods: A total of 357 posts from a COVID-19 OHC on the MedHelp platform were annotated according to an open-coding process. Participants' engagement patterns, topics of posts, and sources of information were quantified.

Results: Participants who offered informational support had a significantly higher percentage of responding more than once than those seeking information (*P*<.001). Among the information-seeking topics, symptoms and public health practice and psychological impacts were the most frequently discussed, with 26% (17/65) and 15% (10/65) of posts, respectively. Most informational support was expressed through feedback/opinion (181/220, 82.3%). Additionally, the most frequently referenced source of information was news outlets/websites, at 55% (11/20). Governmental websites were referenced less frequently.

Conclusions: The trends of this community could be useful in prioritizing public health responses to address the most common questions asked by the public during crisis communication and in identifying which venue of communication is most effective in reaching a public audience during such times.

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KEYWORDS

COVID-19; informational support; online health; online health communities; health information; online platform; pandemic; social support

Introduction

Background

Since the start of the COVID-19 pandemic, the disease has been a topic of unceasing concern worldwide. The onset of SARS-CoV-2 created many uncertainties, particularly pertaining to the epidemiology of the virus and its impact on people. Especially in the beginning phases of the SARS-CoV-2 epidemic, the symptoms and severity of the disease varied from person to person, and the transmission of the virus was not well understood [1]. The impact of COVID-19 has been shown to cause psychological distress by vicarious trauma not only among health care workers but also in members of the general public [2]. As the novel circumstances created by COVID-19 evolve, these unknown factors continue to be a point of discussion and revelation in efforts to mitigate health concerns and apprehension among the public [3]. Coping with the effects of COVID-19 has become a new challenge globally, and one coping method among many is seeking social support [4]. With the ongoing pandemic, efforts to disseminate and provide support have become increasingly important to offer solace and guidance.

Particularly, given the current climate, transitioning many aspects of pre–COVID-19 life to a web-based format has become a movement in itself. With the shift to virtual classrooms, conferences, and clinics (telemedicine), the emphasis on the internet is as dominant as ever. Online support communities offer accessibility to provide comfort to those who are seeking it. Historically, online health communities (OHCs) or forums have been used as a platform for a variety of conditions, particularly chronic diseases. OHCs provide empathic peer-to-peer support by giving participants a safe space to offer shared connections and emotional understanding [5]. In addition to the emotional aspect of social support, these communities provide informational support to those who are seeking advice [3]. Analysis of the interaction within these communities has provided insight about information exchange and behaviors for many established diseases [6,7].

However, given the novelty and impact of COVID-19, the response of COVID-19 support communities may not be similar to those of established diseases. The departure from the norm of chronic diseases presents a unique opportunity to observe the needs of this community (eg, where participants are getting their information and how outlets of information may be directed in these scenarios in the future). The presence of these communities dedicated to COVID-19 appears to have a wide spectrum of focus and social support. In social media platforms such as Reddit, many public health issues have emerged as popular topics for discussion [8]. However, the public nature of these popular platforms makes them susceptible to an *infodemic*, or the spread of misinformation across media [9]. In contrast, dedicated OHCs, such as MedHelp, offer expert-moderated content to improve the accuracy of information. The participants are typically patients, caretakers, and health care professionals, who may form another layer of resistance to misinformation. Research has been active on popular social media platforms (eg, Twitter and Weibo) and COVID-19 [10-15]; however, there appears to be a gap in knowledge about how established, health-tailored communities have been responding to COVID-19. For these reasons, we will focus on a new COVID-19 community on MedHelp.org [16] for this study.

Social support can be organized into four broad types of supportive behaviors: emotional, instrumental, informational, and appraisal support. These behaviors are not mutually exclusive and may coexist in a single social exchange [17-19]. Bates [20] argues that information-seeking behavior is not only social and cultural but is also embedded in the biological and physical anthropological layers of human existence. In the context of COVID-19, investigating people's health concerns and informational needs is particularly important to determine actionable steps to provide reassurance and safety at the emergence of a previously unknown disease. By examining the originating posts in this OHC, our goal is to identify the topics of information that the participants are seeking. Additionally, studying the types of informational support in the form of responding posts would give a sense of how members of this community are interpreting the pandemic as a whole and how they are engaging and managing the information around them. In the participants' responses, the sources of information would help provide a better understanding of where people are receiving most of their information and what resources might be lacking in delivering patient education materials. Especially given the accompanying infodemic, investigating where most sources are referred to would help formulate possible future directives for information dissemination. To summarize, we aim to address three research questions (RQs) through our investigation:

1. What patterns of engagement did participants have in the newly formed OHC?
2. What were the topics of information-seeking posts and types of informational support?
3. What sources of information were referenced most frequently?

Prior Work

Social Support in OHCs

There is a robust body of literature investigating social support in online health forums or communities. Many are related to chronic health conditions such as cancer, diabetes, or substance use disorder [5,7,21-23]. These established diseases are typically in chronic care or require a degree of maintenance. Acute episodes are possible, but the overall projection is long-term; thus, attention should be paid to factors beyond physical medical treatment, such as the psychological implications, which are garnered through social support.

In terms of the nature of social support in online communities for health causes, Coulson [24] examined five thematic social support categories: emotion, esteem, information, network, and tangible assistance. Among these categories, informational support was used the most for areas of symptom interpretation, illness management, and interaction with health care providers [24]. Online support for alcoholism in an OHC showed subcategories of informational support that included advice, referral, fact, personal experience, and opinions; facts were the most frequently exchanged [6,25]. Additional studies show that informational and emotional support is the most frequently offered form of social support and is key to the functioning of online groups [26,27]. In investigating the patterns of social support exchange between OHC participants, Zhang and Yang identified four behaviors, including active giving, active receiving, passive giving, and passive receiving [7]. Empathy analysis of OHCs demonstrated that empathy develops through shared experiences [22], and empathy was perceived through effectiveness of information seeking rather than general social support [28]. Broader functions served by general-purpose online social platforms include raising awareness, fundraising, and commercial promotional content [5,21].

Information Studies Related to COVID-19

As COVID-19 quickly spread in 2020, an increasing amount of research work was performed to understand how the public was responding to the pandemic by analyzing social media data. Applications of qualitative and quantitative methods to topic identification and modeling were the most common studies, and general-purpose microblogging sites such as Twitter and Weibo served as much of the research corpora. One study identified the top concerns among Twitter users to be the origin of the virus; its sources; its impact on people and society; and ways of mitigating the risk of infection [29]. Xue et al [14] used latent Dirichlet allocation to identify popular unigrams and bigrams representative of salient topics and sentiments in the collected COVID-19 tweets, and they found that confirmed cases and death rates, preventive measures, health authorities and government policies, COVID-19 stigma, and negative psychological reactions (eg, fear) were the dominating topics on Twitter [14]. Chang et al [12] developed online non-negative matrix factorization algorithms to detect the evolving COVID-19 topics over time on Twitter; government policy, economic crisis, COVID-19-related updates and events, prevention, vaccines and treatments, and COVID-19 testing were some of the most important evolving topics identified. Zhao et al [15] explored the types of information most frequently searched by Chinese netizens during the pandemic on Weibo: accessing medical treatment, confirmatory testing, managing self-quarantine, and offline-to-online support.

The public sentiment during the pandemic is another area of focus. Boon-Itt and Skunkan [11] found that Twitter users had a negative outlook towards COVID-19, and fear was the most frequent negative sentiment. Lwin et al [13] found that the emotions of the public shifted from fear to anger over the course of the COVID-19 pandemic on Twitter, and sadness and joy began to surface as people lost loved ones or expressed gratitude and hope for recovery.

In addition to topic and sentiment analysis, social media data were also analyzed for syndromic surveillance, fulfilling the notion of infodemiology [30]. Alanazi et al [10] collected tweets about COVID-19 and found that the 3 most commonly mentioned symptoms were fever, headache, and anosmia. Researchers in China analyzed the symptom descriptions and clinical test results posted voluntarily by Weibo users [31].

Finally, a limited number of studies sought to analyze the characteristics of the information posted on the web, such as its validity and patterns of spreading. Jo et al [32] identified the topics and appropriateness of questions related to COVID-19 at the early stage of the outbreak posted on a popular Q&A web forum (Naver Jisik-In) in South Korea; they concluded that the answers to suspected physical symptoms were relatively accurate, but a high proportion of answers related to self-protection methods contained misinformation or advertisement content. Park et al [33] studied how COVID-19–related news articles circulated on Twitter in Korea; they found that the choice of words for referencing the disease affects the speed of information spread, and medical-themed articles are more popular than nonmedical reporting of the disease.

To summarize, research on COVID-19–related web-based discussions published to date has primarily focused on identifying the topics and public sentiment reflected by the content. The identified topics, while informative, are diverse and lack a common framework to generalize for future public health emergency planning. Furthermore, these studies used general-purpose social media platforms, whose content may be generated by news publishing organizations, commercial accounts, or special interest groups that are not representative of the average health consumers. Meanwhile, studies on social support seeking as a means of disease management have been abundantly studied for many existing health conditions, our understanding of how the public seeks support in the face of an emerging pandemic is limited. In this study, we focus on the characteristics of the informational support exchange related to COVID-19 among OHC participants. In particular, we investigate the patterns of participation, topics of information seeking, types of informational support, and sources of information referenced.

Methods

Data Source

We collected data from MedHelp [16], an online health and wellness forum with more than 150 support communities dedicated to individual health topics, regarding COVID-19 discussions between March 12 and June 25, 2020. COVID-19 began to significantly impact life in the United States in March 2020, and this month is also when the MedHelp COVID-19 community began its activity. The unit of analysis is a post. During this time, there were a total of 83 originating posts and 274 responding posts. The originating posts were questions raised by participants who were seeking information. The responding posts were answers offered by other participants. In addition to the responding posts, participants were able to provide comments on the responses, which were excluded because they may not have a direct relation to their corresponding post. All data collected are publicly and freely accessible on the internet.

Data Analysis

Qualitative content analysis was performed on posts for information seeking and informational support. The posts and responses were exported from the platform into an Excel file (Microsoft Corporation). The variables in this document included a numerical ID of the post, the post topic, the post content, the post creator, the post date, a numerical ID for the response, the response topic, the response content, and the response creator. These variables were then reviewed and coded by one researcher, who is a medical student. Annotations included categorizing the topics of information-seeking posts, the types of informational support responses, and the sources of information for referral posts. The annotated results were randomly sampled and reviewed by another researcher with experience in qualitative data analysis. The researchers discussed the ontology and clarified concepts that might fall under multiple categories. For example, posts inquiring about mask-wearing can be categorized under transmission, protection, and public health practices and psychological impacts, but we focused on their different emphases: transmission is about people wanting to understand the mechanism underlying how a particular protection measure might work; protection is about seeking information on a specific protective measure; and public health practices and psychological impacts is about building consensus on protective practices for group well-being. The coding definitions and examples are provided below. The frequency of each of the topics for information seeking and the types of informational support were then quantified.

Topics of Information Seeking

To understand participants' inquiries about different aspects of COVID-19, the topics of information seeking were coded for the 83 originating posts. Common topics were identified based on the subject matter and context of the post. These included health risk, symptoms, transmission, prevention, prognosis, protocols, disease management, and public health and psychological impacts (Table 1).

Table 1. Topics of information seeking, their definitions, and examples.

Name of topic	Definition of topic	Example posts
Health risk	Having a notable past medical history that includes pre-existing conditions, such as diabetes, lupus, and cancer, or past traumatic events, such as hospitalizations and treatments	• "I had a septic blood disease 5 years ago which caused spots on my lung and my brain. I was hospitalized for 32 days over the course of three months...Does this make my immune system more susceptible to catching the coronavirus at this time?..." • "So in layman's terms, who is high risk? Are people of a certain age automatically high risk, even if we're healthy?..." • "I'm in my 70s, but healthy. If I don't have diabetes, heart disease or lung issues, do I have to stay inside?"
Symptoms	Specific characteristics that are relevant to the presentation of COVID-19, such as cough and loss of smell. These also include differentiating factors from other similar disease presentations, such as influenza.	• "I've had this left side throat pain for about 4-5 days now…I don't have any trouble breathing, stuffy/dripping nose, aches/pains, I'm not dry coughing and I'm not running a fever. Should I be worried about this?" • "…I was diagnosed with sinusitis on Thursday... Monday morning I woke up with a low grade fever of 100.1 and a sore throat...I have no other symptoms...any advice?..." • "Does the normal Flu [influenza] have SOB [shortness of breath]?" • "…i've lost my smell and taste. Had a mild cough a few days before this. Is it covid19?..." • "Covid Toes, what are they?"
Transmission	Means by which COVID-19 can be transferred, be passed on, or travel	• "…I was washing produce that was brought from the grocery…and water splashed my face. My wife…mentions that's how this can spread…Is it possible that she may be right?" • "My daughter ordered two tee shirts…I put them in the tub with detergent and scrubbed them…and some water splashed into my eye… She [received] the order in only 3 days. How long would it stay on it? And could the germs be that potent to get into my eye?" • "…I saw a suspect 10 feet away while walking, he was asking the security guard for Covid 19 testing area. I did not go closer or touch. I was wearing face mask I came home and washed everything and sanitised my self by taking a bath. I'm i [*sic*] at any risk of catching the virus? Does it transmit through air?..."
Prevention	How to avert or avoid contracting the virus, or prophylactic measures taken to lessen the potential response to the body	• "I'm interested in a discussion about how to keep my immune system top notch to help fight the corona covid 19 virus should I get it. Should we use more vitamin C? Drink fluids? Vitamin D? Suggestions?" • "… I have been wearing masks when flu season starts, for many years.…So is K N95 the same as N95??" • "Has there been any study or proof of breathing 1 to 2 deep breaths of diethyl ether fume to kill bacteria or viruses in nasal area or lungs.being as a preventive measure against getting the virus…"
Prognosis	The course of the disease, which includes the timeline, recovery, progression, outcomes, and lasting effects	• "Can anyone who RECOVERED from Covid19 please post some info? The community would very much appreciate some actual details about the good, the bad, and the ugly. Is the situation so dire that no one can post details here?" • "What is the expectation of longer term lung damage after COVID-19? My experience with the Hepatitis C has taught me a virus can leave its mark even after cured." • "How long do people actually have it? What is the typical recovery time?"
Protocols	The testing for the virus, which may include nasal swabbing, antibody testing, or questions about operations in handling specific scenarios	• "How long after exposure would the virus be detected by a PCR [polymerase chain reaction] test?" • "A nurse in a nursing home tested positive to covid 19. They had been in direct contact with residents on their unit. What should have been done was it was known that the nurse was positive?" • "I…have a deviated septum and possibly some other structural differences in my nose…Could this affect whether the swab can be inserted far enough back to get enough of a sample for the test?"

Name of topic	Definition of topic	Example posts
Disease management	Handling of the disease, such as treatments, medications, therapies, and ventilator use	• "Are there truly any medications or treatments for COVID/19?" • "Would hyperbarics [*sic*] chambers oxygenize in a different way than ventilators, or is it the same thing?..." • "…Why not avoid aggravating the lungs by "working with" the symptoms by filling the lungs with high-Oxygen liquid?..."
Public health practices and psychological impacts	Broad range of questions that stem from effects of COVID-19; public health concerns may vary from topics such as social distancing to quarantine/shelter-in-place. Psychological concerns involve discussion about anxiety and depression.	• "There seems to be so much conflicting info on masks. Are you wearing one? Why or why not? What kind are you wearing, if you are?" • "What are you personally going to do in order to protect you and your loved ones as so many locations begin coming back online?" • "How are you all coping with the inevitable fear. Fear of our health, our finances, life changing forever. What are your coping strategies? Anything you are looking at in a new way now verses before?" • "I'm really worried like I'm sure a lot of people are. Anxiety is running high. I'm also feeling really shut in and trapped due to social isolating and distancing. How are people handling this?"
Not applicable	Content that is not defined by the other topics of information seeking and is not directly relevant to health matters of COVID-19. These topics may include conversation starters and optimistic ideas. Topics that are not involved in direct information-seeking but are presented as a post are also included here. These may include references or resources that are not linked to specific information seeking.	• "... What have you had positive come from this? Do you know a positive story?" • "... Think any of the changes you are making will become new habits? Let me know what you think and which ones will be your new normal habit!" • "Washington Examiner article excerpts below suggesting only 70% sensitivity. They don't mention specificity %. https://www.washingtonexaminer.com/news/health-experts-believe-1-in-3-infected-patients-getting-negative-coronavirus-test-results...." • "https://www.upworthy.com/doctor-shares-potential-life-saving-coronavirus-breathing-technique"

Types of Informational Support

The study of the exchange of seeking and furnishing informational support is not complete without studying the participants' responses to the originating posts. A total of 274 responses were reviewed and annotated following the types of informational support outlined by Chuang and Yang [6] and Cutrona and Suhr [34], including reference/referral, advice, feedback/opinion, facts, personal experience, and perceptual knowledge (Table 2).

Due to the circumstances of the COVID-19 pandemic, distinguishing the facts remains a challenge because of the many unknown factors, the unique presentations per person, and the fact that information about the disease is constantly changing. Therefore, the definition of *fact* based on previous literature is not applicable. Similarly, the definition of *perceptual knowledge* from previous literature cannot be applied in this context.

Table 2. Types of informational support, their definitions, and examples.

Name of support type	Definition of support type	Example post
Reference/referral	Responses that directly provide a source of information for the user to refer to. These responses also include sources or links embedded in a response.	• "Results from new studies reported in livescience.com say…" • "https://www.lupus.org/news/coronavirus-update-access-to-hydroxychloroquine-plaquenil-for-people-with-lupus"
Advice	Responses that offer suggestions to a specific problem or concern that a user may have	• "we do want to let you know that if you can't breath [*sic*], you should seek immediate emergency care" • "definitely talk to your oncologist when you face such an important question. Ask him or her if untreated cancer is more dangerous or if the chemo would be more dangerous for some reason."
Feedback/opinion	Responses that reflect the responder's judgment of a certain situation or idea. These include responses that are not directly referenced by a source but through general information heard about the disease summarized and given as information, interpretation of a reference or source, or interpretation of a situation.	• "it's a blood clotting problem from what I've heard. This virus is weird. It affects different people very differently. It can adversely affect virtually every major organ in the body…" • "I have read that this loss of smell and taste is definitely commonly reported as an early symptom. This virus has a lot involved with it. This is an easy one to spot.
Personal experience	Responses that are an anecdotal recounting of a user's story to provide insight to a post. These may also include conditions relevant for support and reflections on their own experience handling the situation.	• "I had the virus early April…" • "I also get allergies when the weather changes…"
Fact	Responses that reassure the user about the facts of the disease	No instances found
Perceptual knowledge	Responses that provide sensory information to the user that helps reassess the situation	No instances found
Not applicable	Responses to originating posts that are in the "not applicable" category	• "Fewer cars, clearer air. I also like getting some sleep." • "My hair has gotten longer in quarantine (the last appointment I canceled when we got word that we were about to go on lockdown was a haircut). When it's shorter I have to air style to look presentable..."

Sources of Information Referenced

We also documented the sources of information referenced in the responses. These sources were reviewed and defined through open coding and then categorized. Among the references, 6 categories were created to categorize the source of information. These categories are listed below.

1. News outlet/website: references to general news sources, health news, international news, etc
2. Government: references to governmental websites, such as the US Centers for Disease Control and Prevention
3. Medical journal: references to peer-reviewed journals, such as *The Lancet*
4. Health website: references to specific sites about diseases, such as lupus, cardiac disease, and COVID-19
5. World Health Organization: references to the World Health Organization (WHO)
6. Other: references to social media, specific product websites, or other MedHelp communities

Results

RQ1: What Patterns of Engagement Did Participants Have in This New Community?

In the newly formed OHC, participants established meaningful connections by creating and responding to posts about COVID-19 to seek information and offer support. A total of 78 participants contributed to information seeking and offering. Among them, 45% (36/78) only contributed to information seeking, 36% (27/78) contributed only to information offering, and 19% (15/78) contributed to both information seeking and offering.

Furthermore, among the 51 participants who sought information, the majority (86%, 44/51) posted only once, with 1 person making 12 posts (Figure 1). In comparison, a total of 42 participants contributed to information offering, among whom 20 (20/42, 48%) posted once, 14 (14/42, 33%) responded 2-10 times, 4 (4/42, 10%) responded 11-20 times, and 4 (4/42, 10%) responded more than 20 times, with the highest number of responses being 42 (Figure 2). Information seeking and offering by the participants demonstrated similar patterns in that most participants interacted with the community via only 1 thread of conversations, although those who offered information had a significantly higher percentage of responding more than once ($P<.001$).

Figure 1. Histogram of participation frequency related to information seeking.

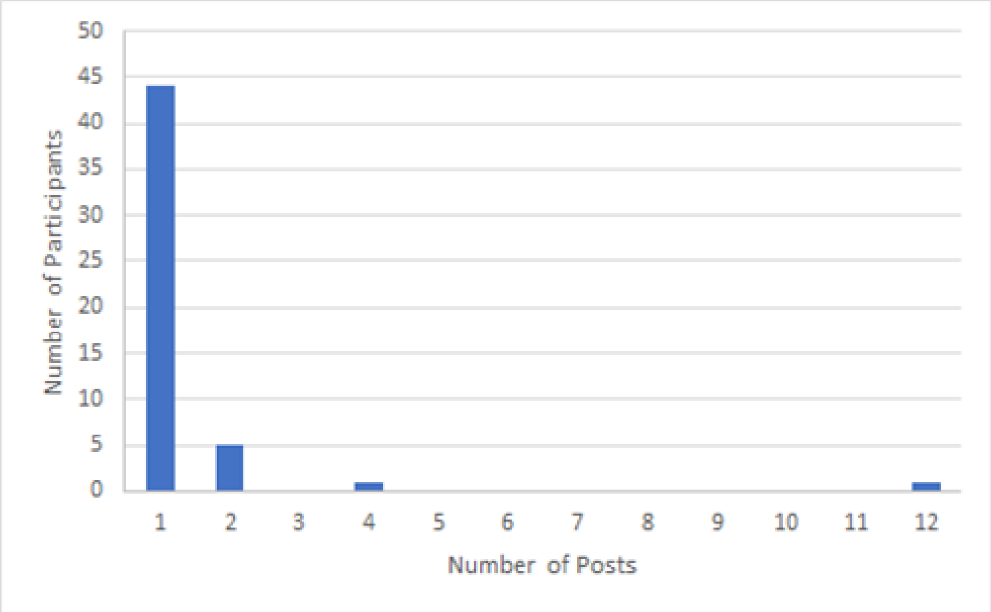
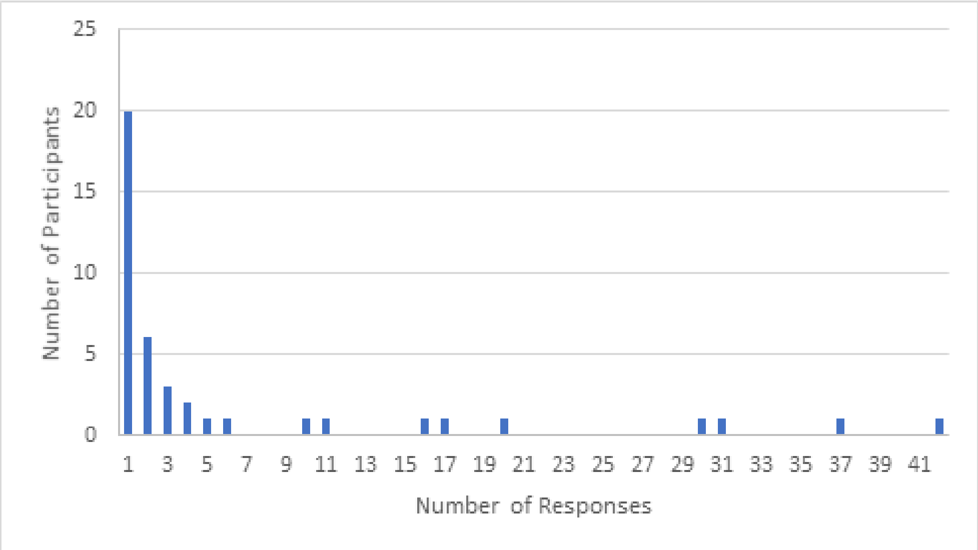


Figure 2. Histogram of participation frequency related to information offering.



RQ2: What Were the Topics of Information-Seeking Posts and Types of Informational support?

The content of information seeking holds importance in evaluating the most pertinent information that needs to be addressed for the general public at the beginning of a pandemic. The responses to these posts are the informational support offered by the members of this community. The distribution of these responses gives insight to how members of this community are offering their support and which information-seeking type elicits the most conversation.

Out of the total 83 originating posts, 65 posts were relevant to participants seeking information. Among the information-seeking topics, symptoms were the most frequent (17/65, 26%), followed by public health practice and psychological impacts (10/65, 15%) and transmission (10/65, 15%) (Table 3).

Table 3. Distribution of the information-seeking types categorized into the number of information-seeking posts, the number of responses corresponding to the information-seeking category, and the response-to-post ratios.

Information-seeking topic	Posts (n=65), n (%)	Responses to posts (n=220), n (%)	Response-to-post ratio
Symptoms	17 (26.2)	32 (14.5)	1.9
Public health practice and psychological impacts	10 (15.4)	61 (27.7)	6.1
Transmission	10 (15.4)	28 (12.7)	2.8
Health risk	9 (13.8)	29 (13.2)	2.8
Disease management	7 (10.8)	23 (10.5)	3.3
Prognosis	5 (7.7)	22 (10)	4.4
Prevention	4 (6.2)	19 (8.6)	4.8
Protocol	3 (4.6)	6 (2.7)	2.0
Not applicable	18 (27.7)	54 (24.5)	N/A[a]

[a]N/A: not applicable.

Within the total 274 informational support responses, 220 responses correspond to informational support (Table 3). The most common informational support responses were related to public health practices and psychological impacts (61/220, 27.7%) followed by symptoms (32/220, 14.5%). There were similar distributions of transmission (28/220, 12.7%) and health risk (29/220, 13.2%) as the next most common categories. Disease management (23/220, 10.4%), prognosis (22/220, 10.0%), and prevention (19/220, 8.6%) were also generally evenly distributed among the total responses to information-seeking posts. The protocol topic had the lowest number of responses (6/220, 2.7%).

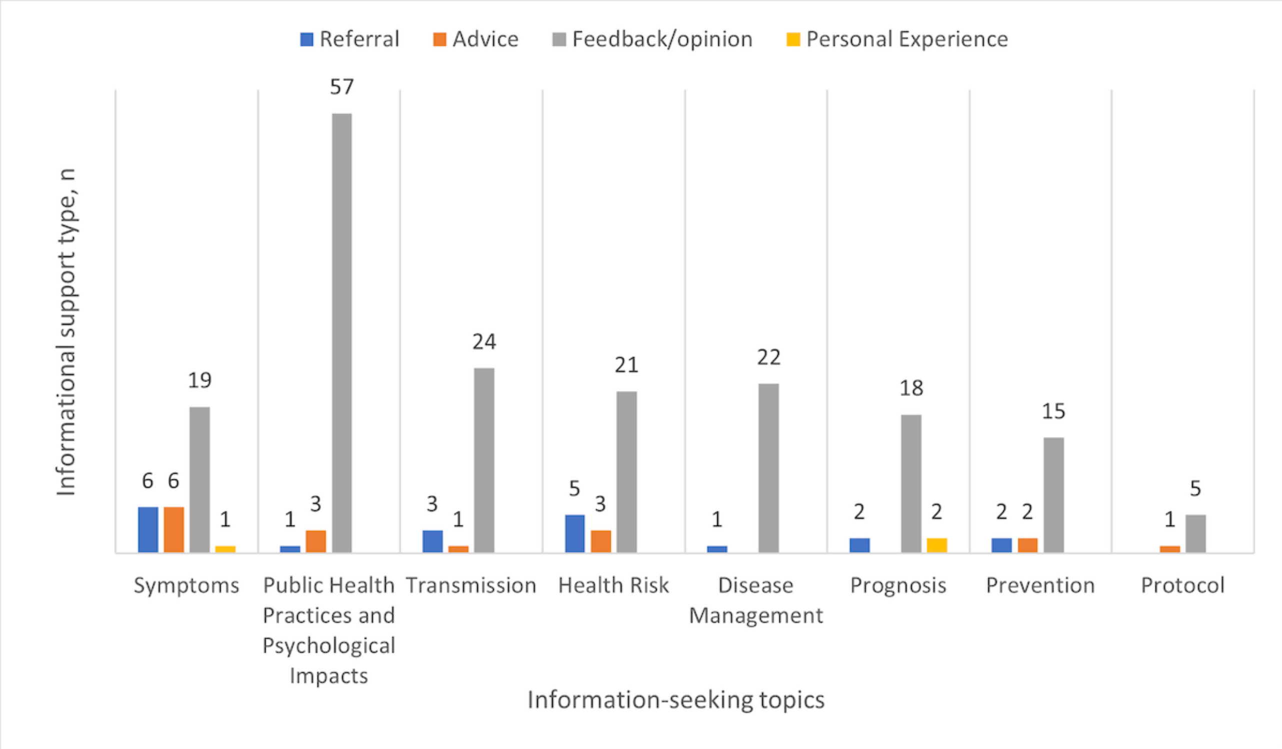
The number of responses to information seeking was compared with the number of originating posts in their corresponding categories to evaluate which information-seeking topics offered more discussion than others in terms of response-to-post ratio. Interestingly, the category of information seeking with the highest response-to-post ratio was public health practices and psychological impacts, with a ratio of 6.1 responses per post, while the lowest was symptoms, with a ratio of 1.9 responses per post. Public health practices and psychological impacts generated more discussion than symptoms; however, the latter had the highest number of information-seeking posts.

Among the types of informational support, feedback/opinion was dominant, with 181 responses (181/220, 82.3%; Table 4). Within the feedback/opinion type, the majority (57/181, 31.5%) of responses addressed the topic of public health practices and psychological impacts (Figure 3). Within the topic of symptoms, feedback/opinion was still the most common type (19/32, 59%); moreover, compared to the other topics, symptoms received the most referrals (6/32, 19%) and advice (6/32, 19%). Prognosis and symptoms were the only topics that had personal experience responses (2/22, 9%, and 1/32, 3%, respectively). There were no responses for facts or perceptual knowledge.

Table 4. Frequency of the informational support responses.

Informational support type	Responses (n=220), n (%)
Feedback/opinion	181 (82.3)
Referral	20 (9)
Advice	16 (7.7)
Personal experience	3 (1.4)
Fact	0 (0)
Perceptual knowledge	0 (0)
Not applicable	54 (24.5)

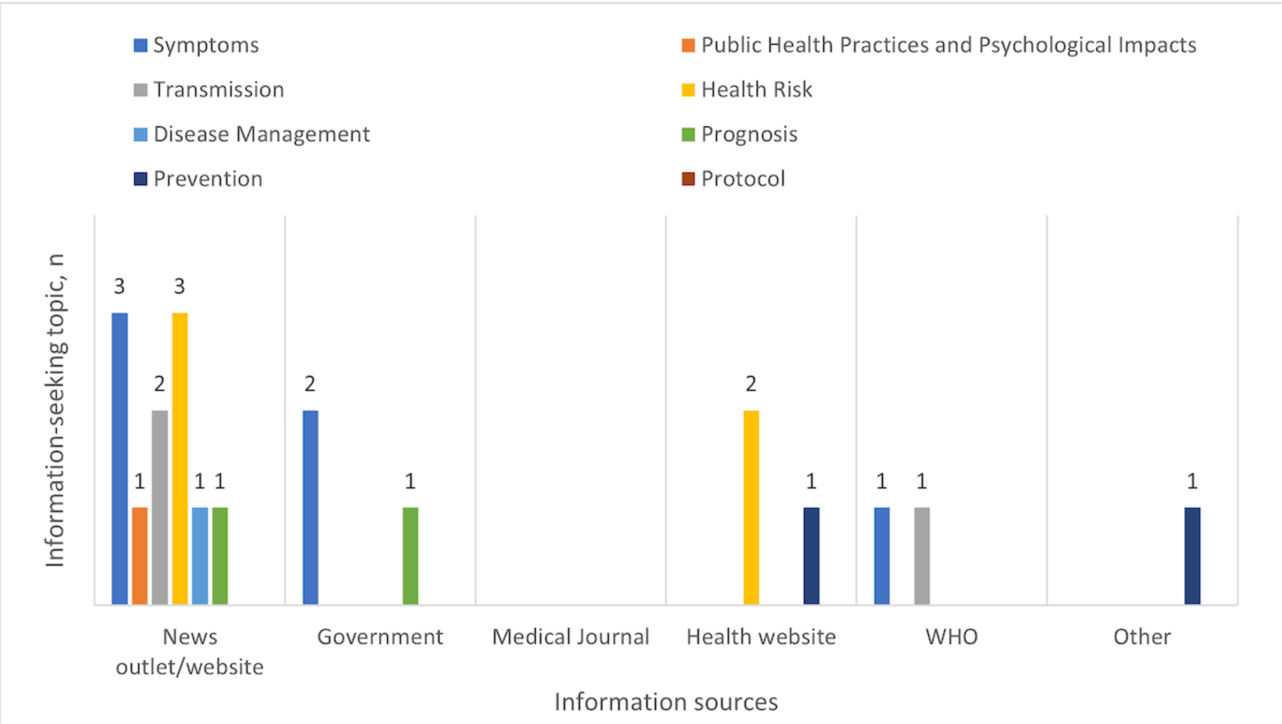
Figure 3. Distribution of information support for the subcategories of information seeking. The frequency of each is noted on top of the bar corresponding to its color.



RQ3: What Sources of Information Were Referenced Most Frequently?

The different types of reference sources reflect how members of the MedHelp COVID-19 community were receiving their information and which venues they may have found to be relevant for informational support. A total of 20 responses corresponded to the reference/referral type of informational support, among which 11 references (55%) used news outlets/websites, 3 (15%) used governmental websites, 3 (15%) used health websites, 2 (10%) used information from the WHO, 1 (5%) used information from other sources, and none used information from medical journals (Figure 4).

Figure 4. Distribution of sources of information by information-seeking topic. WHO: World Health Organization.



Participants referenced news outlets/websites when responding to posts with the topics of symptoms, public health practices and psychological impacts, transmission, health risk, disease management, and prognosis. Governmental sites were referenced in the symptoms and prognosis subcategories. Health websites were referenced in the health risk and prevention subcategories. The WHO was referenced in the symptoms and transmission subcategories. Other sites were referenced for prevention only. There were no direct references to medical journals for information seeking posts, and no references were made to a protocol.

Discussion

Principal Results

In this study, we investigated the characteristics of a newly formed OHC dedicated to COVID-19, including participation patterns, topics of concern, and sources of information. A total of 78 participants generated 83 originating posts and 274 responses during a 3-month period at the onset of the COVID-19 pandemic in the United States. Within these posts, 65 posts were categorized as information-seeking and 220 responses were identified as offering informational support. Among the participants, 65% (51/78) sought information and 54% (42/78) provided informational support, with a large majority of information-seekers (44/51, 86%) and a slight minority of information providers (20/42, 48%) posting only once. The most common topic of information seeking was related to symptoms of COVID-19 (17/65, 26%), followed by public health practices and psychological impacts (10/65, 15%), and mechanisms of transmission (10/65, 15%). The topics that garnered the most responses were public health practices and psychological impacts (61/220, 27.7%), symptoms (32/220, 14.5%), and health risk (29/220, 13.2%). Among these popular topics, public health practice and psychological impacts saw the highest response-to-post ratio (6.1); symptoms had the lowest ratio, at 1.9 responses per originating post. Most informational support was in the form of feedback/opinion (181/220, 82.3%), which reflected the responder's judgment of a certain situation, followed by information references as a distant second (20/220, 9.1%). The participants primarily relied on news outlets (11/20, 55%) as sources of information.

The participation trends reflect the power law distribution that is common in social networks, where the majority of participants may only contribute once or a few times and there are a few individuals with high numbers of posts (Figure 1 and Figure 2). A few considerations related to the reason for the greater activities of certain members are having a health care background, personally knowing someone infected with or at risk of COVID-19, familiarity with the platform, or other factors. In addition, some participants were members of multiple communities in MedHelp prior to COVID-19, who readily contributed social support in other communities.

The study shows that the general public may be most concerned with the symptoms and manifestation of a disease when confronted by a previously unknown disease at the beginning of an epidemic. Considering the timeframe of these posts, the highest frequency of information seeking in symptoms is understandable because during this time, there were many unknown factors regarding SARS-CoV-2 and COVID-19. Additionally, the devastation in previously affected countries may have led to the development of insecurities and fear in the public. Knowing that symptoms are the first signs of the manifestation of a disease, the frequency of inquiries about this category does seem to be the most reasonable finding given the public's concern regarding their well-being and how certain symptoms present in association with the disease. Furthermore, symptoms also had the lowest response-to-post ratio, suggesting a paucity of relevant information among the public. Public health professionals may focus on educating the public about known symptoms to reduce the potential of misinformation.

Compared to symptoms, the topics of public health practice and psychological impacts were not only among the most requested topics but also received the highest response-to-post ratios. At the onset of the pandemic in the United States, various levels of health and safety measures were put in place by different states, possibly creating confusion and debate among the public about best practices (eg, whether mask-wearing is effective). Meanwhile, reports of the rising hospitalizations, the lack of protective gear and equipment, and a growing list of newly discovered complications may have taken a toll on the psychological well-being of the general public. The public health practice and psychological impacts of the pandemic were affecting the daily life and social activities of every person. Many participants were responding to this topic, and the majority of informational support was in the form of feedback and opinion. Out of 61 posts offering informational support to the public health practice and psychological impacts, there was only one reference to information from a news outlet or website.

The topic of *protocol* had the lowest number of posts, which may also be attributable to the timeline. With more information about the disease, there could be better means to expedite patient education information and to implement actions for testing and better management of containment. The responses being primarily driven by feedback/opinion reflects the lack of concrete information during this time as well. It is also possible that the general public views the protocols of testing and hospital operations as requiring the expertise of health care professionals and thus not an area of interest to discuss.

These trends could indicate that among the participants of this community, their concerns pertained not only to the pandemic itself but also to how the pandemic affected their daily lives. The low response-to-post ratio for symptoms could indicate that on one hand, the general public lacked the knowledge to offer support, and on the other hand, the posts for symptoms may have been phrased as recounts of individual circumstances to solicit reassurance, thereby leaving less space for a community discussion on what may be considered symptoms of COVID-19.

Feedback/opinion is the most frequent informational support type (181/220, 82.3%). It is provided as a respondent's judgment without referencing any information source but only offering their opinions based on what they have heard or interpreted. This finding shows that there is a lack of authoritative information to support the community. Users are mainly relying on their own judgment to support others, and theirs interpretations of the information they acquire can be unreliable in some cases.

Referral was the second highest informational support type (20/220, 9.1%). Among all the information sources, news outlets and websites were the most frequently referenced information sources (11/20, 55%) by the participants. Governmental and WHO sources as references appear to be underused or insufficient when referencing circumstances surrounding this pandemic. The trends within this community may demonstrate where information dissemination is most effective. Possible reasons for the frequent use of new outlets and websites include memorable anecdotal accounts of the disease, more immediate coverage, and accessibility. With the changing guidelines in protocols, public health measures, and disease information, it is understandable that there is difficulty maintaining consistency in the shifting landscape. However, maintaining consistency with so many unknown factors and fluctuations is important for safety and reassurance. The news outlets and websites likely provided this community with reassurance and updates more reliably than the other types of sources.

Limitations

Only one coder annotated the study. Although this is helpful in terms of consistency in annotation and interpretation, having more than one coder could have been beneficial in determining nuances in the contents of the posts and responses. The time frame of the study provides only a snapshot of the beginning of the disease progression and is not predictive of the course of how this platform will continue to respond as the disease progresses. The annotated posts do not reflect the views of people who visit the OHC without posting or responding.

Conclusions

The MedHelp OHC for COVID-19 reflects real-time concerns during the pandemic. These concerns are important in understanding how OHCs facilitate the exchange of information at the onset of a pandemic. Among the information-seeking topics, interest in symptoms was highest, followed by the public health practices and psychological impacts. However, there was a higher number of responses per post for posts related to public health practices and psychological impacts compared to posts about symptoms. Feedback and opinion was the most frequent type of informational support, followed by referrals. The most referenced source of information referral was through news outlets/websites. Government websites and the WHO were less frequently used. The referral trends suggest that news outlets/websites are the most effective mode of communication that individuals can refer to. These findings may be useful in prioritizing public health responses to address the most common questions sought by the general public during crisis communication and in identifying which venue of communication is most effective in reaching the public audience during these times.

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Conflicts of Interest

None declared.

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Abbreviations

OHC: online health community
RQ: research question
WHO: World Health Organization

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Original Paper

Social Media Polarization and Echo Chambers in the Context of COVID-19: Case Study

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Abstract

Background: Social media chatter in 2020 has been largely dominated by the COVID-19 pandemic. Existing research shows that COVID-19 discourse is highly politicized, with political preferences linked to beliefs and disbeliefs about the virus. As it happens with topics that become politicized, people may fall into echo chambers, which is the idea that one is only presented with information they already agree with, thereby reinforcing one's confirmation bias. Understanding the relationship between information dissemination and political preference is crucial for effective public health communication.

Objective: We aimed to study the extent of polarization and examine the structure of echo chambers related to COVID-19 discourse on Twitter in the United States.

Methods: First, we presented Retweet-BERT, a scalable and highly accurate model for estimating user polarity by leveraging language features and network structures. Then, by analyzing the user polarity predicted by Retweet-BERT, we provided new insights into the characterization of partisan users.

Results: We observed that right-leaning users were noticeably more vocal and active in the production and consumption of COVID-19 information. We also found that most of the highly influential users were partisan, which may contribute to further polarization. Importantly, while echo chambers exist in both the right- and left-leaning communities, the right-leaning community was by far more densely connected within their echo chamber and isolated from the rest.

Conclusions: We provided empirical evidence that political echo chambers are prevalent, especially in the right-leaning community, which can exacerbate the exposure to information in line with pre-existing users' views. Our findings have broader implications in developing effective public health campaigns and promoting the circulation of factual information online.

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KEYWORDS

social media; opinion; infodemiology; infoveillance; COVID-19; case study; polarization; communication; Twitter; echo chamber

Introduction

Background

As the unprecedented COVID-19 pandemic continues to put millions of people at home in isolation, online communication, especially on social media, is seeing a staggering uptick in engagement [1]. Prior research has shown that COVID-19 has become a highly politicized subject matter, with political preferences linked to beliefs (or disbeliefs) about the virus [2,3], support for safe practices [4], and willingness to return to activities [5]. As the United States was simultaneously undergoing one of the largest political events—the 2020 presidential election— public health policies may have been undermined by those who disagree politically with health officials and prominent government leaders. As it happens with topics that become politicized, people may fall into *echo chambers*—the idea that one is only presented with information they already agree with, thereby reinforcing one's confirmation bias [6,7].

Social media platforms have been criticized for enhancing political echo chambers and driving political polarization [8-10]. In part, this is due to a conscious decision made by users when choosing who or what to follow, selectively exposing themselves to content they already agree with [6]. This may also be a consequence of the algorithms social media platforms use to attract users [9]. Numerous studies have shown that echo chambers are prevalent on Twitter [7,8,11-13]; however, most past works are done on topics that are political in nature. In the case of COVID-19, the risks of political polarization and echo chambers can have dire consequences in politicizing a topic that is originally of public health. The lack of diversity in multiperspective and evidence-based information can present serious consequences for society by fueling the spread of misinformation [14-16]. For instance, prior research revealed that conservative users push narratives contradicting public health experts (eg, antimask) and misinformation (eg, voter fraud) [17]. Another study showed that the consumption of conservative media is linked to an increase in conspiracy beliefs [18]. Understanding the degree of polarization and the extent of echo chambers can help policymakers and public health officials effectively relay accurate information and debunk misinformation to the public.

Research Questions

In this paper, we focused on the issue of COVID-19 and presented a large-scale empirical analysis on the prevalence of echo chambers and the effect of polarization on social media. Our research was guided by the following research questions (RQs) surrounding COVID-19 discussions on Twitter:

- RQ1: What are the roles of partisan users on social media in spreading COVID-19 information? How polarized are the most influential users?
- RQ2: Do echo chambers exist? And yes, what are the echo chambers and how do they compare?

The technical challenge for addressing these questions is posed by the need to build a scalable and reliable method to estimate user political leanings. To this end, we proposed Retweet-BERT, an end-to-end model that estimates user polarity from their profiles and retweets on a spectrum from left to right leaning.

Methods

Data

We used a large COVID-19 Twitter data set collected by Chen et al [19], containing data from January 21 to July 31, 2020 (v2.7). All tweets collected contain keywords relevant to COVID-19. The tweets can be an original tweet, retweets, quoted tweets (retweets with comments), or replies. Each tweet also contains the user's profile description, the number of followers they have, and the user-provided location. Some users are verified, meaning they are authenticated by Twitter in the interest of the public, reducing the chance that they are fake or bot accounts [20]. All users can optionally fill in their profile descriptions, which can include personal descriptors (eg, "Dog-lover," "Senator," "Best-selling author") and the political party or activism they support (eg, "Republican," "#BLM").

Interaction Networks

The retweet network $G_R=(V,E)$ was modeled as a weighted, directed graph. Each user $u \in V$ is a node in the graph, each edge $(u,v) \in E$ indicates that user u has retweeted from user v, and the weight of an edge $w(u,v)$ represents the number of retweets. We used the terms retweet interaction and edges of the retweet network interchangeably. Similarly, we constructed the mention network G_M, where the edges are mentions instead of retweets. A user can be mentioned through retweets, quoted tweets, replies, or otherwise directly mentioned in any tweet.

Data Preprocessing

We restricted our attention to users who are likely located in the United States, as determined by their self-provided location [4]. Following Garimella et al [21], we only retained edges in the retweet network with weights of at least 2. Since retweets often imply endorsement [22], a user retweeting another user more than once would imply stronger endorsement and produce more reliable results. As our analyses depend on user profiles, we removed users with no profile data. We also removed users with degrees less than 10 (in- or out-degrees) in the retweet network, as these are mostly inactive Twitter users. To remove biases from potential bots infiltrating the data set [23], we calculated bot scores using the methodology of Davis et al [24], which estimates a score from 0 (likely human) to 1 (likely bots), and removed the top 10% of users by bot scores as suggested by Ferrara [23].

Our final data set contained 232,000 users with 1.4 million retweet interactions among them. The average degree of the retweet network was 6.15. For the same set of users in the mention network, there were 10 million mention interactions, with an average degree of 46.19. Around 18,000, or approximately 8% of all, users were verified.

Estimating User Polarity

This section describes our proposed method to estimate the polarity of users in a spectrum from left to right. We first surveyed related work and used weak-supervision to detect two polarized groups of users, which we treated as seed users. Then, we explored various models to predict the political leaning of users. Finally, these models were evaluated on labeled data using 5-fold cross-validation and the best model was applied to the remaining users to obtain their polarity scores.

Related Work

Representation Learning on Twitter

Analysis of Twitter data takes the form of two, often combined, approaches, namely content-based and network-based. In content-based approaches, users are characterized by the account metadata, hashtags, tweet content, and other language-related features extracted from their profiles [25-27]. In network-based approaches, users are represented in the retweet network or the mention network, both being directed networks where edges indicate the flow of communication [8,28]. The use of user-follower networks is rare due to the time-consuming nature of its data collection [29].

Both approaches can benefit from recent advances in representation learning, and specifically embedding methods. Techniques like word embedding [30], or more recently transformers [31], have been shown to improve sentiment analysis on tweets [32] and tweet topic classification [33]. These models generate a vector representation of text so that semantically similar words and texts share similar representations. The concept of word embeddings can also be applied to networks, where node presentations embody their homophily and structural similarity [34]. Network embedding can aid user-type detection. For instance, Ribeiro et al [35] used representation learning on both the retweet network structure and the tweet content to detect hateful users. Xiao et al [36] used network representations to classify users in a politically centered network. In this work, we proposed a new strategy based on combining content and network embedding for user polarity detection.

Ideology Detection

The ability to detect user ideology is of interest to many researchers, for example, to enable studies of political preference. Most methods are rooted in the observation that people sharing similar political beliefs are often situated in tightly knit communities [8]. Earlier methods (eg, Conover et al [8]) classified users' political leanings based on the hashtag they used. The same challenge has been tackled with label propagation, with users who have linked left-winged or right-winged media outlets in their tweets as seed users [26,27]. Barberá et al [7] proposed a latent space model to estimate the polarity of users, assuming that users tend to follow politicians who share similar ideological stances. Darwish et al [37] developed an unsupervised approach to cluster users who share similar political stances based on their hashtags, retweet texts, and retweet accounts. Word embeddings have also been applied to user tweets to generate clusters of topics, which helps inform the political leaning of users [38]. Recently, Xiao et al [36] formulated a multirelational network to detect binary ideological labels. Our proposed method stands out because it (1) combines both language and network features for a more comprehensive estimation of ideology, and (2) is scalable and can be trained within a limited time with limited labeled data.

Pseudo Label Generation

We used two weakly supervised strategies to find the pseudo labels of political leanings for a subset of users (ie, seed users). For the first method, we gathered the top 50 most-used hashtags in user profiles and annotated them as left- or right-leaning depending on what political party or candidate they support (or oppose). Of these hashtags (uncased), 17 were classified as left-leaning (eg, #TheResistance, #VoteBlue) and 12 as right-leaning (eg, #MAGA, #KAG). Users were labeled as left-leaning or right-leaning if their profile contains more left-leaning or right-leaning hashtags, respectively. We did not consider hashtags used in tweets, for the reason that hashtags in tweets can be used to inject opposing content into the feed of other users [8]. Instead, in line with Badawy et al [26] and Addawood et al [27], we assume that hashtags appearing in user profiles would more accurately capture true political affiliation.

An alternative method makes use of the media outlets mentioned in users' tweets through mentions or retweets [39-41]. Similar to Ferrara et al [41], we identified 29 prominent media outlets on Twitter. Each media outlet has its media bias scored by the nonpartisan media watchdog AllSides.com on a scale of 1 to 5 (left, center-left, neutral, center-right, right). An endorsement from a user was defined as either an explicit retweet from a media's official Twitter account or a mention of a link from the media's website. Given a user who has given at least two endorsements, we calculated their media bias score from the average of the scores of their media outlets. A user was considered left-leaning if their media bias score was equal to or below 2 or right-leaning if above 4.

Using a combination of the profile hashtag method and the media outlet method, we categorized 79,370 (34% of all) users as either left- or right-leaning. In case of any disagreements between the two detection methods, we deferred to the first one (the hashtag-based method). We referred to these users as seed users for political leaning estimation. A total of 59,832, or 75% of all, seed users were left-leaning, compared to 19,538 who were right-leaning, consistent with previous research which revealed that there are more liberal users on Twitter [42].

Polarity Estimation Models

To predict user political leanings, we explored several representation learning methods based on the users' profile description and/or their retweet interactions. We provided an overview of natural language processing techniques to extract information from profile descriptions, as well as network embedding techniques to extract information from retweet interactions. We then proposed a new model that includes both components. All models were evaluated on the binary classification task of predicting (pseudo label) political leanings for the subset of seed users.

In the following two subsections, we describe various ways to get word embeddings, sentence (ie, profile) embeddings, and node embeddings. An embedding is a low-dimensional, vectorized representation of the word, sentence, or node relative to other inputs of the same kind. Embeddings capture the semantic (for language) or structural (for network) similarity of the inputs. Embeddings can be pretrained and transferred across data sets or tasks. Once trained, every word, sentence, or node can be mapped to a continuous vector embedding, where semantically similar words or sentences or structurally similar nodes share similar embeddings with each other.

Language-Based Methods

Word Embeddings

Word2Vec [30] and GloVe [43] are word embedding methods that learn word associations from a large corpus of text without supervision. Word2Vec considers a word and its surrounding words as the context in a sentence, while GloVe considers the global word-word co-occurrence matrix. Once trained, both models produce embeddings that capture the semantic similarity between words.

As baselines, we used pretrained Word2Vec and GloVe word embeddings from Gensim [44]. We formed profile embeddings by averaging the word embeddings of each word in the profile description. We fit a logistic regression model on the profile embeddings for the classification task.

Transformers

Transformers such as BERT [31], RoBERTa [45], and DistilBERT [46] are pretrained language models that have led to significant performance gains across many natural language processing tasks. Unlike word embeddings, transformers can disambiguate words with different meanings under different contexts. Transformers are deep learning models that are trained to understand sequential texts by way of predicting missing tokens (words) in the text and/or predicting the next sentence. They are also designed to easily adapt to various downstream tasks by fine-tuning the output layers.

There are a few ways to adapt transformers for profile classification. Transformers, which are already pretrained, can be directly applied to each individual profile. The outputs of a transformer include an initial token embedding (eg, [CLS] for BERT, <s> for RoBERTa) of the profile description as well as contextualized word embeddings for each token of the profile. One way to use transformers for classification is to *average* the output embeddings of each word in the profile, followed by a logistic regression model. The other, more time-consuming method is to *fine-tune* the *head* of the transformer through the initial token embedding by adding a set of deep-learning layers designed for classification. We used the sequence classification head published with *HuggingFace*'s open-sourced transformers library [47], which adds a linear dense layer on top of the pooled output of the initial token embedding of the transformers. This classification head outputs a single value between 0 and 1 using a sigmoid activation function.

S-BERT

Transformers in and of themselves are not suitable for large-scale sentence-based tasks. To remedy this, Reimers and Gurevych [48] proposed Sentence Transformers (S-BERT), which consists of Siamese and triplet networks to produce semantically meaningful sentence embeddings. S-BERT outperforms naive transformer-based methods for semantic textual similarity tasks, while massively reducing the time complexity. During training, S-BERT takes two sentences in parallel through an identical transformer (Siamese), adds a pooling operation to their outputs, and learns to predict predefined sentence pair objectives, such as measuring the similarity between the two sentences.

Using S-BERT models pretrained for semantic textual similarity, we retrieved embeddings for every profile. The profile embeddings were fit with a logistic regression model for classification.

Network-Based Methods

Similar to how word or sentence embeddings can be generated text, we can generate node embeddings for nodes in a network. Such node embeddings can capture network structure similarities and homophily. One network embedding model is node2vec [49], which learns node embeddings from random walks over the network. An important drawback of node2vec is that it cannot be used on isolated nodes. GraphSAGE [50] is another network embedding method that also utilizes node attributes and is inductive, meaning it can be applied to isolated nodes. We can use any of the aforementioned profile embeddings retrieved from any language models as the node attributes.

Another popular network-based method for node classification is label propagation, which deterministically propagates labels from seed users in the network. Label propagation also cannot predict for isolated nodes.

Proposed Method: Retweet-BERT

Inspired by S-BERT [48], we propose Retweet-BERT (visualized in Figure 1), a sentence embedding model that incorporates the retweet network. We based our model on the assumption that users who retweet each other are more likely to share similar ideologies. As such, the intuition of our model is to make profile embeddings more similar for users who retweet each other. Specifically, using any of the aforementioned models that can produce sentence-level embeddings, let s_i denote the profile embedding for user i. For every positive retweet interaction from user i to j (ie, $(i,j) \in E$), we optimized the objective:

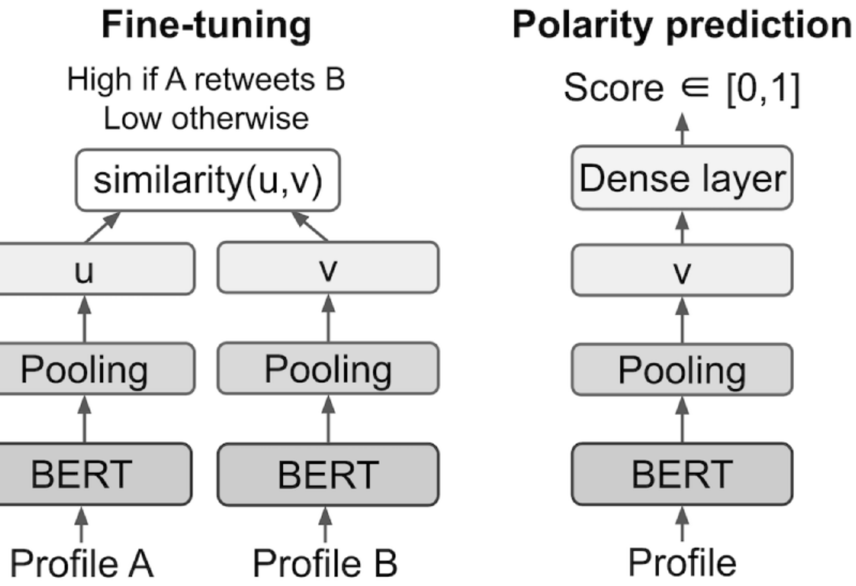
$$\sum_{k\in V,(i,k)\notin E} \max\left(\|s_i - s_j\| - \|s_i - s_k\| + \in, 0\right) \quad \textbf{(1)}$$

where is a distance metric and $\in$ is a margin hyperparameter. We followed the default configuration of S-BERT, which uses the Euclidean distance and $\in = 1$.

To optimize the training procedure, we used two negative sampling strategies. The first was negative sampling (one-neg), in which we randomly sampled one other node k for every anchor node in each iteration [30]. For simplicity, we assumed all nodes are uniformly distributed. The second was multiple negative sampling (mult-neg), in which the negative examples are all of the other examples in the same batch [51]. For instance, if the batch of positive examples are $[(s_{i1},s_{j1}),(s_{i2},s_{j2}),\ldots,(s_{in},s_{jn})]$, then the negative examples for pair at index k are (s_{ik},s_{jk}) are all the $\{s_{jk'}\}$ for $k' \in [1,n]$ and $k' \neq k$.

It is worth noting that Retweet-BERT disregards the directionality of the network and only considers the immediate neighbors of all nodes. In practice, however, we find that this model balances the trade-off between training complexity and testing performance. Building on the convenience of S-BERT for sentence embeddings, we used the aforementioned S-BERT models pretrained for semantic textual similarity as the basis for fine-tuning.

Figure 1. Illustration of the proposed Retweet-BERT. We first fine-tuned it on the retweet network (left) using a Siamese network structure, where the two BERT networks share weights. We then trained a denser layer on top to predict polarity (right).



Polarity Estimation Results

We included an overview of the experiment results in Multimedia Appendix 1. Our proposed model, Retweet-BERT, achieves the best result with a BERT base model trained with the multiple negatives training strategy. It attains 96% cross-validated AUC (area under the receiver operating characteristic curve), which is a common metric for use in measuring binary classification in unbalanced classes. Previously, we also conducted an in-depth evaluation of our model (Jiang et al, unpublished work). We trained Retweet-BERT on all of the seed users with political leaning pseudo labels and inferred polarity scores for the rest of the users, ranging from 0 (far-left) to 1 (far-right). These scores will be referred to as *polarity scores*. Since there were more left-leaning seed users, the polarity scores were naturally skewed toward 0 (left). Therefore, similar to previous work [23,26,28], we binned users by evenly distributed deciles of the polarity scores, with each decile containing exactly 10% of all users.

Results

The Roles of Partisan Users

We first examined the characteristics of extremely polarized users, defined as the users in the bottom (left-leaning/far-left) or top (right-leaning/far-right) 20% of the polarity scores. As a point of comparison, we also included neutral users who were in the middle 20% of the polarity scores. Considering various aspects of user tweeting behaviors, we characterized the Twitter user roles as follows:

1. Information creators: those who create original content and are usually the source of new information.
2. Information broadcasters: those who foster the distribution of existing content, such as through retweeting other people and promoting the visibility of other's content.
3. Information distributors: those whose contents are likely to be seen by many people, either through passive consumption by their followers or through broadcasting (retweeting) by others.

According to these definitions, a user can be all of these or none of these at the same time. In Figure 2, we plot several Twitter statistics regarding the polarized and neutral users, disaggregated by their verification status.

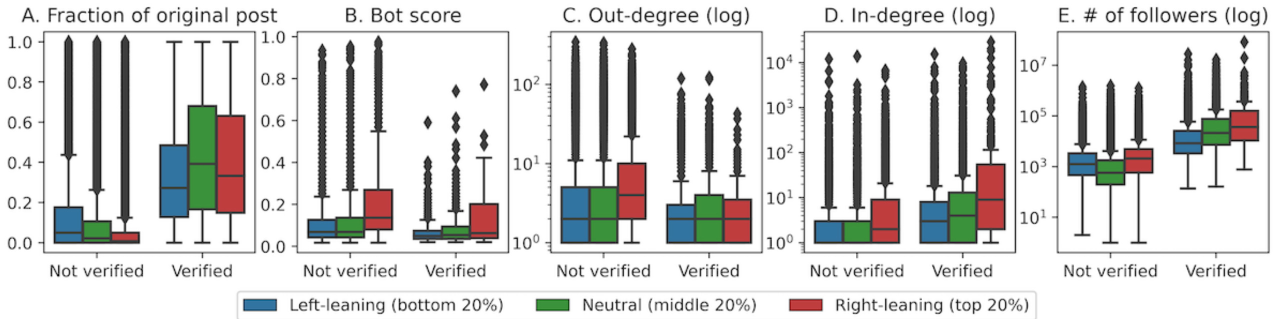
Compared to unverified users, verified users were more likely to be information creators. This is unsurprising, given that verified users can only be verified if they demonstrate they are of public interest and noteworthy. Comparatively, left-leaning verified users had the smallest fraction of original posts. However, this was reversed for unverified users, with unverified left-leaning users having the highest fraction of original content and unverified right-leaning users having little to no original content. We noted that this may be related to the distribution of bot scores. If bots infiltrated users of different partisanship equally, we expect to find similar distributions of bot scores across all users. However, Figure 2B reveals that right-leaning users scored significantly higher on the bot scale. Since bots retweet significantly more than normal users [52], we cannot rule out the possibility that right-leaning bots were confounding the analysis, even though those scoring the highest on the bot scale have already been removed from the data set.

Unverified right-leaning users, in comparison with their left-leaning counterparts, were more likely to be information broadcasters as they had the highest out-degree distribution (Figure 2C). As out-degree measures the number of people a user retweets from, a user with a high out-degree plays a critical role in information broadcasting. The fact that they also had very little original content (Figure 2A) further suggests that unverified right-leaning users primarily retweeted from others.

Finally, all right-leaning users functioned as information distributors regardless of their verification status. Their tweets were much more likely to be shared and consumed by others. Their high in-degree distribution indicates they got retweeted more often (Figure 2D), and the higher number of followers they have indicates that their posts were likely seen by more people (Figure 2E).

As right-leaning users played larger roles in both the broadcasting and distributing of information, we questioned if these users formed a political echo chamber, wherein right-leaning users retweet frequently from, but only from, users who are also right-leaning. As shown later in the paper, we did indeed find evidence that right-leaning users form a strong echo chamber.

Figure 2. Data set statistics of left-leaning (bottom 20%), neutral (middle 20%), and right-leaning (top 20%) users, partitioned by their verification status. The degree distributions are taken from the retweet network. All triplets of distributions (left-leaning, neutral, and right-leaning) are significantly different using a one-way ANOVA (analysis of variance) test (P<.001).



The Polarity of Influencers

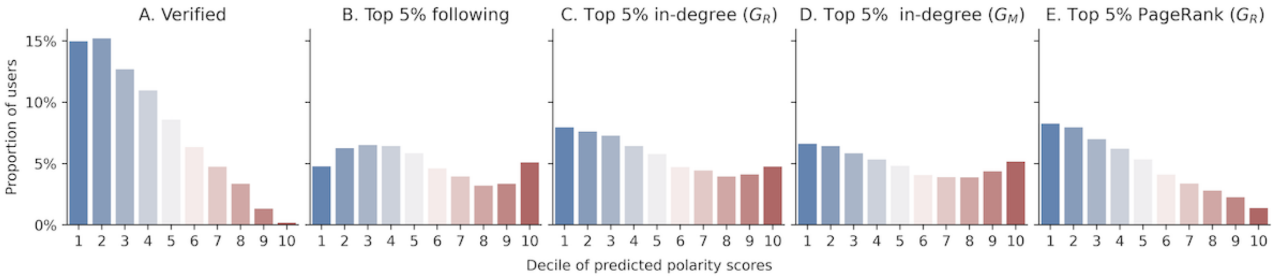
The above characterizes the Twitter activities of users who are extremely left- or right-biased. However, the majority of the social influence is controlled by a few key individuals [53-55]. In this section, we considered five measures of social influence: verification status, number of followers, number of retweets, number of mentions, and PageRank in the retweet network [56]. A user is considered influential if they are in the top 5% of all people according to the measure of influence. Figure 3 reveals the proportion of users in each decile of the polarity score that is influential. We showed that consistent with all of the influence measures above, partisan users are more likely to be influential.

The verification status is correlated with partisan bias, with the proportion of verified users decreasing linearly as we move from the most left- to the most right-leaning deciles of users (Figure 3A). Of the total, 15% of users in the first and second deciles, which are most liberal, were verified, compared to less than 1% of users in the extremely conservative 10th decile. As verified accounts generally mark the legitimacy and authenticity of the user, the lack of far-right verified accounts opens up the question of whether there is a greater degree of unverified information spreading in the right-leaning community. We stress, however, that our result is cautionary. A closer investigation is needed to establish if there are other politically driven biases, such as a liberal bias from Twitter as a moderating platform, that may contribute to the underrepresentation of conservative verified users.

While being verified certainly aids visibility and authenticity, users do not need to be verified to be influential. We observed bimodal distributions (U-shaped) in the proportion of users who are influential with respect to their polarity according to three measures of influence: top-most followed, retweeted, and mentioned (Figure 3B-D), indicating that partisan users have more influence in these regards. In particular, far-right users had some of the highest proportion of most-followed users. Far-left users were more likely to be highly retweeted and mentioned, but the far-right also held considerable influence in those regards.

Lastly, we looked at PageRank, a well-known algorithm for measuring node centrality in directed networks [56]. A node with a high PageRank is indicative of high influence and importance. Much like the distribution of verified users, the proportion of users with high PageRank in each polarity decile was correlated with how left-leaning the polarity decile is (Figure 3E), which suggests that left-leaning users hold higher importance and influence. However, this phenomenon may also be an artifact of the much larger left-leaning user base on Twitter.

Figure 3. Proportion of users in each decile of predicted political bias scores that are (A) verified, (B) top 5% in the number of followers, (C) top 5% of in-degrees in the retweet network (most retweeted by others), (C) top 5% of in-degrees in the mention network (most mentioned by others), and (E) top 5% in PageRank in the retweet network.

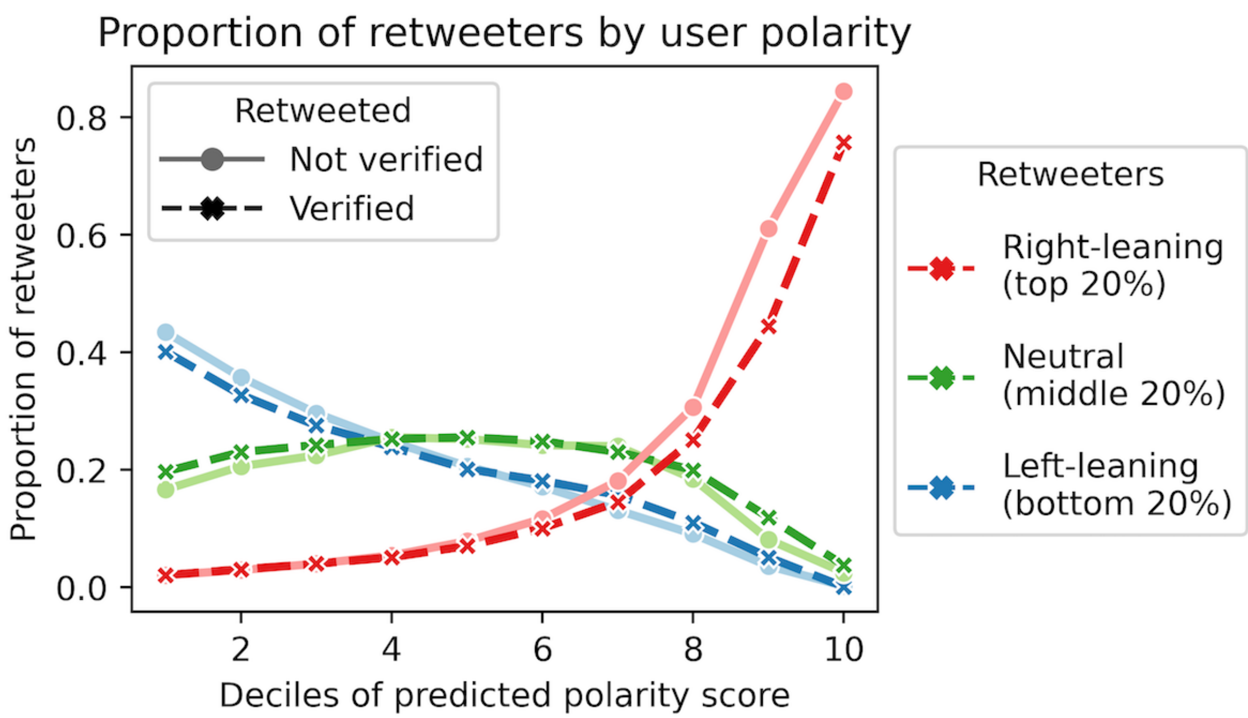


Echo Chambers

As most influential users are partisan, we questioned the prevalence of echo chambers, if they exist. We began by exploring the partisan relationship between the retweeted and the retweeter, where the latter is considered as the (immediate) audience of the former. Figure 4 plots the proportion of left-leaning, neutral, or right-leaning retweeters for users in each of the 10 deciles of polarity scores, revealing that users on both ends of the political spectrum reached an audience that primarily agrees with their political stance. In fact, the far-left and far-right users had virtually no retweeters from supporters of the opposite party. However, the echo chamber effect was much more prominent on the far-right. About 80% of the audience reached by far-right users were also right-leaning. In comparison, only 40% of the audience reached by far-left users were also left-leaning. There was little difference in the distribution of retweeters between verified and unverified users.

Since the polarized users are mostly preoccupied in their echo chambers, the politically neutral users (Figure 4, green) would serve the important function of bridging the echo chambers and allowing for cross-ideological interactions. Most of them (30%-40%) retweeted from sources that were also neutral, and around 20% of them retweeted from very liberal sources. When it came to broadcasting tweets from far-right users, they behaved similarly to the far-left retweeters: almost no neutral users retweeted from far-right users. Such observations would imply a much stronger flow of communication between the far-left users and neutral users, whereas the far-right users remained in a political bubble.

Figure 4. The distribution of left-leaning (bottom 20% of the polarity scores), center (middle 20%), and right-leaning (top 20%) retweeters (y-axis) for users across the polarity score deciles (x-axis). The retweeted users are either verified or not verified.



Random Walk Controversy

Previously, we explored the partisan relationship between users and their immediate audience. To quantify how information is disseminated throughout the Twitter sphere and its relationship with user polarity, we conducted random walks on the graphs to measure the degree of controversy between any two polarity deciles of users. Our method extends the Random Walk Controversy (RWC) score for two partitions [21], which uses random walks to measure the empirical probability of any node from one polarity decile being exposed to information from another.

A walk begins with a given node and recursively visits a random out-neighbor of the node. It terminates when the maximum walk length is reached or if a node previously seen on the walk is revisited. Following Garimella et al [21], we also halted the walk if we reached an authoritative node, which we defined as the top 1000 nodes (≈4%) with the highest in-degree in any polarity decile. By stopping at nodes with high in-degrees, we can capture how likely a node from one polarity decile receives highly endorsed and well-established information from another polarity decile. To quantify the controversy, we measure the RWC from polarity decile *A* to *B* by estimating the empirical probability:

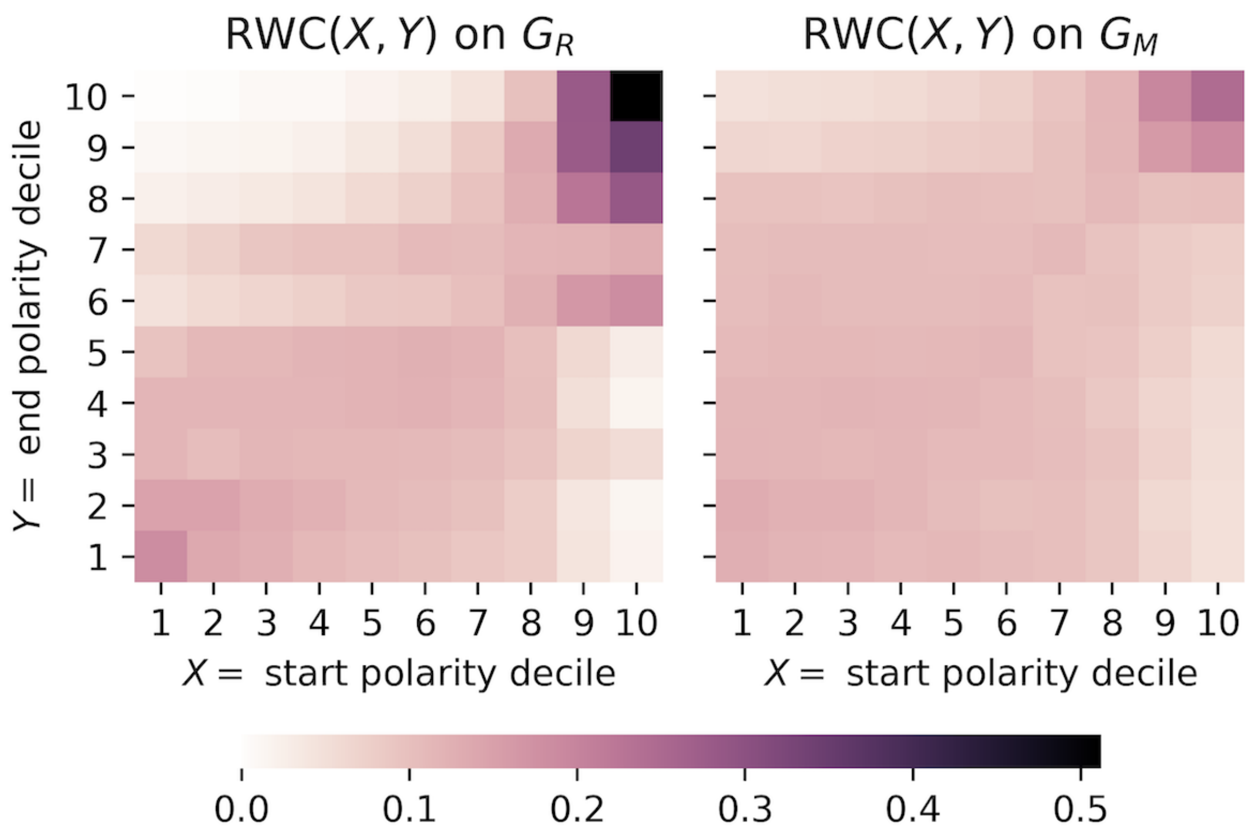
$$\mathrm{RWC}(A,B) = Pr(\text{start in } A \mid \text{end in } B) \quad \textbf{(2)}$$

The probability is conditional on the walks ending in any partition to control for varying distribution of high-degree vertices in each polarity decile. RWC yields a probability, with a high RWC(*A*,*B*) implying that random walks landing in *B* started from *A*. Compared to the original work by Garimella et al [21], we simplified the definition of RWC as we did not need to consider the varying number of users in each echo chamber.

We initiated the random walks 10,000 times randomly in each polarity decile for a maximum walk length of 10. The RWC between any two polarity deciles for the retweet and mention networks are visualized in Figure 5. For both networks, the RWC scores were higher along the diagonal, indicating that random walks most likely terminate close to where they originated. Moreover, the intensities of the heatmap visualizations confirmed that there were two separate echo chambers. The right-leaning echo chamber (top-right corner) was much denser and smaller than the left-leaning echo chamber (bottom-left corner). Any walk in the retweet network that originates in polarity deciles 9 and 10 will terminate in polarity deciles 8 to 10 about 80% of the time. In contrast, walks that started in deciles 1 to 7 had a near equal, but overall much smaller, probability of landing in deciles 1 to 7. In essence, users who are right-leaning formed a smaller but stronger echo chamber, while other users formed a larger and more distributed echo chamber.

The RWC scores on the mention network confirmed the presence of the two echo chambers, but the intensities were reduced. Compared to random walks on the retweet network, those on the mention network were much more likely to end far away. As a result, while there were rarely any cross-ideological retweet interactions, there existed a greater degree of direct communication through mentions, likely done to speak to or criticize against the opposing side [8]. We note that, because the RWC scores were highly symmetrical about the diagonals, there was little difference in the cross-ideological interaction between opposite directions of communication flow.

Figure 5. The RWC(X,Y) for every pair of polarity deciles X and Y on the retweet (left) and mention (right) networks using equation 2.



Popular Users Among the Left and Right

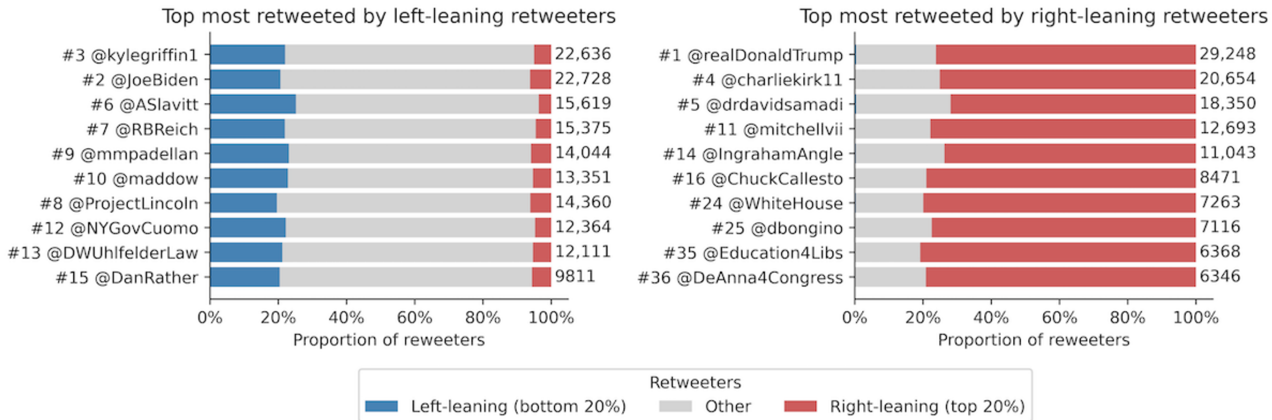
Retweeting is the best indication of active endorsement [22] and is commonly used as the best proxy for gauging popularity and virality on Twitter [57]. Figure 6 shows the most popular users among the left and the right according to the number of left- or right-leaning retweeters they have.

Analyzing the identities of the top-most retweeted users by partisans provides us the first hint at the presence of political echo chambers. There was no overlap between the most retweeted users by the left-leaning and by the right-leaning audience, and they tended to be politically aligned with the polarization of their audience. Almost all users who were most retweeted by left-leaning users were Democratic politicians, liberal-leaning pundits, or journalists working for left-leaning media. Notably, @ProjectLincoln is a political action committee formed by the Republicans to prevent the re-election of the Republican incumbent Donald Trump. Similarly, almost all users who were most retweeted by right-leaning users were Republican politicians, right-leaning pundits, or journalists working for right-leaning media. Despite its username, @Education4Libs is a far-right account promoting QAnon, a far-right conspiracy group. As of January 2021, @Education4Libs had already been banned by Twitter.

These popular users were not only popular among the partisan users but were considerably popular overall, as indicated by the high overall rankings by the number of total retweeters. With a few exceptions, users who were popular among the left were more popular among the general public than users who were popular among the right.

The distribution of the polarity of retweeters of these most popular users revealed another striking observation: the most popular users among the far-right rarely reached an audience that was not also right, whereas those of the far-left reached a much wider audience in terms of polarity. Users who were popular among the far-left hailed the majority of their audience from nonpartisan users (around 75%) and, importantly, drew a sizable proportion of the far-right audience (around 5%). In contrast, users who were popular among the far-right had an audience made up almost exclusively of the far-right (around 80%) and amassed only a negligible amount of the far-left audience.

Figure 6. Users with the highest number of retweeters from left- and right-leaning users. The bar plots show the distribution of their unique retweeters by political leaning. Users are also ranked by their total number of retweeters (ie, "#1 @realDonaldTrump" means that @realDonaldTrump has the most retweeters). Numbers appended to the end of the bars show the total number of retweeters.



Discussion

In this paper, we study the extent of echo chambers and political polarization in COVID-19 conversations on Twitter in the United States. We proposed Retweet-BERT, a model that leverages user profile descriptions and retweet interactions to effectively and accurately measure the degree and direction of polarization. Applying Retweet-BERT, we provided insightful characterizations of partisan users and the echo chambers in the Twitter sphere to address our research questions.

RQ1: What Are the Roles of Partisan Users on Social Media in Spreading COVID-19 Information? How Polarized Are the Most Influential Users?

From characterizing partisan users, we found that right-leaning users stand out as being more vocal, more active, and more impactful than their left-leaning counterparts.

Our finding that many influential users are partisan suggests that online prominence is linked with partisanship. This result is in line with previous literature on the "price of bipartisanship," which is that bipartisan users must forgo their online influence if they expose information from both sides [28]. In another simulated study, Garibay et al [58] showed that polarization can allow influential users to maintain their influence. Consequently, an important implication is that users may be incentivized to capitalize on their partisanship to maintain or increase their online popularity, thereby further driving polarization. Information distributed by highly polarized yet influential users can reinforce political predispositions that already exist, and any polarized misinformation spread by influencers risks being amplified.

RQ2: Do Echo Chambers Exist? If Yes, What Are the Echo Chambers and How Do They Compare?

Though COVID-19 is a matter of public health, we discovered strong evidence of political echo chambers on this topic on both ends of the political spectrum, but particularly within the right-leaning community. Right-leaning users were almost exclusively retweeted by users who were also right-leaning, whereas the left-leaning and neutral users had a more proportionate distribution of retweeter polarity. From random walk simulations, we found that information rarely traveled in or out of the right-leaning echo chamber, forming a small yet intense political bubble. In contrast, far-left and nonpartisan users were much more receptive to information from each other. Comparing users who are popular among the far-left and the far-right, we revealed that users who were popular among the right were *only* popular among the right, whereas users who were popular among the left were also popular among all users.

Implications

Despite Twitter's laudable recent efforts in fighting misinformation and promoting fact checking [59], we shed light on the fact that communication is not just falsely manipulated, but also hindered, by communication bubbles segregated by partisanship. It is imperative that we not only dispute misinformation but also relay true information to all users. As we have shown, outside information is extremely difficult to get through to the right-leaning echo chamber, which could present unique challenges for public figures and health officials outside this echo chamber to effectively communicate information. Existing research suggests that right-leaning users are more susceptible to antiscience narratives, misinformation, and conspiracy theories [2,3,17,18], which given the echo chambers they are situated in can worsen with time. Our work has implications in helping officials develop public health campaigns, encourage safe practices, and combat vaccine hesitancy effectively for different partisan audiences.

Future Direction

Though the question of whether social media platforms *should* moderate polarization is debated, we note that *how* they can do so remains an open problem. It is unclear how much of the current polarization is attributed to users' selective exposure versus the platform's recommendation algorithm. Moreover, whether users are even aware that they are in an echo chamber, and how much conscious decision is being made by the users to combat that, remains to be studied in future work.

Another future avenue of research could focus on studying how misinformation travels in different echo chambers. Since our study highlights that there is an alarmingly small number of far-right verified users, and given that verified users are typically believed to share legitimate and authentic information, further research is required to establish if the right-leaning echo chamber is at greater risk of being exposed to false information from unverified users. A detailed content analysis of tweets can reveal if there are significant disparities in the narratives shared by left- and right-leaning users. Crucially, our work provides a basis for more in-depth analyses on how and what kind of misinformation is spread in both echo chambers.

Limitations

There are several limitations regarding this work. First, we cannot exclude any data bias. The list of keywords was manually constructed, and the tweets collected are only a sample of all possible tweets containing these keywords. Since the data was collected based on keywords strictly related to COVID-19, we only gathered data that is relevant to the virus and not tainted by political commentary. Therefore, the data provides us a natural setting to study the polarization of COVID-19 discourse on Twitter.

Second, our study hinges on the fact that retweets imply endorsement, which may be an oversimplification. To reduce noisy, isolated retweet interactions, we considered only retweets that have occurred at least twice between any two users.

Finally, our political detection model was built on a weakly supervised labeling of users using politically relevant hashtags and the polarization of news media as the sources of ground-truth. We took a conservative approach and only seeded users who explicitly used politicized hashtags in their profile or had repeatedly interacted with polarized new sources.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary material.
[PDF File (Adobe PDF File), 93 KB - xmed_v2i3e29570_app1.pdf]

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Abbreviations

AUC: area under the receiver operating characteristic curve
RQ: research question
RWC: Random Walk Controversy

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Original Paper

The Influence of COVID-19 Vaccination on Daily Cases, Hospitalization, and Death Rate in Tennessee, United States: Case Study

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Abstract

Background: The COVID-19 outbreak highlights our vulnerability to novel infections, and vaccination remains a foreseeable method to return to normal life. However, infrastructure is inadequate for the immediate vaccination of the whole population. Therefore, policies have adopted a strategy to vaccinate older adults and vulnerable populations while delaying vaccination for others.

Objective: This study aimed to understand how age-specific vaccination strategies reduce daily cases, hospitalizations, and death rates using official statistics for Tennessee, United States.

Methods: This study used publicly available data on COVID-19, including vaccination rates, positive cases, hospitalizations, and deaths from the Tennessee Department of Health. Data from the first date of vaccination (December 17, 2020) to March 3, 2021, were retrieved. The rates were adjusted by 2019 data from the US Census Bureau, and age groups were stratified into 10-year intervals starting with 21 years of age.

Results: The findings showed that vaccination strategy can reduce the numbers of patients with COVID-19 in all age groups, with lower hospitalization and death rates in older populations. Older adults had a 95% lower death rate from December to March; no change in the death rate of other age groups was observed. The hospitalization rate was reduced by 80% for people aged ≥80 years, while people who were 50 to 70 years old had nearly the same hospitalization rate as prior to vaccination.

Conclusions: This research indicates that targeting older age groups for vaccination is the optimal way to avoid higher transmissions and reduce hospitalization and death rates.

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KEYWORDS

COVID-19; pandemic; vaccination; vaccine; strategy; vaccination strategy; hospitalization; mortality rates; older adults; mortality

Introduction

In December 2019, the novel coronavirus SARS-CoV-2 in Wuhan, China, caused an outbreak of the disease COVID-19 [1]. In the next few weeks, COVID-19 became the main headline worldwide, and daily cases and deaths increased considerably [2]. By the end of November 2020, more than 14 million infections and 279,000 deaths had been confirmed nationally in the United States, making it the country with the highest number of cases in the world at that time [3]. With more than 368,000 daily cases and 4500 deaths, Tennessee has been identified as one of the hardest-hit states in the United States [3].

Vaccination and social distancing are essential factors for COVID-19 prevention [4]. COVID-19 vaccination rollout in Tennessee started on December 17, 2020, and by March 3, 2021, 13.3% of the population had already received an mRNA vaccine such as the Pfizer BNT162b2 (Tozinameran) and the Moderna mRNA-1273 [5,6]. In addition to reduced interpersonal contact and physical distancing, vaccination programs control virus spread and reduce the number of deaths [7]. While COVID-19 cases and deaths were highest in January 2021 in the United States, manufacturers currently cannot cover the enormous vaccination demand. As the vaccine supply is limited, it is crucial to prioritize who receives the vaccine; therefore, groups at the highest risk of getting the virus or individuals who are seriously ill have been prioritized for vaccination. Previous research has shown that prioritizing younger populations will significantly impact the reduction of COVID-19 cases relative to prioritizing older age groups. However, prioritizing younger age groups is associated with the lowest reduction in COVID-19 mortality compared to other approaches [8]. In addition, Tennesseans are eligible for vaccines based solely on their age, and these age-based phases have run simultaneously with those with high-risk health conditions.

The objective of this paper was to model how the vaccination program in Tennessee is likely to change COVID-19 daily cases, hospitalization, and deaths among adults.

Methods

This study used publicly available data on COVID-19, including vaccination rates, positive cases, hospitalizations, and deaths from the Tennessee Department of Health at the state level [9]. The rates were also adjusted by 2019 data from the US Census Bureau [10].

Measures

This study comprised data from the first date of vaccinations, December 17, 2020, to March 3, 2021. The Tennessee Department of Health provides data on the first and second doses of vaccinations, cases, hospitalization, and deaths daily. The data were stratified based on 10-year intervals starting from 21 years of age to ≥81 years.

Statistical Analysis

The methodology for generating a descriptive time series of vaccinations, daily cases, hospitalizations, and deaths involved two steps. The first was to convert aggregate data to daily data to create time-series data. The second was to adjust the data for each age group by the census data, including the percentage of Tennesseans who received vaccines, had COVID-19, were hospitalized, and died. The goal was to produce a series of trends over consecutive time intervals to understand the changes in COVID-19 cases, hospitalizations, and deaths after the onset of vaccinations. The data were analyzed with the R programming language (version 3.5.2, R Core Team) [11].

Results

During the first 78 days of vaccination in Tennessee, 953,568 individuals received their first dose, and 495,032 individuals received their second dose. Of those vaccinated, 18.2% (n=173,549) and 30.3% (n=288,931) of vaccines were administered to people of aged ≥81 years and 71-80 years, respectively, which shows that nearly half of the vaccines were given to those older than 71 years. Figure 1 indicates the percentage of those who received their first vaccine from December 17, 2020, to March 3, 2021. Individuals who were under 70 years had a higher vaccination rate before January 2021; however, from January to March 3, 40% of people aged ≥81 years and 36% of those aged 71-80 years had been vaccinated, which shows that most of the vaccines were administered to these two age groups. Figure 2 shows that only 25% (n=63,202) of Tennesseans who were older than 81 years received their second vaccine, while a smaller percentage of other age groups were also vaccinated. Although those aged 71-80 years had an approximately equal rate of receiving the first vaccine dosage compared to those aged ≥81 years, they received their second dosage at a similar rate to other age groups.

Daily cases for all age groups decreased inevitably after the onset of vaccination to day 78 (Figure 3). Daily cases decreased for younger people from approximately 0.2% at the end of January to less than 0.05% at the end of the study period. The proportional changes were considerably higher for older adults during the study period (from 0.1% to nearly 0.01% of daily cases). Before vaccination, older age groups had the highest hospitalization rates (Figure 4). The rate decreased at the end of the study period from 0.01% of Tennessee's older population to 0.003%. There was no substantial change in other age groups' hospitalization rates, although the age groups of 51-60 years and 61-70 years had high hospitalization rates on some days. From mid-February, the ≥71 years age group did not experience high hospitalization rates, and the 51-60 years age group had nearly the highest daily hospitalization rate. Lastly, the death rates among those aged ≥71 years decreased, while there was no change in the death rates of other age groups during the study period. Although Tennesseans over 71 years accounted for 0.015% of the daily deaths pertaining to COVID-19 at the end of 2020, this percentage decreased substantially to 0.003% at the end of the study period (Figure 5). The results showed that the gap between older and younger adults was high prior to vaccination, and after vaccination, the differences diminished, which indicates that all age groups had a similar death rate.

Figure 1. First-dose vaccine distribution of Tennesseans by age group.

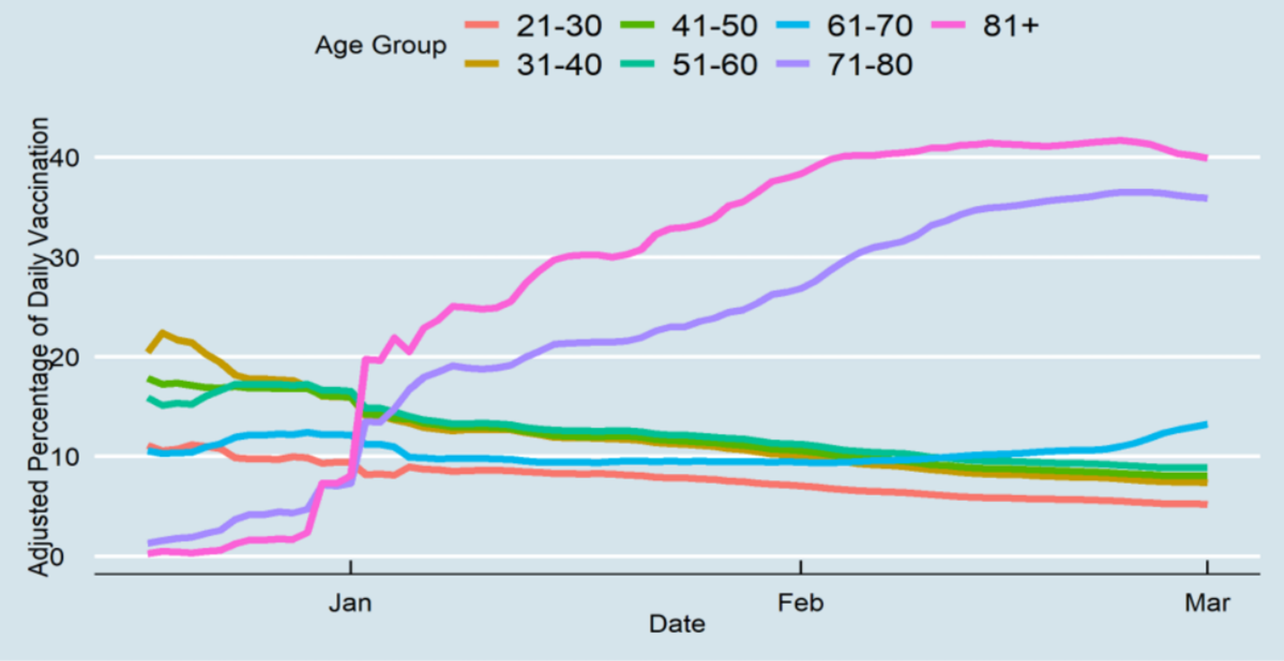


Figure 2. Daily fully vaccinated rates of Tennesseans by age group.

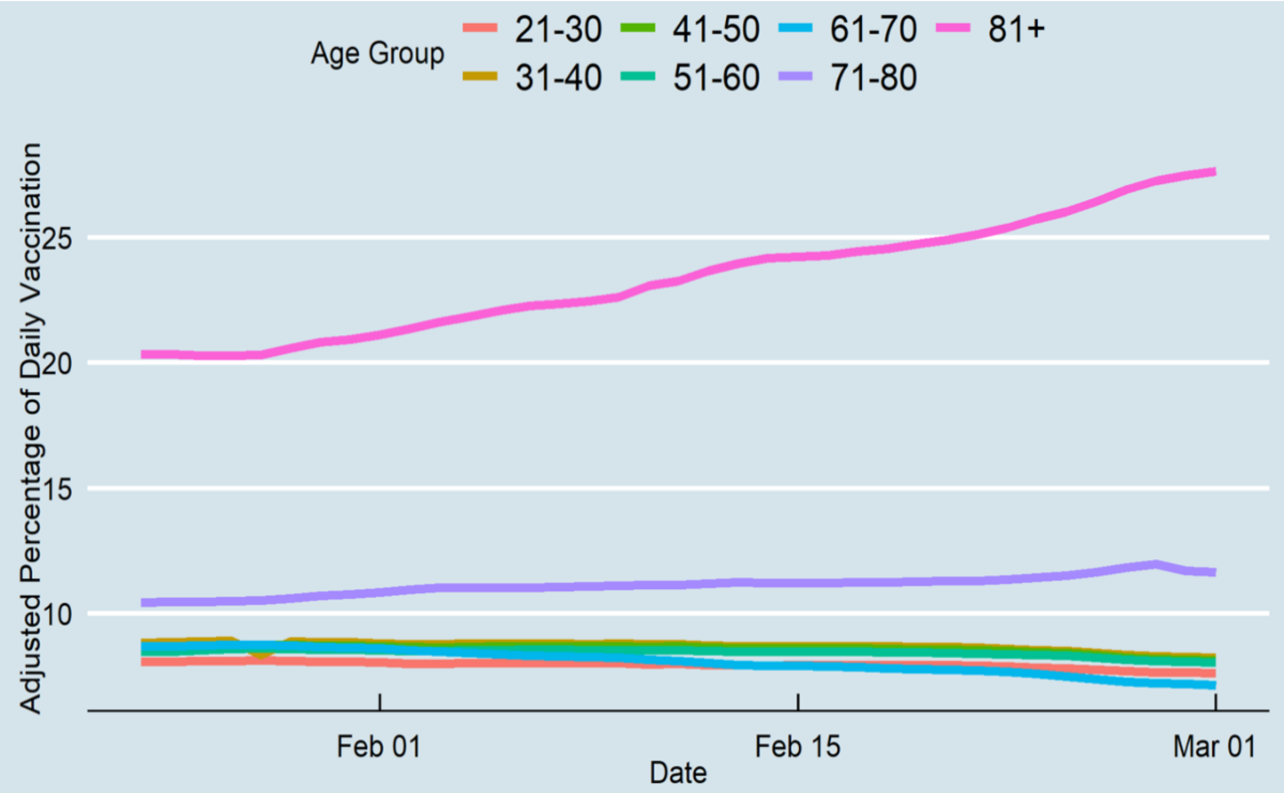


Figure 3. COVID-19 daily cases in Tennessee.

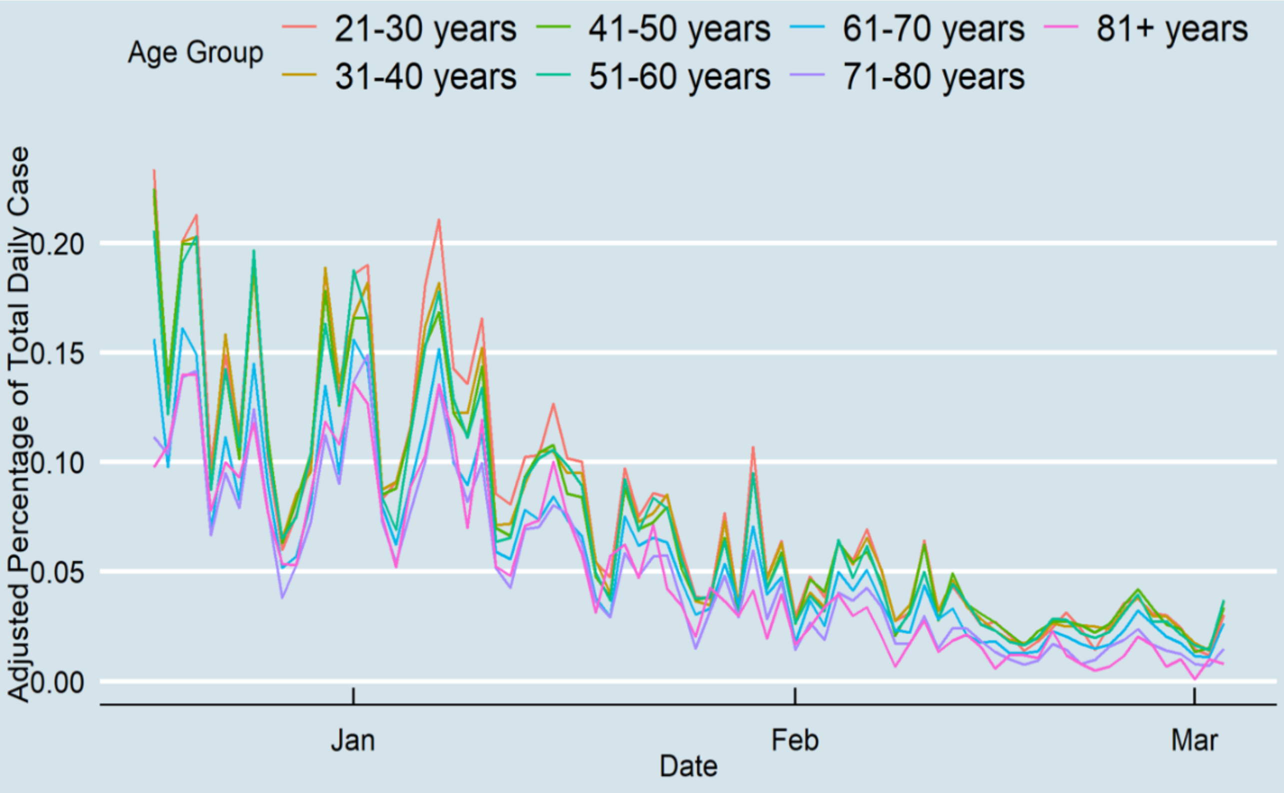


Figure 4. COVID-19 daily hospitalizations in Tennessee.

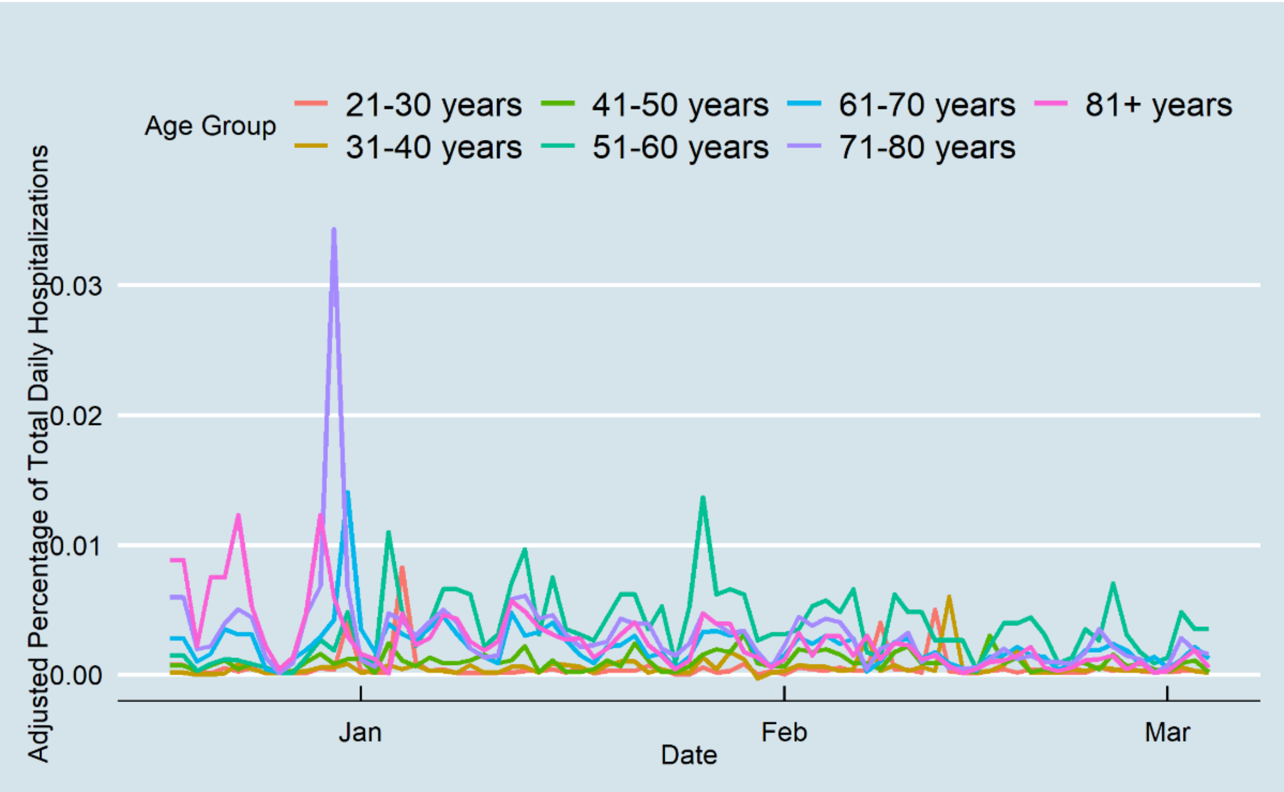
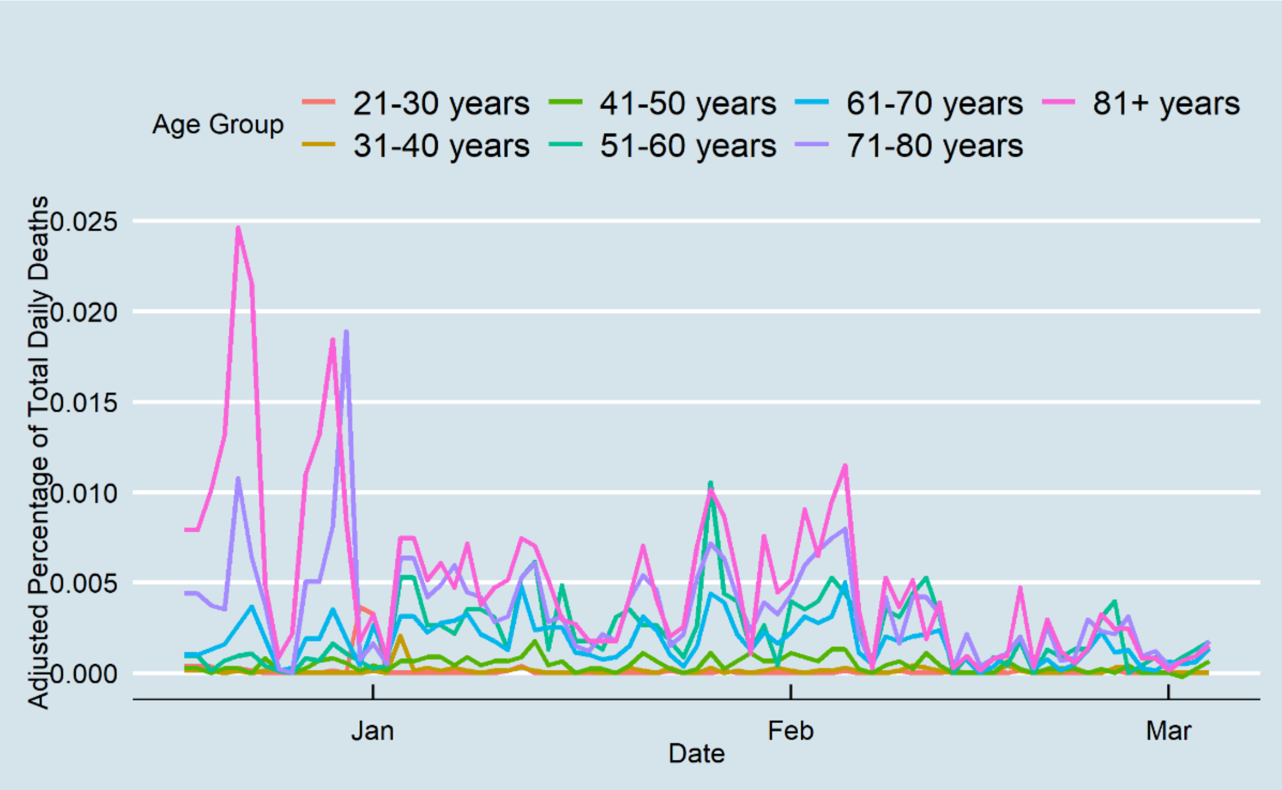


Figure 5. COVID-19 daily deaths in Tennessee.



Discussion

Principal Findings

COVID-19 continues to spread in the United States, and hospitalization and death rates remain high. Vaccines offer hope for better conditions, but an effective vaccination strategy is needed to stop the pandemic and restore people's everyday lives. Unfortunately, vaccine doses are being delivered slowly and sporadically, which means it is difficult for most people to be vaccinated at this time, even if they are eligible. Based on the current policy, high-risk groups such as first responders, older adults, and individuals with high-risk health conditions should receive the vaccines first [12]. In this study, data from the onset of COVID-19 vaccination in Tennessee (December 17, 2020) was used to understand how age-specific vaccination strategies changed daily cases, hospitalization, and death rate. The figures indicate that phase 1 of the vaccination strategy reduced the number of patients in all age groups, with lower hospitalization and death rates for older adults. The finding demonstrates that more than half of the vaccines were administered to those greater than 70 years; this was a practical approach in blocking transmission in the older adult population and other age groups. COVID-19 daily cases in older groups decreased by 90% from the end of 2020 to the end of February 2021. In addition, less than half of the vaccines were used for those aged under 70 years; this group had 80% lower daily cases at the end of the study period compared to the vaccine initiation date. Although this study cannot confirm the association between the onset of vaccination and the considerable reduction in COVID-19 transmission among younger age groups, the data indicate a significant decrease in daily cases among Tennesseans in all age groups. Moreover, 25% of people who were older than 81 years received the vaccines, and around 10% of other age groups received the second dosage. However, the ≥81 years age group did not have better results than their counterparts aged 71-80 years in terms of hospitalizations and death rate. This study included 78 days of vaccination statistics; thus, it is too early to draw conclusions on the influence of the second dose. Future studies should be conducted over a longer period to obtain more accurate results concerning the second dose.

Vaccines led to substantial reductions in hospitalization and mortality among older age groups in Tennessee. People older than 80 years had a 95% reduced death rate compared to mid-December. The death rate of the 71-80 years age group decreased during the study period as well; however, the 61-70 years age group had almost the same death rate from mid-December to the end of February. The data showed that there was no change in death rate in other age groups. Hospitalization of Tennesseans aged greater than 80 years was reduced by 80% in the study period, while people between 50-70 years experienced nearly the same hospitalization rate. Indeed, individuals who were between 51-60 years of age had the highest hospitalization rates in Tennessee. Although the data cannot identify people with higher risk, the higher hospitalization rate among the younger population implies that the health system in Tennessee could not efficiently identify people at higher risk. A previous study showed that a significant proportion of people who had two or more chronic conditions simultaneously are more likely to be hospitalized due to SARS-CoV-2 infection [13]. Additionally, while health workers are placed at the highest risk groups, immunizing this population and supplying personal protective equipment will help increase the resiliency of the health system during the epidemic [14].

Limitations

The findings should be considered in the context of several data limitations. Individual-level data was not used to estimate hospitalization risks, mortality rate, and COVID-19 transmissions. Moreover, several studies [15,16] indicate that racial and ethnic disparities in health systems increase the risk of getting sick, being hospitalized, and dying from COVID-19. Future studies should examine vaccination in different racial groups by age to estimate to prioritize vaccination. Additionally, the data do not include nonpharmaceutical public health control measures, which would be an essential way of controlling daily cases [17]. Although statistics on cases, hospitalizations, and deaths prior to the onset of vaccination could provide a more accurate picture regarding the changes due to vaccination, the preliminary analysis showed that the gaps between older and younger age groups were consistent before the onset of vaccination up to the end of January. Since February, however, the gap between older and younger age groups has diminished considerably. The reason why there were no immediate changes after vaccination uptake could be due to two factors. First, previous research has shown that it takes some time to protect those who are vaccinated [18]. To test the effectiveness of COVID-19 vaccines, we need to have a longer period of observation and more fully vaccinated people, as only around 35% of the older age group was vaccinated by the end of February. Second, it was not possible to distinguish between the daily cases, hospitalizations, and death rates of those who were and were not vaccinated.

Conclusion

Vaccination in Tennessee began at the start of the “third wave,” and SARS-CoV-2–positive cases and hospitalizations had increased considerably by December and January. This work concentrated on the COVID-19 dynamics of Tennessee. The primary finding is that the vaccine should be optimally targeted at older adults as a first step, indicating that vaccination reduces daily cases for the whole population while reducing hospitalization and death rates in the older population. This study, consistent with previous studies [17], shows that mRNA COVID-19 vaccines have a protective effect for blocking transmission even after a single dose. This study also indicates that prioritizing the vaccination of the older adult population is a practical approach for reducing the number of deaths and hospitalizations.

Conflicts of Interest

None declared.

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Original Paper

Risk Factors of SARS-CoV-2 Infection: Global Epidemiological Study

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Abstract

Background: Since the first recognition of the pandemic characteristics of SARS-CoV-2 infection, and before substantial case fatality data were available worldwide, public health agencies warned the public about the increased dangers of SARS-CoV-2 to persons with a variety of underlying physical conditions, many of which are more commonly found in persons over 50 years of age or in certain ethnic groups.

Objective: To investigate the statistical rather than the physiological basis in support of the abovementioned warnings, this study examines correlations globally on a nation-by-nation basis between the statistical data concerning COVID-19 fatalities and the statistics of potential comorbidities that may influence the severity of infection.

Methods: This study considers the statistics describing the populations of the 99 countries with the greatest numbers of SARS-CoV-2 infections at the time of the data cutoff. As national compilations of direct measures of immune system strength are not publicly available, the frequency of fatalities in those countries due to a variety of serious diseases is used as a proxy for the susceptibility of those populations to those same diseases.

Results: The analysis produces plots and calculations of correlations and cross-correlations of COVID-19 case fatality rates and the risks of other potential cofactors. It exposes some reasons that may underlie the degree to which advanced age increases the risk of mortality of infection with SARS-CoV-2. In contrast with the strong influences of comorbidities on the seriousness of consequences of influenzas and their associated pneumonias, the correlations of the same set of risk factors with SARS-CoV-2 infection are considerably weaker. The general characteristics of the observed correlations strengthened through 3 cycles of analysis, starting in September 2020. The strongest correlations were with chronic kidney disease and coronary disease (approximately 0.28 and 0.20, respectively).

Conclusions: This study confirms early clinical observations that infection with SARS-CoV-2 presents an increased risk to persons over the age of 65 years. It does not support the suggestions presented by government agencies early in the pandemic that the risks are much greater for persons with certain common potential comorbidities.

(JMIRx Med 2021;2(3):e28843) doi:10.2196/28843

KEYWORDS

COVID-19; pandemic; public health; mortality; infection; risk; risk factors; age; epidemiology; infectious disease

Introduction

Background

Only a few months after its disclosure by Chinese health authorities, SARS-CoV-2 had spread worldwide. By late winter of 2020, the World Health Organization (WHO) had designated the disease caused by the virus, COVID-19, to be a worldwide epidemic [1]. As can be seen from the effects of the approximately 80 million infections reported by the end of 2020, COVID-19 can manifest as mild, influenza-like symptoms or, far more seriously, as a severe and often deadly respiratory disease with pneumonia.

From the outset of the COVID-19 pandemic, the public has been exposed to numerous speculations about the degrees to which age and various underlying morbidities may amplify the risk of intensifying the severity of infection with SARS-CoV-2. Authoritative sources such as the US Centers for Disease Control and Prevention (CDC) [2] have issued warnings. Conditions cited by the CDC as increasing risk include cancer, chronic kidney disease, obesity, coronary disease, type 2 diabetes mellitus (DM), and sickle cell disease. The CDC also warns that asthma, hypertension, and liver disease, among other conditions, *may* subject a person to increased risk. In some countries, such as the United States, the incidence of COVID-19 has been more prevalent in some ethnic groups than others [3], leading to speculations that this disparity may be due to biology rather than behavior. Such differences are not unknown; for example, sickle cell disease is most commonly found among persons whose ancestors come from Africa and Mediterranean countries, where malaria is a prevalent affliction [4].

As many of the diseases cited by the CDC are more common in persons in late middle age and older, a common warning early in the pandemic was that SARS-CoV-2 presented a particular danger to persons over 50 years of age. In the initial wave of cases in China [5] and in the strong wave of cases in Italy, the probability of death due to COVID-19 was judged to be a strong function of a patient's age, being only a few percent for those aged less than 50 years and rising to nearly 20% for patients older than 80 years. The large number of fatalities [6] in care homes in New York, the United Kingdom, and elsewhere have fueled speculations about the risks that comorbidities frequently seen in older people will increase the fatality rate of COVID-19. An alternative explanation is the decrease in immune functions with aging [7].

Why is COVID-19 more dangerous to older than to younger persons? Complicating the answer to this question, the actual mortality rate of COVID-19 remains highly uncertain, as the prevalence of asymptomatic and unreported infections has been estimated to be from 2 to 5 times greater than that of infections with clearly defined symptoms. An early exemplary source of testing-based data was provided by the passengers aboard the Princess Line cruise ship, the *Diamond Princess*, on which half of the passengers who tested positive for COVID-19 were asymptomatic or at least presymptomatic [8]. To some degree, that uncertainty may explain the very wide distributions of reported (or apparent) rates of mortality (case fatality rates) of COVID-19 in different countries, ranging from <0.03% (Singapore) to almost 30% (Yemen). Moreover, in most (but not all) countries, by December 2020, the integrated average case fatality rate had declined significantly from the high levels seen in March and April of 2020.

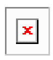
Objective

For a less anecdotal (and less speculative) assessment of risk factors for serious consequences of COVID-19, a data-driven examination of worldwide national statistics seems to be in order, with the goal of identifying strong correlations of mortality due to COVID-19 with other potential comorbidities and even with ethnically specific biological and economic factors. Based on a global investigation of the statistical correlations on a nation-by-nation basis between the statistical data concerning reported COVID-19 fatalities and potential comorbidities, this paper presents a set of calculations of linear and multivariate correlations that may influence the severity of the infection.

Methods

The analysis that follows has not been based on clinical or physiological considerations but rather on national epidemiological statistics as reported to international authorities. Unless otherwise indicated, the following assumptions underlie the subsequent calculations:

1. The *apparent mortality outcomes* (case fatality rates) defined in Equation 1 serve as a *reliable proxy* for actual rates of infection, death, and correlation with comorbidities:



The apparent mortality and case number data used in the following analysis are accurate as of December 30, 2020. This analysis does not and cannot account for any uncertainty due to differing national practices in distinguishing between deaths with COVID-19 and deaths due to COVID-19.

2. The sample of 99 countries across all continents *is representative* of potential correlations between COVID-19 case fatality rates and potential comorbidities or ethnicity. The number of COVID-19 cases in the countries that are not included was not statistically significant at the data cutoff date. Nevertheless, outliers with relatively small statistical significance can skew calculated correlations.

3. *Linear correlations* are examined on the basis of national data for COVID-19 for the year 2020 and comorbidities for the year 2018. The sources that describe the prevalence of disease are the WHO, as reported by World Life Expectancy [9], and

Worldometer [10], and the economic data are sourced from the World Bank as reported by Trading Economics [11]. This analysis *assumes* that the published WHO data concerning the fatalities ascribed to diseases in a given country constitute valid proxies for the prevalence of those maladies in national populations. In the case of obesity, the reported number is the percentage of the population with a BMI exceeding a WHO-established standard for a person of that sex.

The study examined the following factors:

- *Demographics:* geographical region, population, and national median age
- *SARS-CoV-2:* number of COVID-19 tests, confirmed cases of COVID-19 as reported by government authorities, and the apparent case fatality rate
- *Medical factors:* incidence of influenza, lung disease, asthma, obesity, heart disease, common cancers, hypertension, chronic kidney disease, diabetes, and malnutrition
- *Economics:* gross domestic product–purchasing power parity (GDP-PPP), average household size, percentage of the population living in slums, health expenditures per capita, and WHO Universal Health Coverage (UHC) index
- *One random (or pseudorandom) variable* in the range from 0 to 100

Examination of the data began with computing linear correlations between variables. The evaluation of the linear correlation herein uses the Pearson product moment correlation (Equation 2) to evaluate linear relationships between data sets:

One may estimate the *statistical significance* of calculated correlations by computing *r* for two variables that are *uncorrelated by construction* (ie, apparent COVID-19 mortality and a random variable in the range from 1 to 100). Once linear correlations have been computed, the next step is evaluating cross-correlations among variables and performing a multivariate analysis.

The 99 countries sampled in this study were selected as those reporting the largest numbers of COVID-19 infections. The countries listed in Table 1 represent 5 geographical regions: the Americas, Asia, Europe, Africa, and Middle East plus Central Asia. Regional populations were included. The combined population of nearly 5.5 billion persons accounts for the strong preponderance of all cases reported worldwide. The data cutoff date was December 30, 2020.

The SARS-CoV-2–related data are aggregated by sex because many countries still do not report sex-disaggregated data (or make these data available publicly). Therefore, the frequently reported sex-based disparities in contagion and in the case fatality rate could not be examined with respect to sex-based differences in occurrences of potential comorbidities.

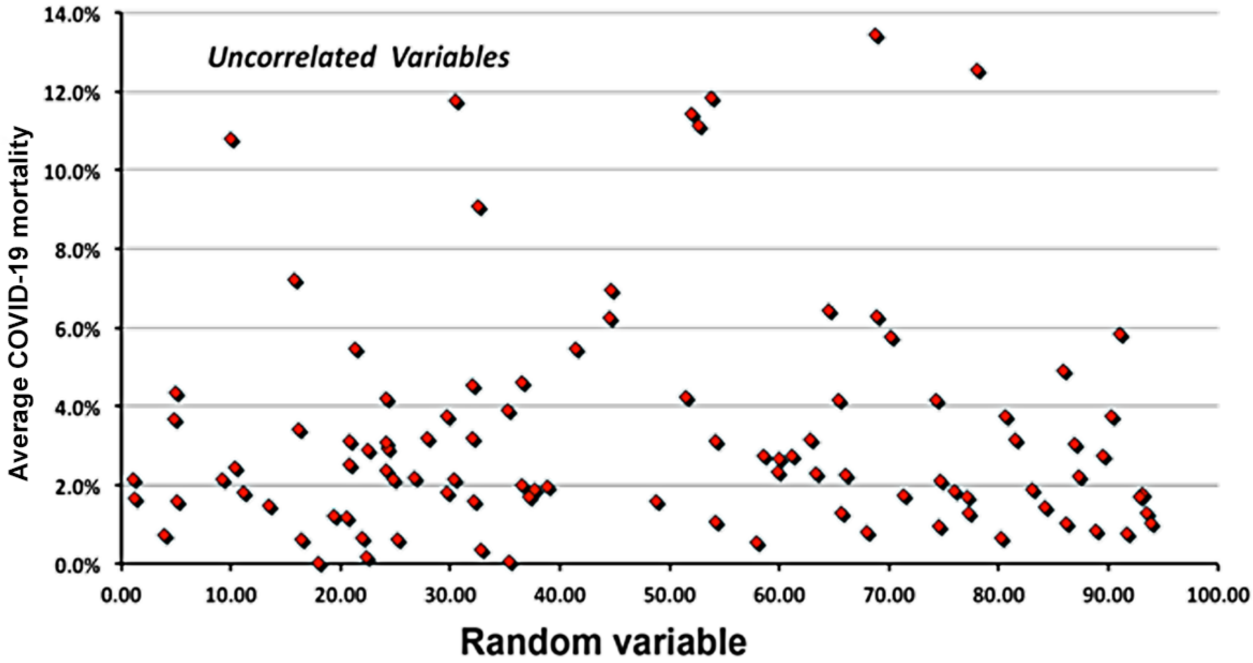
Figure 1 plots the case fatality rates and random numbers that are uncorrelated by construction. The Pearson coefficient for this set of 99 values is 0.053.

A potential limitation of this approach is that all mortality data have equal weight in the calculation of the correlation. One check of whether this ansatz introduces a bias is the correlation between apparent national mortality rates and national populations. Calculating this correlation yields a value of –0.014 which is close to the Pearson coefficient for uncorrelated variables. Another possible way to attribute a rational weighting is to plot the variation of COVID-19 deaths per capita against the possible risk factor. However, the number of fatalities per capita depends strongly on national public health policies, national efforts to prevent the spread of SARS-CoV-2, the GDP, and other nonmedical considerations. The differences in COVID-19 statistics between Norway and Sweden [10] are cases in point.

Table 1. Countries sampled grouped into 5 regions. Note that as Yemen is a statistical outlier in apparent mortality, many plots omit its data point for visual clarity.

Region	Population (million)	Countries
Americas	977	Argentina, Bolivia, Brazil, Canada, Chile, Columbia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, United States, Venezuela
Asia	2504	Australia, Bangladesh, China, India, Indonesia, Japan, Kazakhstan, Kyrgyzstan, Korea, Malaysia, Nepal, New Zealand, Pakistan, Philippines, Singapore, Thailand, Taiwan
Europe	725	Albania, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia, Bulgaria, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Macedonia, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Spain, Sweden, Switzerland, Ukraine, United Kingdom
Africa	768	Algeria, Cameroon, Congo, Ethiopia, Ghana, Ivory Coast, Kenya, Libya, Madagascar, Mali, Morocco, Nigeria, South Africa, Sudan, Uganda, Zambia
Middle East	487	Afghanistan, Bahrain, Egypt, Iran, Iraq, Israel, Lebanon, Kuwait, Oman, Qatar, Saudi Arabia, Turkey, United Arab Emirates, Uzbekistan, Yemen

Figure 1. A plot of the variables uncorrelated by construction.



Results

Examination of Linear Correlations

To gain confidence in this statistical approach, one can plot two variables for which one may expect to see a correlation: GDP-PPP and median age (Figure 2). Here, the linear correlation is quite high (0.625). Closer examination of Figure 2 suggests a limitation of considering only linear correlations. The countries circled in red show a strong correlation, while those in the green ellipses show scarcely any correlation of a nation's wealth with the age of its population. Clearly, a refinement of the statistical approach is needed. Identifying the data underlying each point with each country's region in Figure 3 reveals that median age and national wealth are essentially uncorrelated for European nations but strongly correlated for countries in Africa and Asia. *Regional grouping* was thus adopted throughout this study.

To illustrate the utility of this refinement, Figure 3 shows the correlation between deaths per 100,000 persons due to malnutrition and national wealth measured by GDP corrected for purchasing power (GDP-PPP). The relatively strong (0.455) correlation is driven by the high rates of malnutrition in Africa, Central America, and the less economically advantaged countries of Asia. No such effect is apparent in Europe.

From the outset of the pandemic, national health authorities warned the public about the increased risk of mortality for persons 60 years of age and older. Figure 4 shows an early example of the basis for these warnings in the data provided by the UK Office of National Statistics in September 2020 [12] and also in reference [13]. The UK government website notes several caveats: (1) the figures include deaths of nonresidents of the United Kingdom; (2) they are based on the date that a death was registered rather than when it occurred; (3) they are provisional and use the tenth edition of the *International Classification of Diseases* for definitions of the coronavirus (COVID-19). Again, the question arises of why the severity of COVID-19 infection should be a function of age.

Figure 2. The plot of GDP-PPP corrected for purchasing power versus median age in countries from the 5 regions under study. GDP(PPP): gross domestic product corrected for purchasing power parity; K$: US $1000.

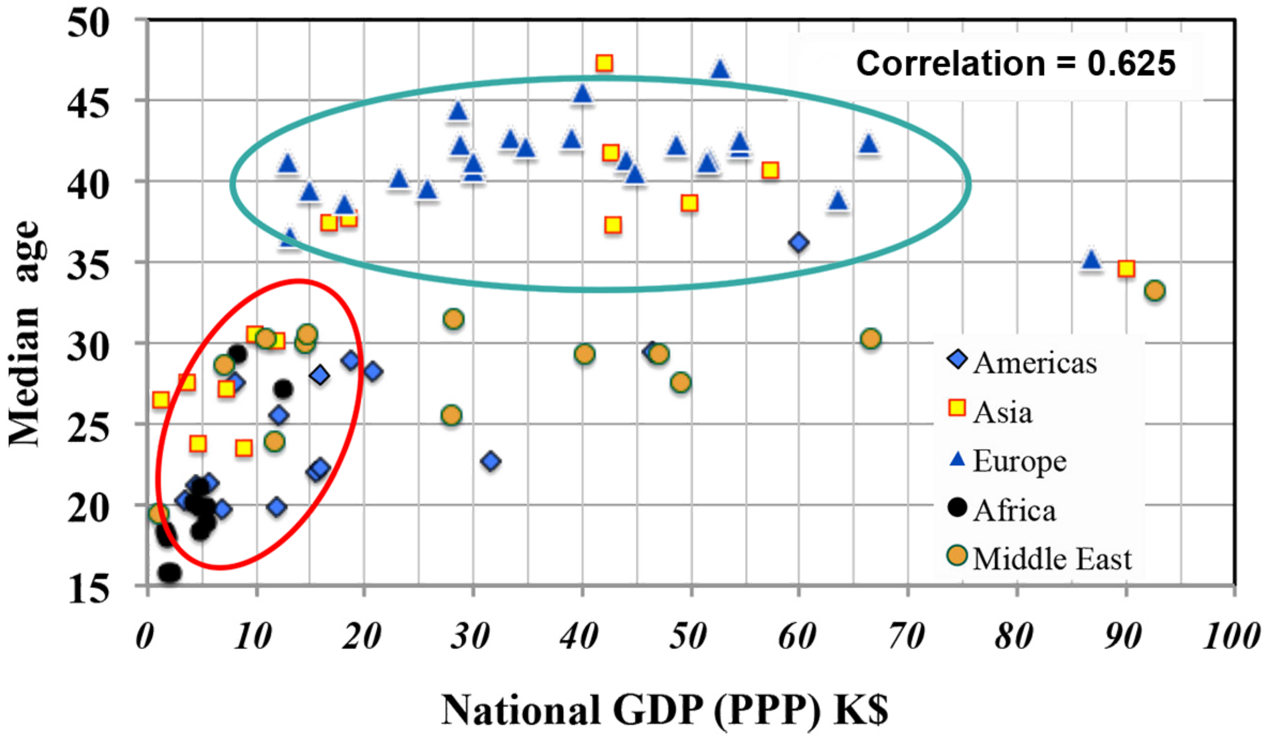


Figure 3. Correlation of poverty with malnutrition. 1K: 100,000 persons; GDP(PPP): gross domestic product corrected for purchasing power parity; K$: US $1000.

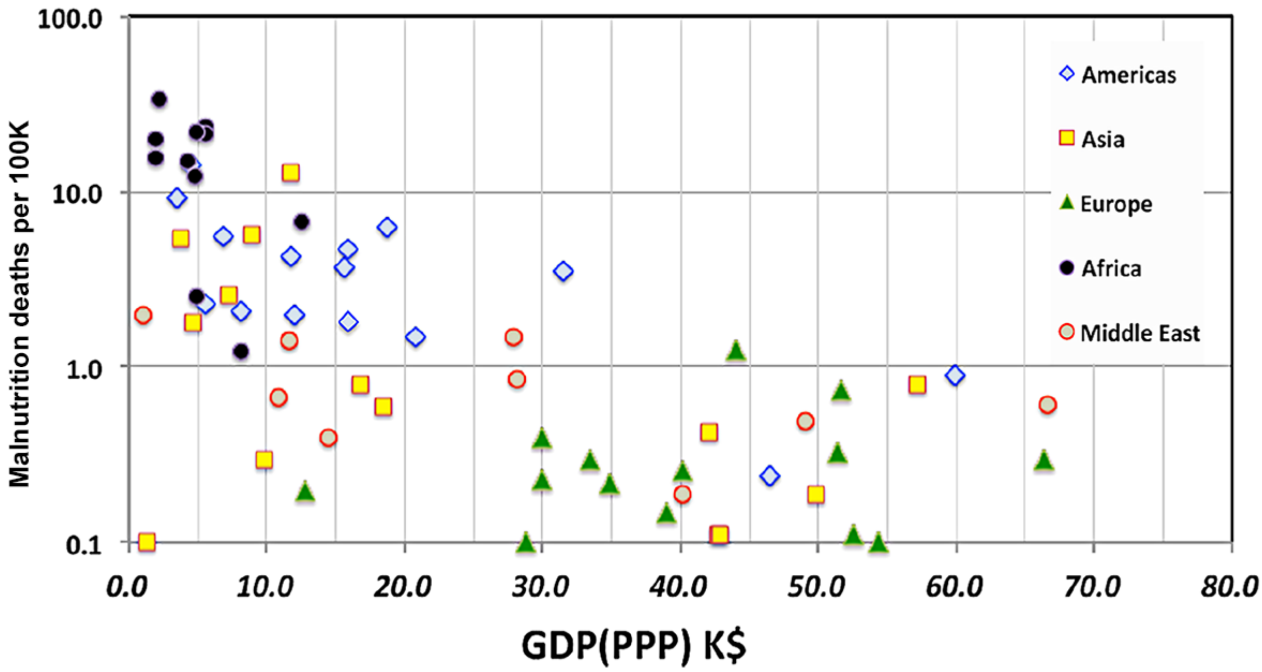
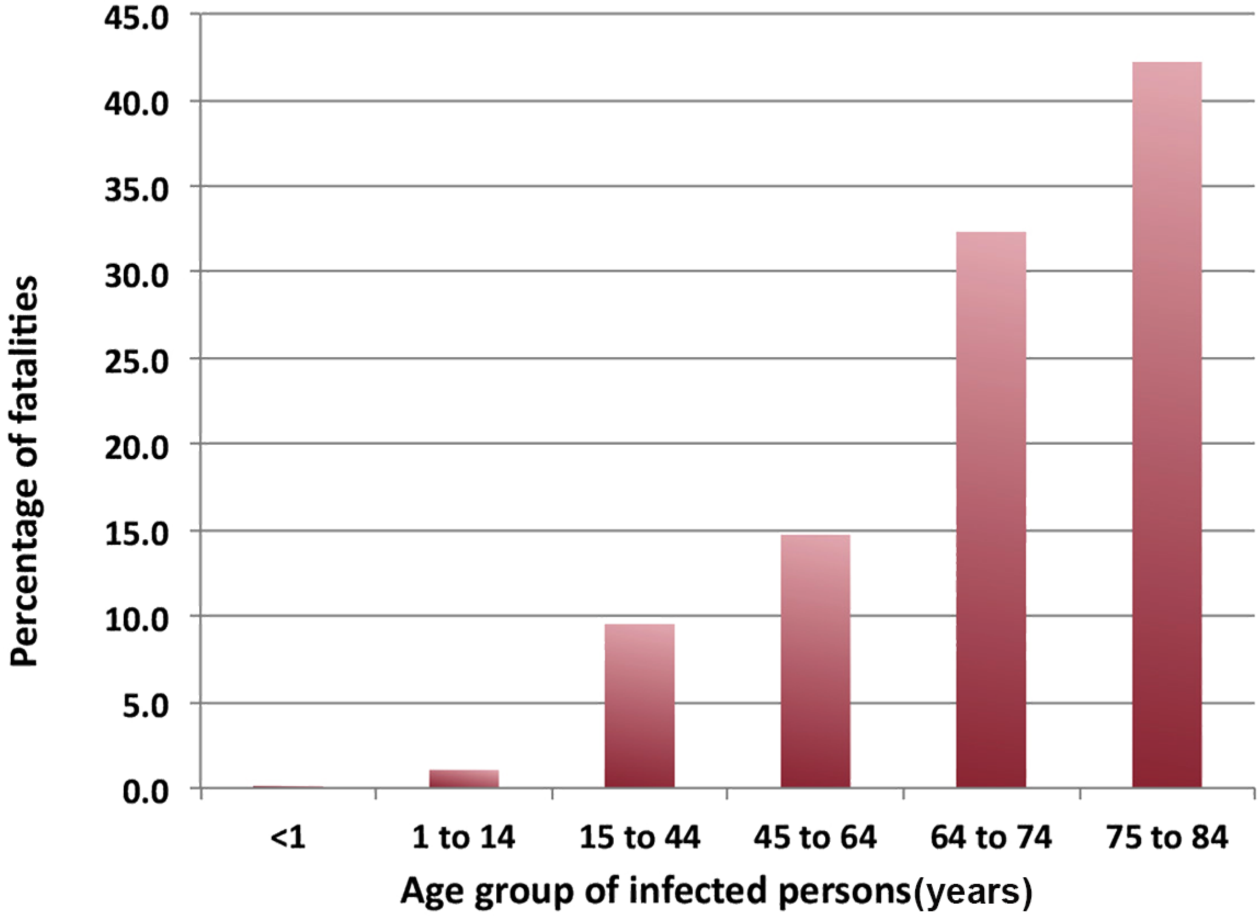


Figure 4. Deaths attributed to COVID-19 by the UK Office of National Statistics [9,10].



From these data, one might expect a strong correlation between the apparent national case fatality rate and the median age of a country's population. Even accepting the hypothesis of universality for the data in Figure 4, one should first multiply these rates by the demographics of a nation's population normalized to the UK population grouped into the same age bins. Such a plot (Figure 5) shows a surprising result. The overall linear correlation is negative, –0.181, partially due to the disparity among the regions: –0.258 for the Americas, 0.052 for Asia, 0.141 for Europe, 0.02 for Africa, and –0.608 for the Middle East and Central Asia.

Rather than plotting the COVID-19 case fatality rate versus the national median age, one might examine the dependence on the percentage of the population of people aged 65 years or greater. In that case, the overall correlation (–0.081) is negative, consistent with reference [14]; however, this is mostly the result of regional variations, with a larger but still relatively low correlation (approximately 0.19) in Europe and Africa.

As a measure of the influence of the age of a population on SARS-CoV-2 contagion, the national rate of confirmed cases of COVID-19 per 1 million persons with respect to the percentage of the population aged older than 65 years (Figure 6) displays a moderate correlation of 0.447.

One may hypothesize that the "care home effect," as in, the large numbers of deaths seen in nursing homes in Italy, the United Kingdom, and the US state of New York, was more the result of overcrowding and poor hygienic practices compounded with the general infirmity and the reduced immune function of nursing home residents than of any extreme dependence of the lethality of COVID-19 on individual, specific, underlying medical disorders. The linear correlations of age with potential causal factors, shown in Figure 7, suggest the strength of candidate cofactors to explain the care home effect. In addition to specific cofactors, the care home effect also reflects a generally very weakened physical condition of many occupants of care homes, which could render any pneumonia-inducing disease potentially lethal. The data in Figure 7 show no evidence that age alone influences the probability of a person becoming infected with SARS-CoV-2.

Figure 7 may explain what appears to be a startling result, namely, the globally negative correlation of the COVID-19 case fatality rate with the age of the national population. The negative value is due to the strong correlations between the national median age and the combination of adjusted GDP (0.64), national health care expenditures (0.48), and the WHO Universal Health Care Index. Nations with the oldest populations are generally those that are the wealthiest and in which health care services are the most robust, thus reducing the level of mortality.

Figure 5. National median age versus case fatality rate for the 5 regions under study.

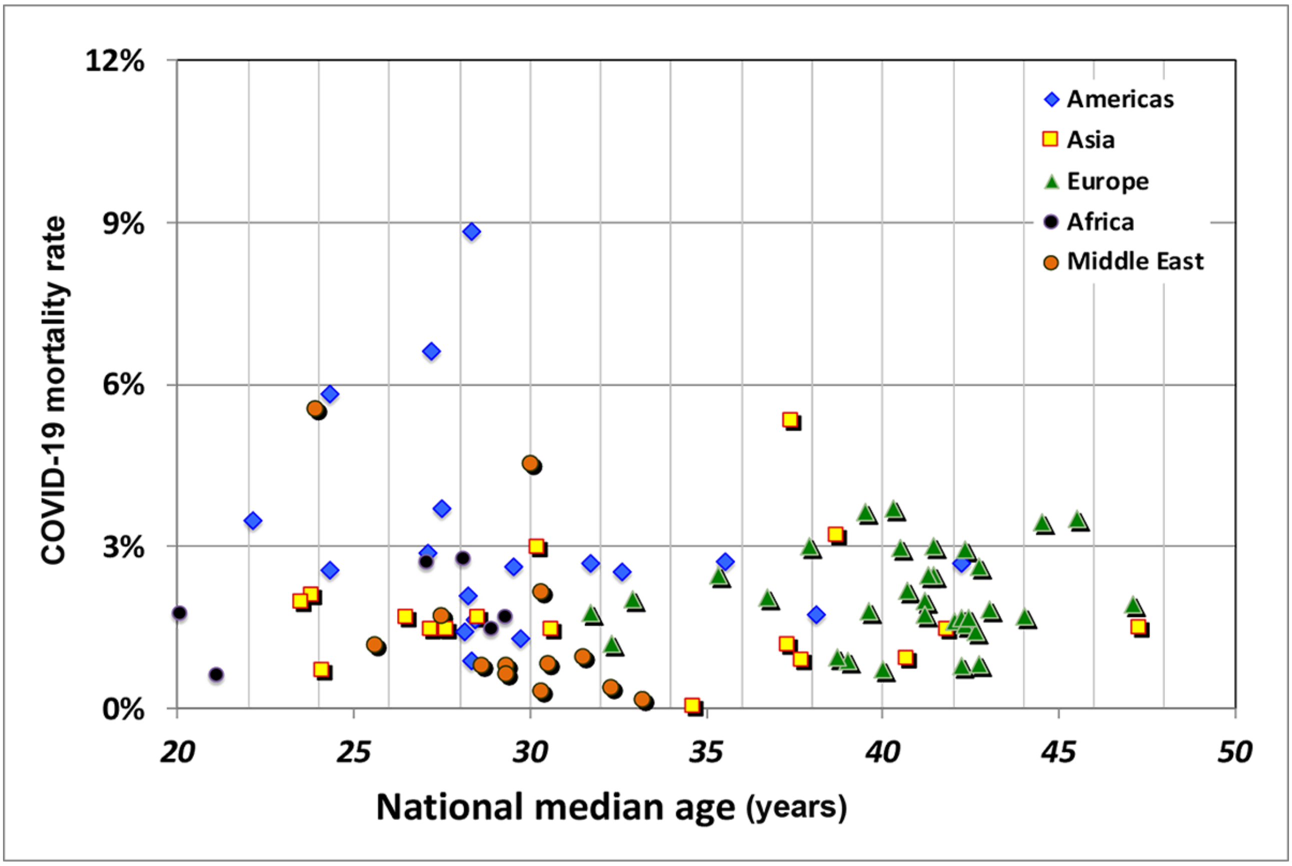


Figure 6. Confirmed COVID-19 cases per 1 million persons as a function of the percentage of the population aged 65 years and older.

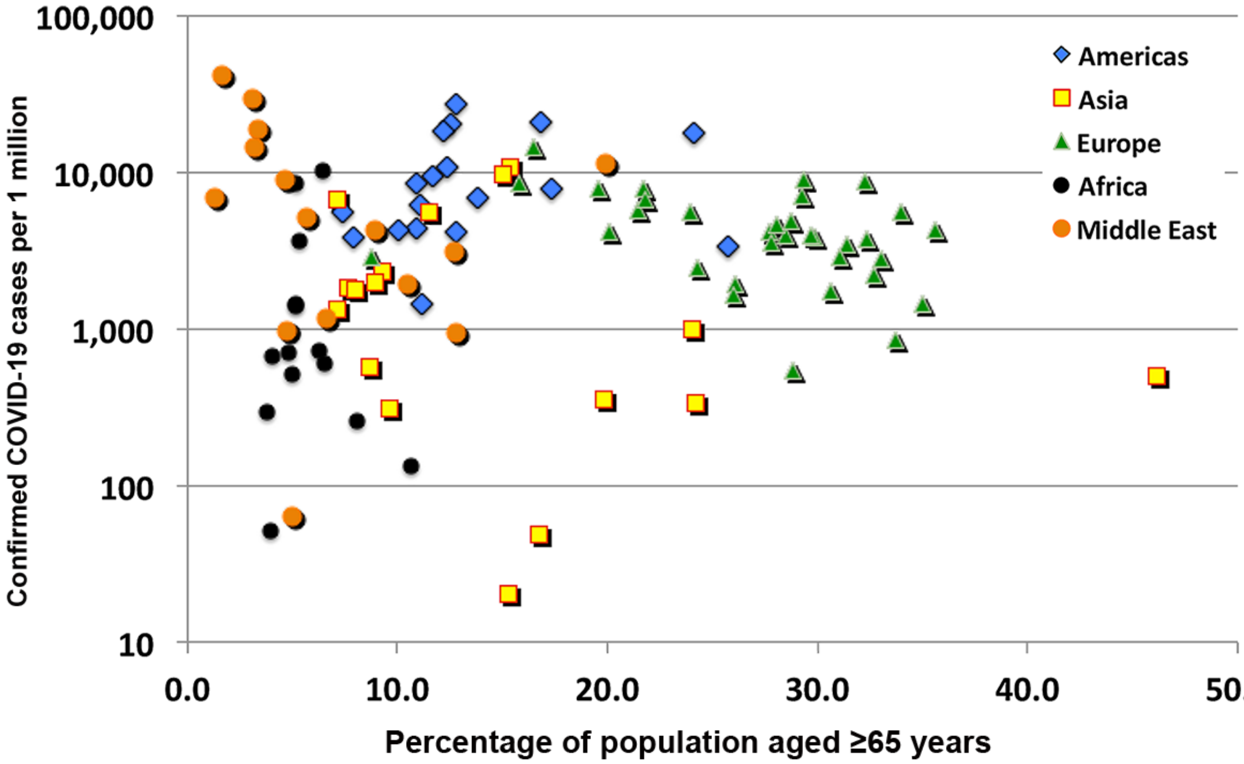
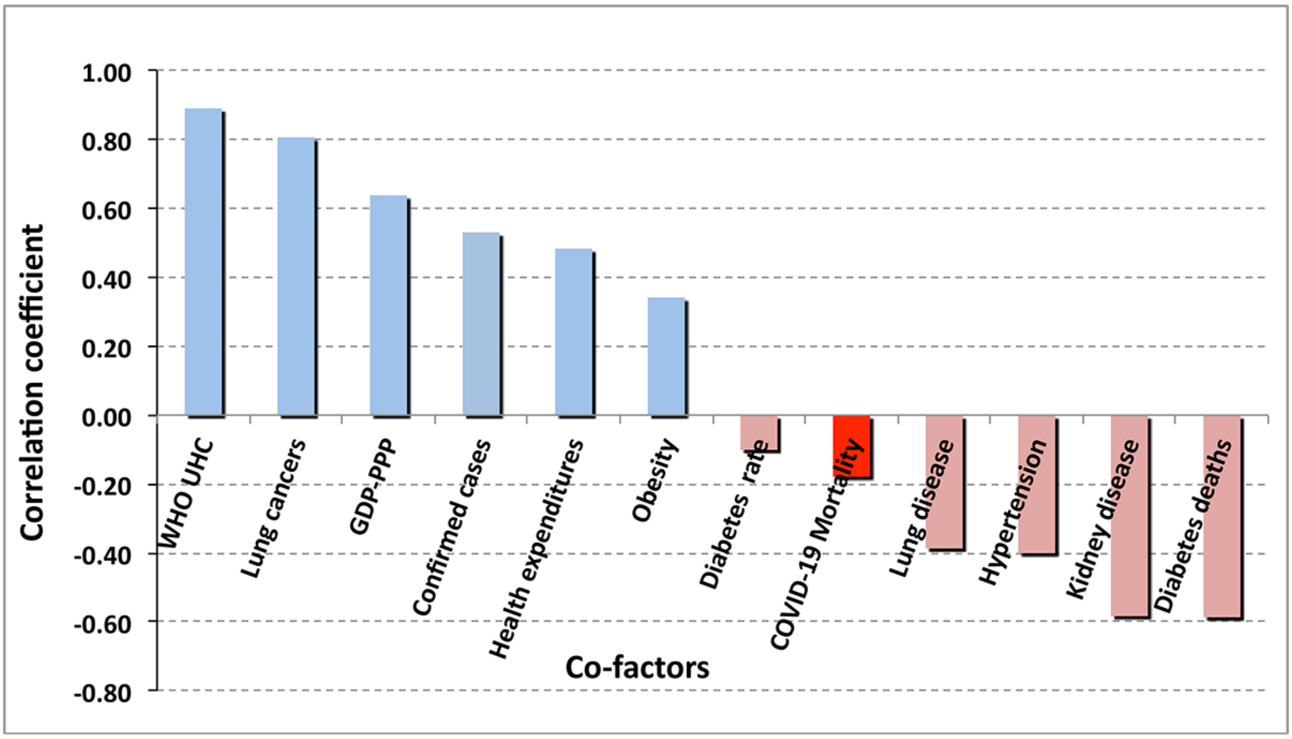


Figure 7. Correlations of potential risk factors with national median age. GDP: gross domestic product; UHC: Universal Health Coverage; WHO: World Health Organization.



In contrast with infections due to SARS-CoV-2, fatalities from influenza-induced pneumonia (Figure 8) are highly correlated (–0.652) with the median age of the population. The correlation also displays a strong regional dependence. The correlation is negative for the same reasons previously explained for COVID-19.

This result for influenza suggests the hypothesis that because COVID-19 typically presents as a severe respiratory disease, the severity of COVID-19 infection may correlate with the incidence of asthma. The global value (Figure 9) is small but not negligible (0.165), largely driven by the strong correlation (0.68) in the Middle East.

Figure 8. Incidence of influenza-related pneumonia deaths as a function of national median age.

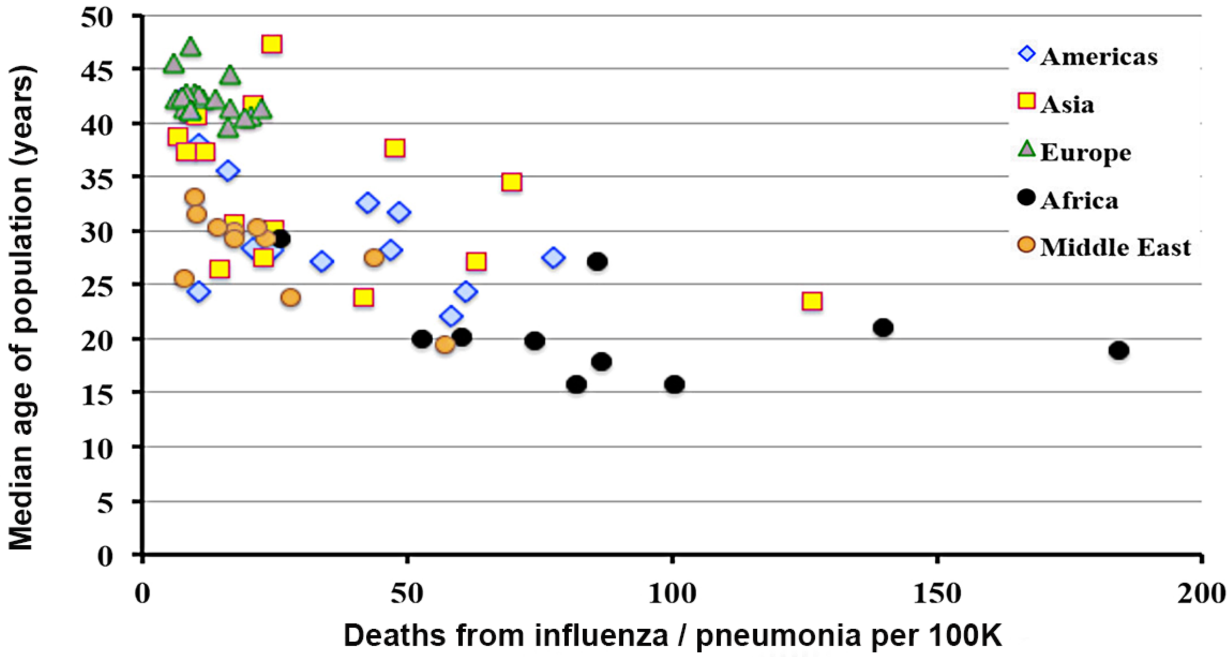
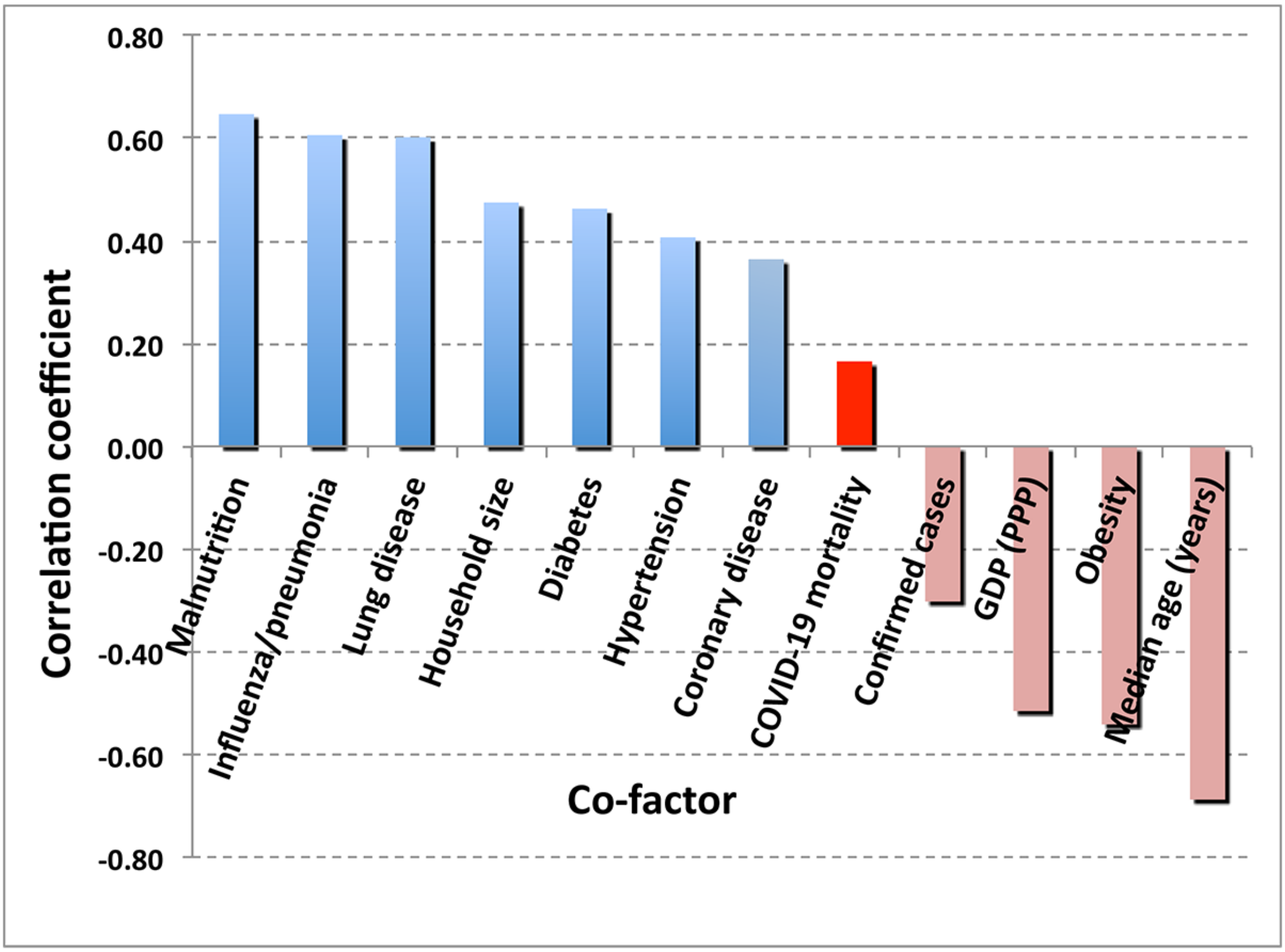


Figure 9. Correlation of severe asthma with the COVID-19 case fatality ratio. GDP(PPP): gross domestic product corrected for purchasing power parity.



For asthma as a cofactor, the contrast with influenza-related pneumonia is striking. A relatively high overall correlation of 0.594 for influenza was observed in all regions. Hence, any reference to COVID-19 as a "flu-like" infection or as a "superflu" is grossly misleading.

The CDC issued a warning early in 2020 that obesity represented a comorbidity that could potentially lead to severe consequences of a COVID-19 infection. However, once again, the actual national data (Figure 10) essentially display no correlation (–0.017) of a country's COVID-19 case fatality rate with the percentage of its population that is considered obese. A better metric of national obesity may be the average BMI (in kg/m^2) of the population. With BMI as the metric of the national prevalence of obesity, the correlation increases to 0.052, which is still very small. Moreover, that figure may itself be misleading when comparing regions, as the correspondence between BMI and body fat percentage varies considerably from country to country (10% to 20%).

The contribution of obesity to the *outcome* of other pulmonary disorders is significantly different from that of COVID-19, as is displayed in Figure 11. Obesity does have a significant correlation (0.516) with the risk of contracting SARS-CoV-2 infection, although not with the apparent outcome of the infection. Observation of increased risk of infection (although not its outcome) was previously reported in [13]. Reference [14] reports an increased risk of infection (0.329) for people with chronic kidney disease. That correlation of risk of infection is not seen in the statistics of this study, which consistently found a temporally increasing negative correlation (–0.046). However, as shown in Figure 10, this study does confirm an increased risk of mortality (0.269) for persons with chronic kidney disease who do develop COVID-19.

Figure 10. Summary of linear correlations with national COVID-19 case fatality ratio data. 1M: 1 million; CFR: case fatality rate; GDP: gross domestic product.

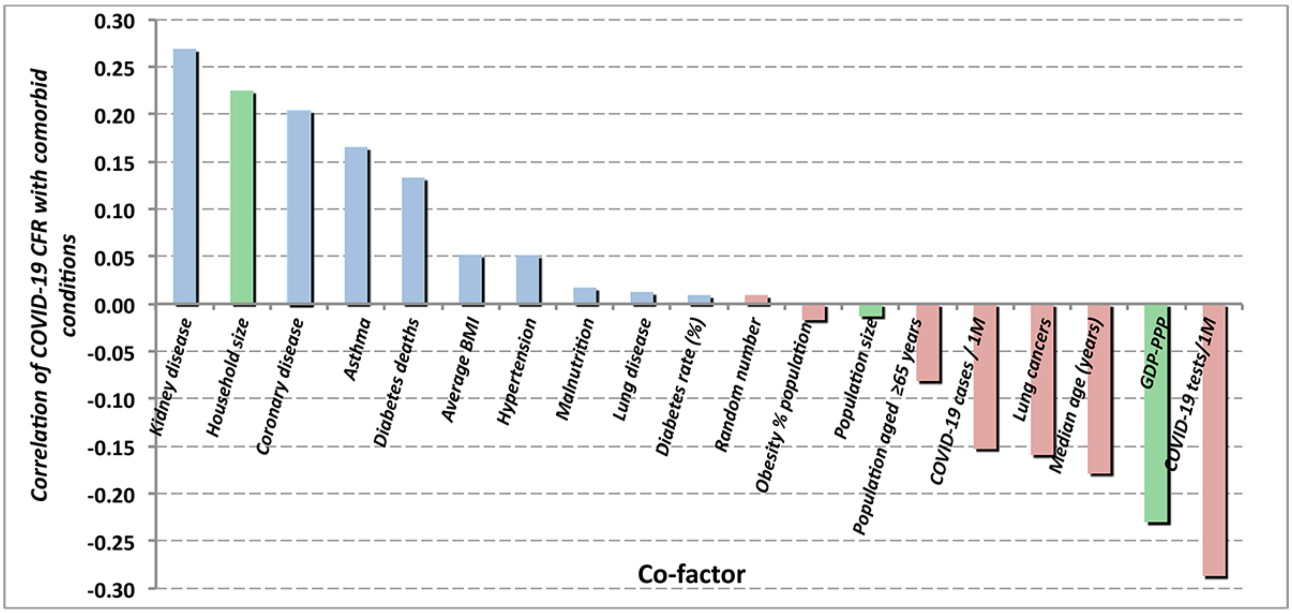
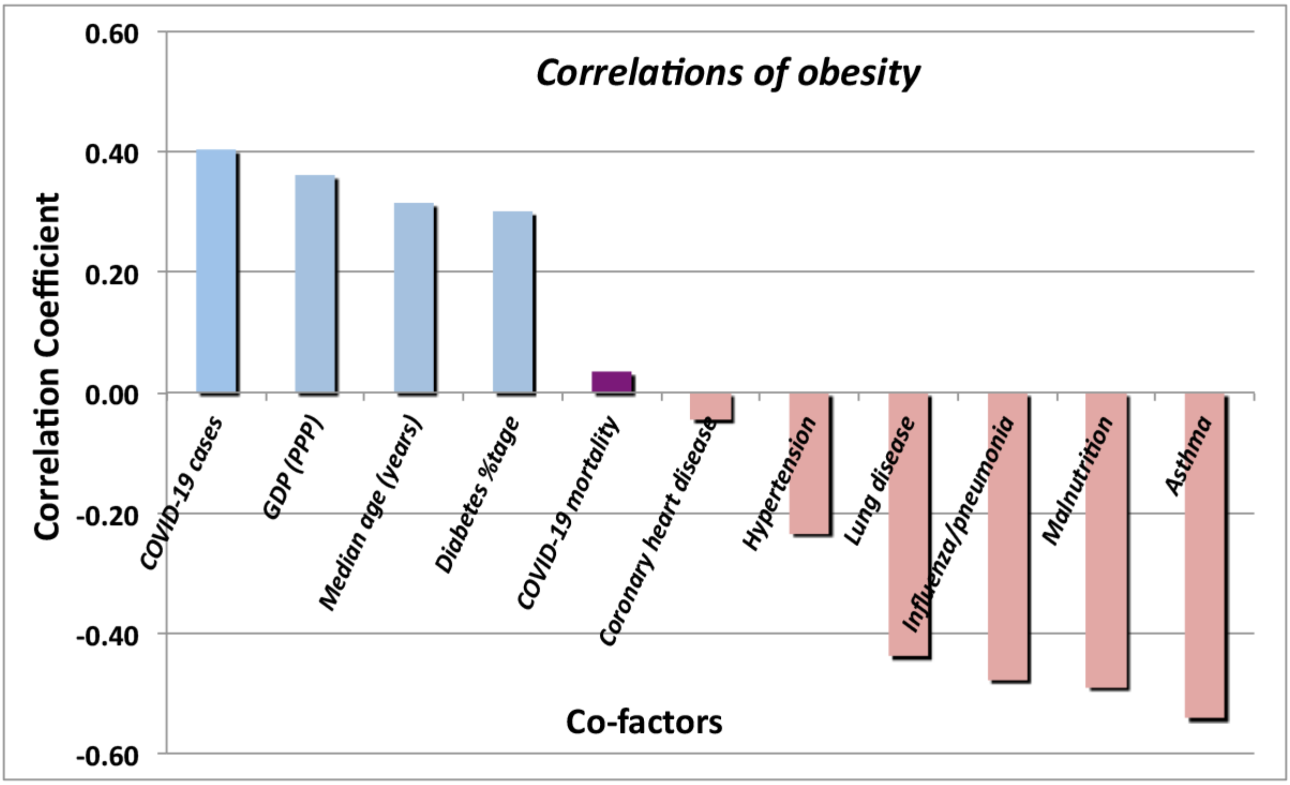


Figure 11. Correlations of obesity rates with COVID-19 mortality and other conditions. For most conditions, rates are based on deaths per 100,000 persons. GDP (PPP): gross domestic product corrected for purchasing power parity.



One might speculate that as a chronic respiratory disorder involving pulmonary airways, asthma would increase the seriousness of the consequences of COVID-19 and its induced pneumonias; this analysis shows no such significant correlation (0.053). Examining the correlation of COVID-19 mortality with other lung diseases also showed a very small correlation (0.013). In contrast, the relationship of influenza-induced pneumonias with asthma and other lung diseases presents correlations that are quite high, 0.594 and 0.348, respectively. With respect to their effects on patients with underlying conditions, influenza and COVID-19 are very different diseases.

Another early warning to persons with underlying conditions concerned DM. That suspicion is echoed by the strong increase of incidence of diabetic conditions with age. Whether one measures the incidence of diabetes by deaths due to diabetes or to the reported national rates of diabetes in adults (20-79 years of age), the correlation with COVID-19 mortality is similarly low (0.109). In *otherwise healthy persons*, diabetes does not appear to be a significant risk factor with respect to the serious complications of infection with SARS-CoV-2.

Figure 10 and Table 2 summarize the linear correlations and their time variations, respectively, of the COVID-19 case fatality rate with underlying medical and economic conditions (green bars in the figure) considered herein. As the percentage of the population over 65 years of age correlates at best weakly with the apparent COVID-19 case fatality rate, one may surmise that poor health care management played a very large role in the care-home effect.

Figure 10 shows a strong negative correlation of the case fatality rate with both COVID-19 tests per million persons and with the number of cases per million persons. More tests mean earlier detection, more detection of mild and weakly symptomatic cases, and better triage followed by earlier and more effective clinical treatments.

Table 2. Correlations with national values of apparent COVID-19 case fatality rates.

Potential cofactor	Correlations with COVID-19 case fatality rate statistics by date		
	December 30	November 20	October 16
Kidney disease	0.269	0.289	0.176
Household size	0.225	0.228	0.126
Heart disease	0.204	0.194	0.099
Asthma	0.165	0.168	0.091
Diabetes deaths	0.133	0.148	0.05
COVID-19 deaths per 1 million persons	0.092	0.07	0.17
Percentage of the population living in slums	0.090	0.072	0.059
Hypertension	0.051	0.049	–0.011
Influenza/pneumonia	0.034	0.040	–0.020
Malnutrition	0.017	0.002	–0.037
Lung disease	0.013	0.024	–0.112
Random number	0.009	–0.024	0.026
Percentage of the population with diabetes	0.009	0.046	–0.043
Population	–0.013	0.000	–0.014
Percentage of the population with obesity	–0.017	–0.006	0.014
Percentage of the population aged ≥65 years	–0.081	–0.103	0.028
COVID-19 cases per 1 million persons	–0.153	–0.163	–0.086
Health care expenditure	–0.155	–0.143	–0.02
Lung cancers	–0.159	–0.179	–0.098
Life expectancy	–0.163	–0.152	–0.055
Median age	–0.179	–0.191	–0.074
World Health Organization Universal Health Coverage index	–0.197	–0.168	–0.076
Percentage of the population living in cities	–0.197	–0.177	–0.121
Adjusted gross domestic product	–0.23	–0.215	–0.119
COVID-19 tests per 1 million persons	–0.287	–0.257	–0.111

Cross-Correlations and Multivariate Analysis

Before investigating cross-correlations for root causes, one should perform a multivariate analysis of the COVID-19 case fatality rate against a common trio of risk factors commonly found in patients in nursing and convalescent homes–namely DM, hypertension, and coronary disease. For that trio, the coefficient of multiple correlation is 0.171, which is not negligible but is unlikely to be the root cause of the care home effect. Computing the correlation of DM, hypertension, and coronary disease with deaths due to influenza and its associated pneumonia yields a stronger correlation of 0.359. Replacing hypertension with asthma in the DM, hypertension, and coronary disease trio reduces the coefficient of multivariate correlation for COVID-19 mortality to 0.121. In contrast, analogous analysis for influenza increases the multiple correlation coefficient to 0.627, demonstrating once again (see Table 3) that influenza and COVID-19 are very different diseases.

Other calculations of multivariate correlations with the apparent national mortality rates of COVID-19 are presented in Table 4.

Table 3. Multivariate correlations for a trio of input variables: diabetes mellitus, hypertension, and coronary disease.

Output variable	Regression coefficient	Pearson *r* values		
		Diabetes mellitus	Hypertension	Coronary disease
COVID-19	0.123	0.035	0.053	–0.041
Influenza/ pneumonia	0.439	0.386	0.147	0.247

Table 4. Multivariate correlations with national COVID-19 mortality data.

Multiple variables	Regression coefficient	Pearson r values
Gross domestic product and household size	0.07	–0.059, 0.056
Obesity and diabetes	0.035	0.035, –0.071
Influenza and lung disease	0.117	–0.064, –0.148
Diabetes, heart, and hypertension	0.123	0.035, 0.053, –0.041
Median age and number of cases	0.138	0.004, –0.137
Influenza deaths and diabetes	0.107	–0.064, 0.035
Influenza deaths and hypertension	0.068	–0.064, –0.041
Obesity, asthma, and diabetes	0.142	0.035, 0.053, 0.035

Cross-Correlations

The previous section argues and Figure 12 illustrates that there is a striking contrast between the correlations of COVID-19 with those of influenza/pneumonia with respect to other potential underlying conditions.

Although obesity appears to be correlated with SARS-CoV-2 contagion, it appears uncorrelated with the outcome of COVID-19 infections, contrary to the findings of reference [15]. Understanding the correlations of obesity calls for a deeper look at the relationship of obesity with the conditions that show the most influence. Already, in the case of contagion, regional differences represent a substantial fraction of the apparent effect. The regional differences could be due to factors such as national median age, or they may be influenced by national wealth reckoned in terms of per capita GDP-PPP, as shown in Figure 13.

As is the case with asthma, DM (Figure 14) shows significant correlations with several medical and economic conditions, such as age, household size, and mortality due to influenza/pneumonia. Once again, no correlation with COVID-19 mortality (red bar) is evident.

Figure 12. Contrast between correlations of COVID-19 with influenza-induced pneumonia. GDP: gross domestic product.

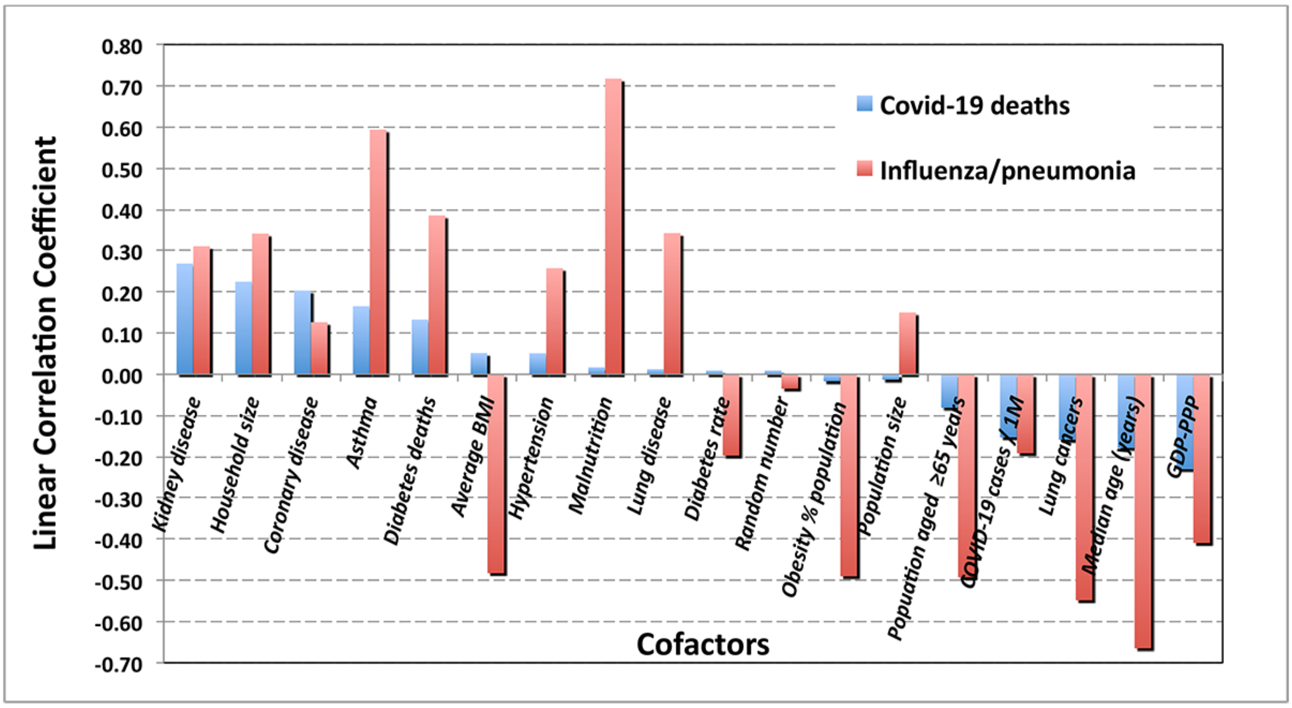


Figure 13. Correlation of regional wealth with obesity. GDP(PPP): gross domestic product corrected for purchasing power parity; K$: US $1000.

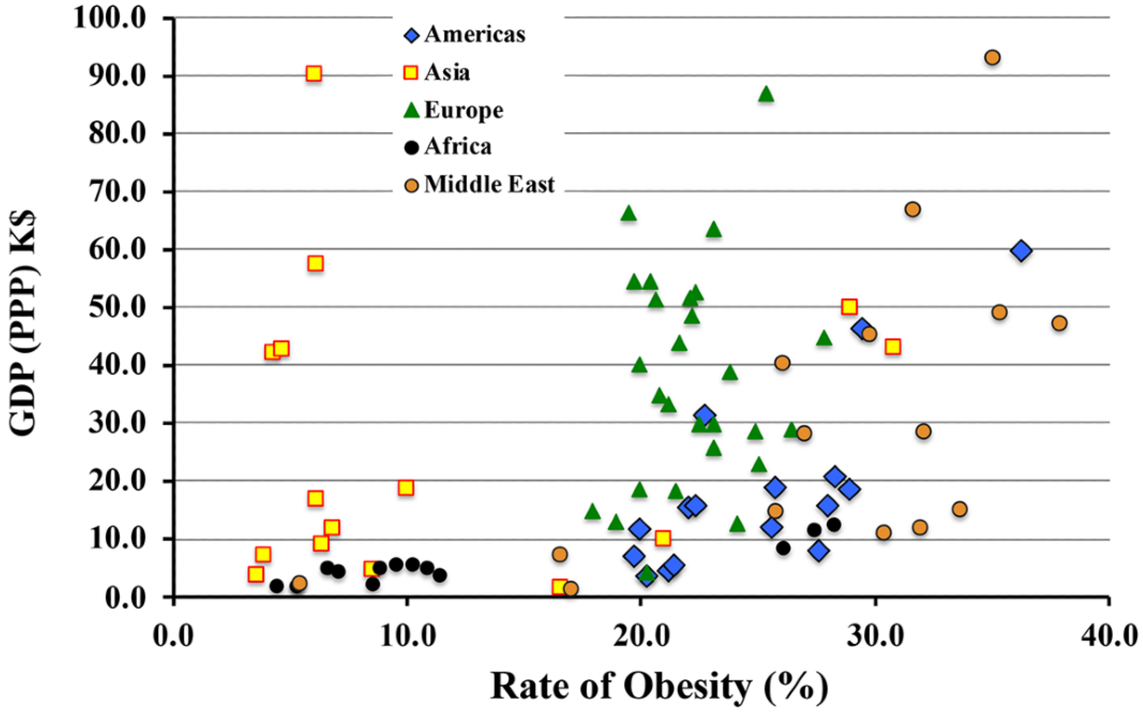
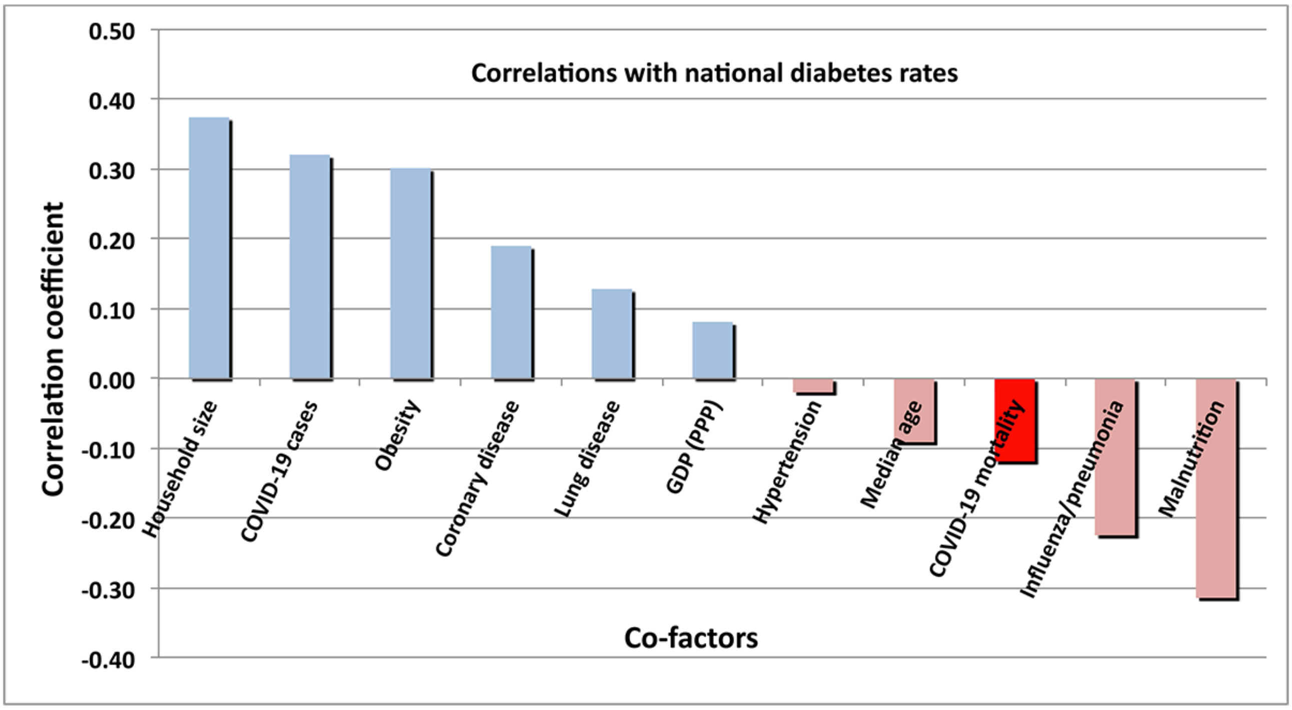


Figure 14. Correlations of national rates of diabetes mellitus with other medical and economic conditions. The red bar represents the correlation with COVID-19 mortality. GDP (PPP): gross domestic product corrected for purchasing power parity.

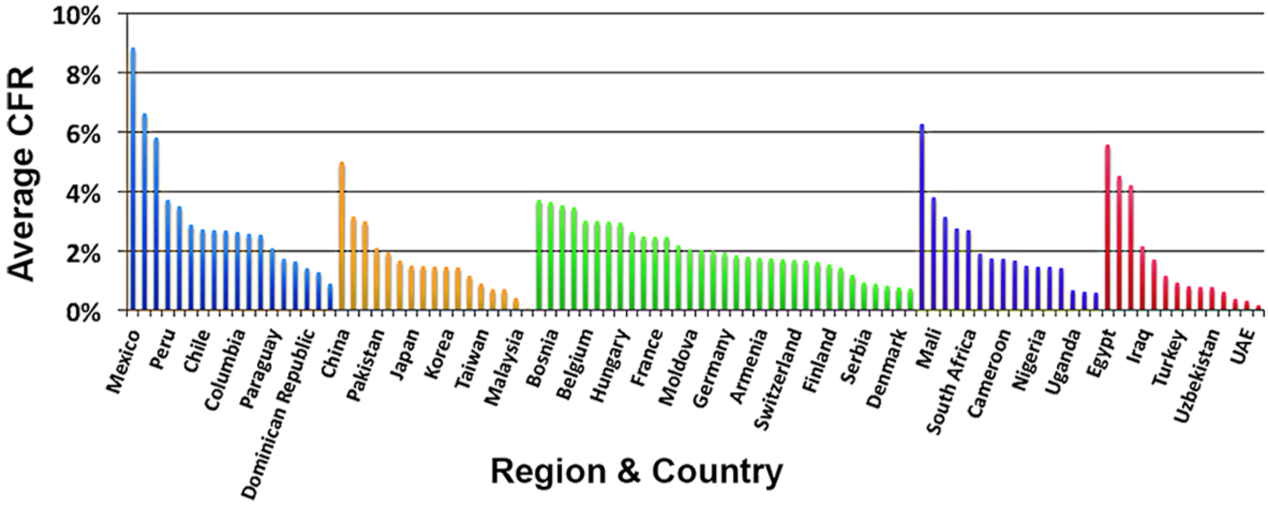


Regional Analysis

A key assumption of this study is the high degree of country dependence of the COVID-19 case fatality rate. Even though the case fatality rate has fallen dramatically in many countries with rates originally greater than 10%, after nearly one year of the pandemic, the disparity by country and by region remains large, ranging over one order of magnitude, as illustrated in Figure 15.

The size of the regional data sets is obviously much smaller and the uncertainties in computed correlations are much higher than those of the aggregated world data. However, examining the regional dependence of the COVID-19 case fatality rates on the most commonly cited comorbidities is instructive. (See Table S1 of Multimedia Appendix 1.)

Figure 15. Average case fatality rate by country and region. CFR, case fatality rate; UAE: United Arab Emirates.



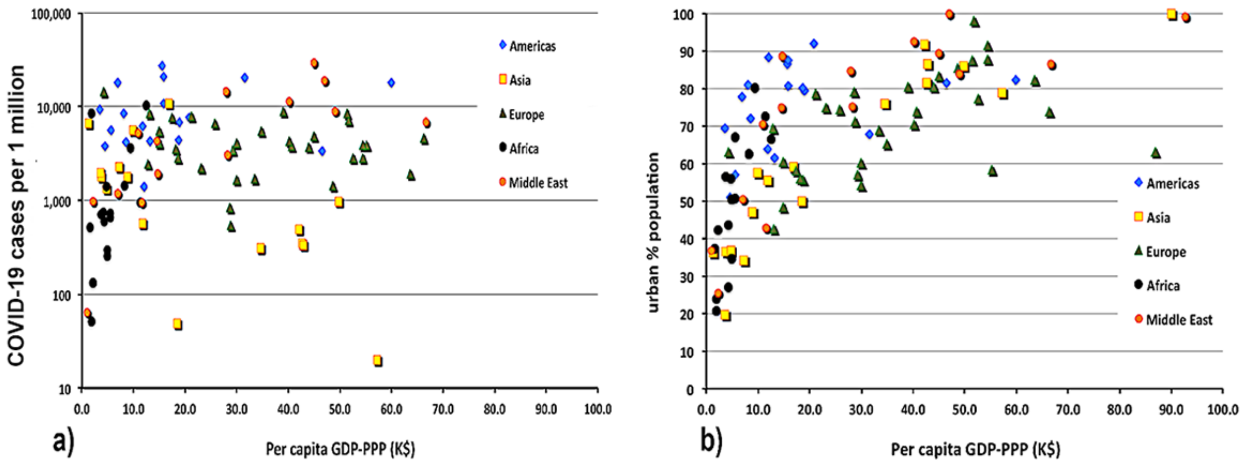
Factors Related to National Economics and Public Health Policies

The differences in the magnitudes, outcomes, and characteristics of the waves of infections among national subregions with roughly equivalent medical factors indicates that economics and public health policies makes a significant difference in the severity of SARS-CoV-2 infection. This section examines dependencies on GDP-PPP, average household size, percentage of the population living in slums, percentage of the population living in cities, health expenditures per capita, and the WHO UHC index.

Figure 3 has already shown an example of economic impact on medical outcomes; the per capita GDP-PPP has a strong influence (–0.446) on the rate of deaths due to malnutrition. That observation is hardly surprising. One might also ask whether per capita GDP-PPP would have a similar impact on mortality due to COVID-19 infections. The distribution of COVID-19 mortality with national wealth shows essentially no correlation (–0.059). The politics of poverty does not, of itself, explain the observed national rates of COVID-19 mortality.

The distribution of contagion of SARS-CoV-2 over the global data set is noticeable and positive (0.299). However, as shown in Figure 16, that value is entirely driven by the strong dependence of the rising contagion on rising income in African countries. If one removes the African countries from the sample, the correlation disappears (0.028).

Figure 16. (a) The distribution of COVID-19 cases with national GDP-PPP. (b) The degree of urbanization with increasing GDP. GDP-PPP: gross domestic product–purchasing power parity; K$: US $1000.



The differing behavior in Africa, which can be observed in Figure 16 (a), may be due to the increase in urbanization with increasing national wealth. One might further suspect that the increase in urbanization is also likely to increase the fraction of the national population living in slums. In fact, the percentage of people living in slums actually decreases with the urbanized fraction of the population.

The correlation of economic and policy factors with contagion (measured in confirmed COVID-19 cases per 1 million persons and apparent COVID-19 mortality) is presented in Table 5. As the mortality rate varies in time and seems to decline as the pandemic progresses (at least in the northern hemisphere), the mortality rate was benchmarked on December 30, 2020. The surprising negative correlation in contagion with the percentage of the urban population living in slums is likely due to the trend in Africa that the smaller the fraction of the population living in cities, the more likely it is that they live in slums (World Bank data).

Table 5. Correlations of economic and political factors with numbers of cases of COVID-19 infection (contagion) and apparent COVID-19 mortality.

Factor	Correlation	
	Contagion	Mortality
Percentage of population living in cities	0.476	–0.085
Testing for COVID-19	0.438	–0.099
Gross domestic product–purchasing power parity	0.32	–0.059
World Health Organization Universal Health Coverage index	0.303	–0.02
Health spending	0.24	0.046
Household size	0.172	0.056
Percentage of urban population living in slums	–0.407	0.041

An examination by region of the impact of economic cofactors in the COVID-19 case fatality rate is shown in Figure 17. The negative correlations with national wealth and with national health care expenditures are to be expected. Nonetheless, these effects are weaker in Africa than in other regions. More detailed investigation of these effects would require examination of underlying conditions on a country-by-country basis.

The correlation with respect to GDP is explained by the correlation of the GDP with the percentage of the population aged over 65 years. The substantial correlation of contagion with testing results from the obvious fact that the more one looks, the more one sees. The correlation of contagion with the percentage of urban population is due to the cross-correlation of GDP with percentage of urban population (0.648) and the high cross-correlation of urban population with testing for COVID-19 (0.497). The values for average health care expenditures and the UHC index of the WHO are similarly explained. The data that underlie the value of case fatality rate versus the percentage of the urban population that live in slums appears in Figure 18.

Figure 17. The impact of economic cofactors on case fatality rates, showing a strong variation by region. GDP: gross domestic product; UNC: Universal Health Coverage; WHO: World Health Organization.

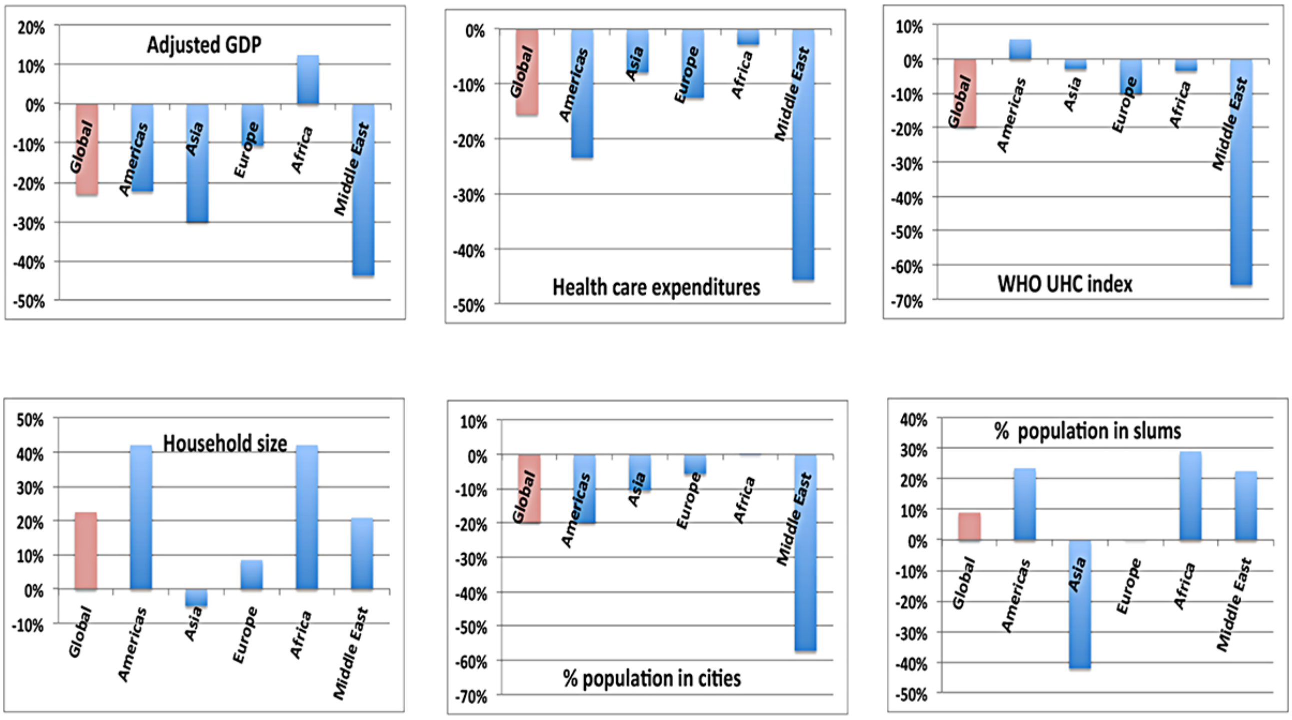
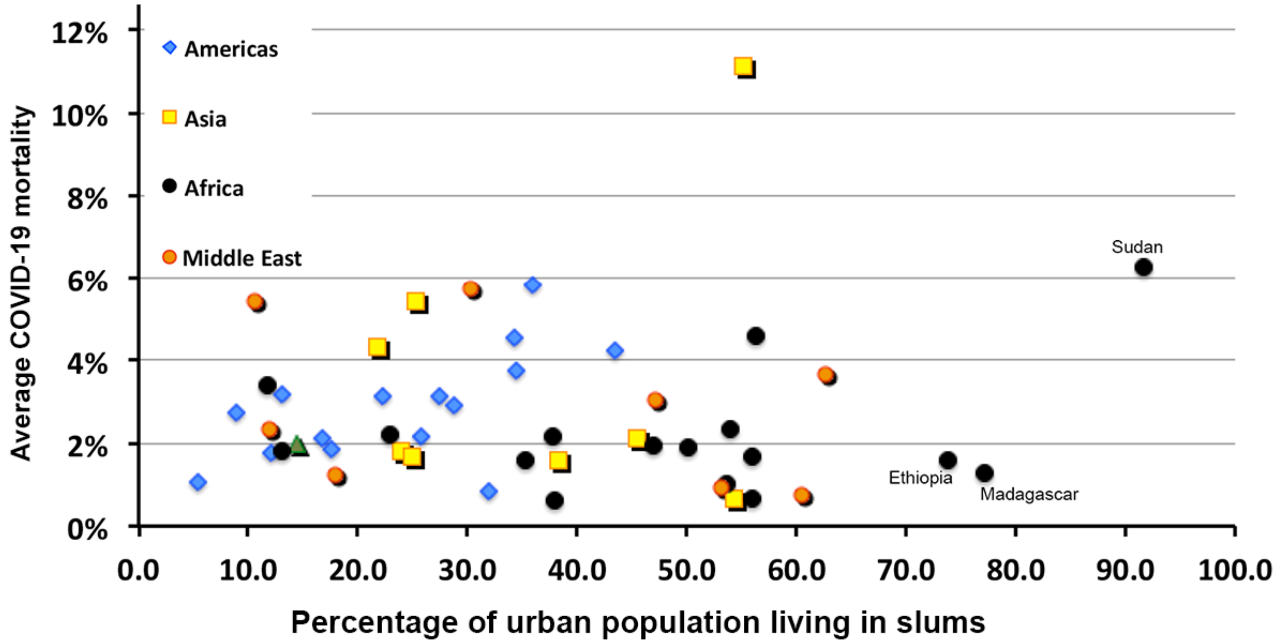


Figure 18. Correlation of COVID-19 mortality with the percentage of the urban population living in slums. The 3 outlying nations are identified.



Discussion

Although this study covering statistics from countries with approximately 70% of the world's population confirms the early clinical observation that infection with SARS-CoV-2 presents an increased risk to persons over the age of 65 years, it does not support the suggestions offered by government agencies early in the pandemic that the risks are much greater for persons with certain common potential comorbidities. Many of the early deaths of older patients early in the pandemic occurred in circumstances that likely promoted rather than impeded contagion among persons already in a generally poor state of health, likely accompanied by compromised immune functions.

Reference [7] and the analysis of Koff and Williams [16] provide plausible explanations for these findings. Namely, the virulence of COVID-19 in older people is strongly driven by the decrease in adaptive and innate immune responses with aging. Koff and Williams recommend that more longitudinal studies be performed in aging populations, including assessing the potential of a decrease in the efficacy of vaccines as being "critical to the future of global health."

Many persons who object to strict measures to prevent the spread of SARS-CoV-2 commonly claim that COVID-19 is similar to influenza, is only slightly more lethal, and should be treated in the same manner as influenza as a matter of public policy. In fact, comparing the severity of medical outcomes of COVID-19 with those caused by influenza strains and their resulting pneumonias displays dramatic differences. Promulgating the idea that COVID-19 is a "flu-like disease" spreads gross misinformation, to the detriment of public health worldwide.

A broader comparative assessment of SARS-CoV-2 and influenza strains against an overall measure of immune system responsiveness to infection would require a global database of an appropriate metric. One potential candidate is the "Wellness Index" proposed by J Han [17]; however, that metric would require genetic sequencing of large, representative samples of individuals over a broad range of countries. Consequently, at present, the possibility that such a database of immune system readiness will be generated seems highly doubtful.

Governmental actions can reduce the consequences of SARS-CoV-2 infection. Comparing the cases of Germany and Italy may be instructive in this regard. By mid-October 2020, Italy had 150% of the numbers of confirmed cases of COVID-19 in Germany [10]. However, the case fatality rate in Italy was roughly triple that in Germany. In early 2020, Germany had established an extensive network of triage and early treatment centers outside of hospitals. Germany also moved quickly to secure adequate supplies of personal protective equipment [18]. Hence, infected patients were identified early in the course of the disease and were treated in a manner that did not overwhelm the central intensive care facilities in hospitals, as happened in the Italian region of Lombardy.

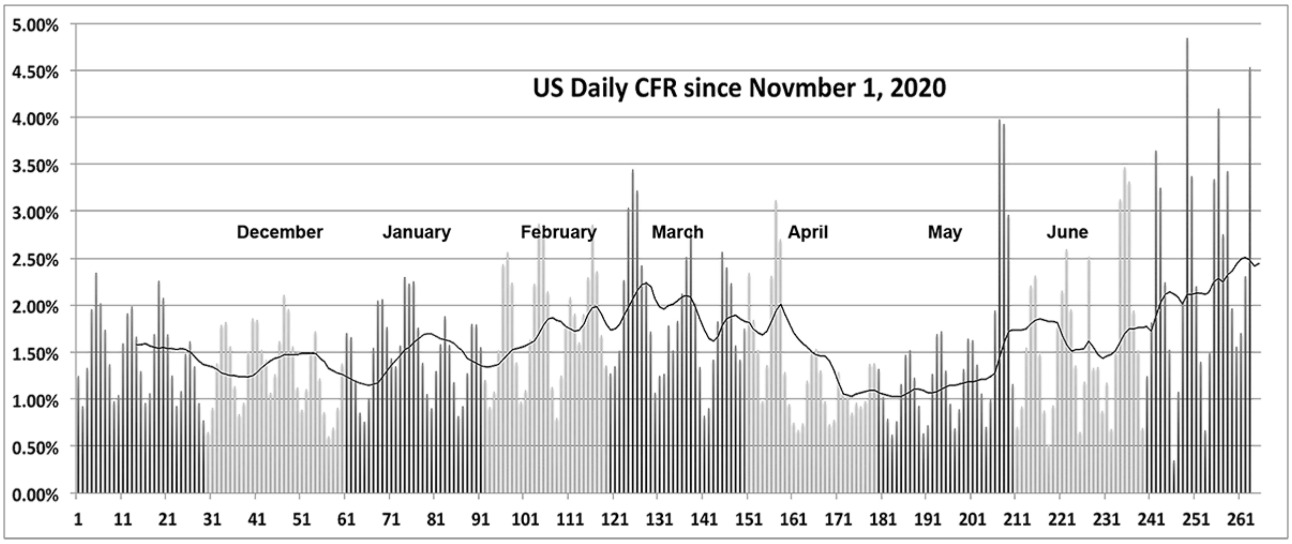
A similar lesson may come from comparing the experience in the United States in California and New York through the fall of 2020. The early lockdown in California more than doubled the duration of the first wave of infections compared with New York, leading to 60% more cases in California; however, the death rate in California was half that in the State of New York, where medical resources were badly stressed [10].

At the data cutoff date of this study, authoritative statistics on a worldwide, country-to-country basis were not publicly available to evaluate the effectiveness of either prevention or treatment modalities. However, clinical trials of multiple vaccines had been completed with highly promising results. Also unavailable over the full range of those countries included in this analysis are the full range of statistics related to COVID-19 disaggregated with respect to sex. When and if such data become available, expanding the analysis with respect to sex-based differences in testing, contagion, and mortality would prove useful.

The rollout of large-scale vaccination programs during a time when the vaccines are in short supply necessitates schemes for prioritizing recipients. If probability of severe illness is a primary consideration, then the early guess about the risks connected with potential comorbidities should be replaced with data such as those presented here along with detailed clinical evaluations accumulated throughout 2020.

A word of caution: Data used in this study were accumulated before the variants of concern of SARS-CoV-2, B.1.1.7, B.1.351, P.1 and B.1.617 began to propagate. Initial evidence suggests that these new strains are somewhat more virulent than the original strain. Examining the national CFR averaged over the duration of the pandemic during early 2021 shows a troubling slight but statistically significant increase in several countries, including the United States. Indeed, based on [10], over the period from November 1, 2020, to June 18, 2021, the apparent case fatality rate in the United States looks significantly higher (Figure 19) than that before the appearance of the B.1.1.7 and B.1.617 strains. Similar behavior is observed in the data from Germany and Canada.

Figure 19. The apparent daily case fatality rate in the United States, showing a disturbing increasing trend after the appearance of the B.1.1.7 and B.1.617 strains. CFR: case fatality rate.



Admittedly, these recent data are much noisier than earlier data through all of 2020 due to the marked decrease in the daily reports of the number of new cases and deaths. Despite the reduced statistical significance, the trend is troubling. It is too soon to judge whether the increase is a reflection of increased virulence in variants of SARS-CoV-2, whether it is an indication of increased susceptibility and physical and psychological stress on so-called essential workers, or whether it is a result of some form of COVID-19–related weariness among large portions of national populations. Differences in virulence of the several variant strains now circulating will complicate the interpretation of national data collected in 2021.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Regional variation of COVID-19 case fatality rate correlations.

[DOCX File , 20 KB - xmed_v2i3e28843_app1.docx]

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Abbreviations

CDC: US Centers for Disease Control and Prevention
DM: diabetes mellitus
GDP-PPP: gross domestic product–purchasing power parity
UHC: Universal Health Coverage
WHO: World Health Organization

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Original Paper

Impact of the COVID-19 Pandemic on the Mental Health of College Students in India: Cross-sectional Web-Based Study

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Abstract

Background: The COVID-19 pandemic has created a mental health crisis among college students in India due to lockdown restrictions, overwhelming numbers of COVID-19 cases, financial difficulty, etc. This mental health crisis has led to high degrees of fear, anxiety, and depression among college students.

Objective: The aim of this study is to investigate symptoms of fear, depression, and anxiety due to the COVID-19 pandemic among college students in India.

Methods: This cross-sectional web-based study was conducted using a Google Forms questionnaire. The Google Form included a sociodemographic questionnaire and psychometric scales evaluating the psychological and behavioral impacts of the COVID-19 pandemic. Thus, both qualitative and quantitative analyses were performed in the study.

Results: A total of 324 college students participated in this study, of whom 180 (55.6%) were male and 144 (44.4%) were female. After assessment of the psychometric scales, it was found that of the 324 students, 223 (68.8%) had high fear of COVID-19, 93 (28.7%) had moderate to severe depression, and 167 (51.5%) had mild to severe anxiety. Among the identified risk factors, having a family member who was infected with COVID-19 was significantly associated with anxiety and depression, with P values of .02 and .001, respectively. In addition, the correlations of the Fear of COVID-19 Scale with the Generalized Anxiety Disorder-7 scale and the Patient Health Questionnaire-9 were found to be 0.492 and 0.474, respectively.

Conclusions: This research concludes that there is a very high fear of COVID-19 among students, along with anxiety and depression symptoms. This study also concludes that the Fear of COVID-19 Scale has a moderate positive correlation with the anxiety and depression scales, respectively.

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KEYWORDS

anxiety; COVID-19; depression; fear; FCV-19S; GAD-7; mental health; pandemic; PHQ-9; students

Introduction

Communicable diseases such as herpes and legionnaires disease in the 1970s, HIV, Ebola, severe acute respiratory syndrome (SARS), and currently, COVID-19, continue to be devastating for global health, creating increasing pressure on people worldwide. The COVID-19 pandemic has kindled a 21st century "viral scare," following the "microbe panic" of the 20th century. Public health acts such as quarantine, physical distancing, wearing of face masks in public places, and hand hygiene are being executed globally to reduce the spread of infection. Although these measures are efficient to mitigate the pandemic, they may be detrimental to people's mental health [1].

The transmission of COVID-19 cases in India started to upsurge in the second week of March 2020. Therefore, to prevent community spread of the infection, as in other countries, the Government of India announced a complete lockdown from March 25, 2020, restricting the movement of the entire population of 1.38 billion people in India; this lockdown was initially intended to last 21 days but was extended to May 31, 2020, with conditional relaxation from May 3, 2020 [2]. During this period, all academic institutes were completely closed, and from December, all schools and universities were slowly reopened to resume a normal mode of teaching.

University students, compared to the general public, have been found to be more susceptible to the adverse effects of the quarantine [3]. Mental health disorders are always a topic of concern among youth, and their incidence has been increasing significantly worldwide. According to a World Health Organization report published in 2008, 1 in every 5 adults had experienced mental health disorders in the past year [4]. However, the COVID-19 pandemic triggered an even more rapid upsurge in mental disorders among adults.

An article published in *The Lancet* in February 2020 [5] showed frightening outcomes for people's mental health even after a quarantine of fewer than 9 days, and these effects could last for up to three years. The very long period of social isolation experienced by students in India during this new epidemic undoubtedly signifies danger, and during this time, the mental health of the students may be affected [6].

Recent studies showed that feelings of anxiety and depressive symptoms, distress, and sleep problems are typical signs of the COVID-19 pandemic. For example, a study conducted by Zhang et al [7] found that 38% of the Chinese population experienced some level of anxiety during the first wave of COVID-19, of whom 16% had severe anxiety; moreover, 49% of the population had depression symptoms, and 14% had severe depression symptoms [7]. Similarly, Wang et al [8] found moderate to severe anxiety, depression, and stress among the Chinese population. Important reasons for these increases in anxiety and depression include the fear of COVID-19 and, more specifically, the fear of becoming infected, along with the loneliness caused by social isolation [6,9]. These findings suggest a negative impact of the COVID-19 pandemic on people's mental health; therefore, it is urgent to study the scope and source of this impact.

Therefore, the primary objective of this study was to understand the impact of the COVID-19 pandemic on Indian students' mental health, as in, fear of COVID-19, anxiety, and depression, and to identify risk factors that amplify the magnitude of the psychological effects of COVID-19. The secondary objective of the study was to examine the concurrent validity of the Fear of COVID-19 Scale (FCV-19S) with the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 scale (GAD-7), respectively.

Methods

Study Design and Study Period

The cross-sectional web-based observational study was conducted between November 2020 and February 2021, during which the data collection period was from mid-November 2020 to mid-December 2020. The survey questions and scales were selected based on the available literature, the authors' knowledge, and the knowledge and experiences of professors and clinicians about the pandemic and its psychological impact. The reporting of the study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [10,11].

Study Site and Population

For this study, we selected students at the Mallige College of Pharmacy in Bangalore, India, who had access to the internet and used social media.

Measures

For this study, a specialized web-based form was developed using Google Forms. The form contained two sections, namely, a sociodemographic section and a psychometric scale section; the latter assessed the psychological and behavioral impacts of the COVID-19 pandemic. The scales are as follows:

Fear of COVID-19: the FCV-19S

This unidimensional, reliable, and valid self-report scale was recently developed to understand the fear of COVID-19 caused by this pandemic. This scale consists of 7 items that attempt to measure the fear of COVID-19. The responses are recorded on 5-point Likert scales with points ranging from 1 to 5. The higher the score, the greater the fear of COVID-19 among the participants. The initial development of the scale showed robust internal reliability, with a Cronbach alpha of .88 among the Iranian population [12]. A study conducted by Chung-Ying Lin et al [13] to measure invariance issues in the FCV-19S across many countries found that it is a good psychometric instrument to access the fear of COVID-19 [13]. The cutoff scores for this scale are shown in Table 1 [1,14]. In this study, we used the English version of the FCV-19S.

Table 1. The score ranges used to evaluate the severity of symptoms of the study participants based on the cutoff scores of the psychometric scales.

Scale	Severity of symptoms (score range)						
	Low fear	High fear	Minimal	Mild	Moderate	Moderately severe	Severe
FCV-19S[a]	0-18	19-35	N/A[b]	N/A	N/A	N/A	N/A
PHQ-9[c]	N/A	N/A	0-4	5-9	10-14	15-19	20-27
GAD-7[d]	N/A	N/A	0-4	5-9	10-14	N/A	15-21

[a]FCV-19S: Fear of COVID-19 Scale.

[b]N/A: not applicable.

[c]PHQ-9: Patient Health Questionnaire-9.

[d]GAD-7: Generalized Anxiety Disorder-7 Scale.

Anxiety: the GAD-7

This self-report scale was developed for initially diagnosing generalized anxiety disorder (GAD). The scale consists of 7 items, in which the participant's responses are recorded on 4-point Likert scales ranging from 0-3. The score of the participant ranges from 0 to 21. The threshold score of 10 has 89% sensitivity and 82% specificity for GAD. The cutoff scores for this scale based on the severity of symptoms are shown in Table 1. In this study, we applied the English version of the GAD-7 [15].

Depression: the PHQ-9

This 9-item self-report scale is used to diagnose major depression and subthreshold depression. The participant's responses are recorded on 4-point Likert scales from 0 to 3. The total score ranges from 0 to 27, and it helps interpret the severity of depression. A score ≥10 signifies moderate to severe depression with significant clinical concern, whereas a score <10 signifies minimal to mild depression. The cutoff scores for this scale based on the severity of symptoms are shown in Table 1. In this study, we applied the English for India version of the PHQ-9 [15].

Sample Size

The survey study was completed using the Raosoft sample size calculator to capture the appropriate sample size [16]. A minimum of 306 samples was required for a 95% confidence interval and a 5% margin of error for the population distribution of 1500 students at 50% response distribution. Thus, a total of 324 students participated in this web-based study.

Inclusion Criteria

All students studying for diplomas or degrees, both undergraduate and postgraduate, were included in the study.

Distribution of the Questionnaire

The Google form was distributed to the students through various social media platforms, such as WhatsApp, Facebook, Messenger, and Telegram. The students were invited to participate in the survey by filling in the Google form without time constraints. Furthermore, the Google feature that limits each respondent to one submission eliminated multiple responses.

Ethical Considerations

The study was approved by the research review board (Approval MCP/RRB/003/20-21) of the Mallige College of Pharmacy before starting the study. The purpose of the study was explained to the participating students, and they were requested to submit their voluntary consent before participation. All the procedures performed in this study were in adherence to the Declaration of Helsinki of 1964 and its later amendment [17]. Furthermore, this study strictly adhered to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines [18].

Statistical Analysis

All the data were recorded in Excel (Microsoft Corporation) and assessed for accuracy [19]. The statistical analysis was completed using SPSS, version 25 (IBM Corporation) [20]. Descriptive statistics were obtained to understand the characteristics of the data. Statistically, to understand the concurrent validity of the FCV-19S with the PHQ-9 and GAD-7, the Pearson correlation was used. Furthermore, to understand the impact of the students' sociodemographic characteristics on these scales, multiple linear regression was used.

Results

Sociodemographic Characteristics

The sociodemographic characteristics of the participants are summarized in Table 2. Among the 324 respondents, slightly more male students (180, 55.6%) participated than female students (144, 44.4%). Of the 324 participants, most were in the age group of 18-21 years (190, 58.6%), and 256 (79%) were enrolled in bachelor's degree programs. In addition, 37/324 participants (11.4%) reported that one of their family members had become infected with COVID-19, which seems to a be very low percentage compared with the recent spread of COVID-19 among the urban population.

Table 2. Sociodemographic characteristics of the study participants (N=324).

Sociodemographic characteristic	Value, n (%)
Age (years)	
18-21	190 (58.6)
22-25	116 (35.8)
26-29	8 (2.5)
≥30	10 (3.1)
Gender	
Male	180 (55.6)
Female	144 (44.4)
Degree enrolled	
Diploma	11 (3.4)
Bachelor's degree	256 (79)
Master's degree	53 (16.4)
PhD	4 (1.2)
Family member infected with COVID-19	
Yes	37 (11.4)
No	287 (88.6)

Psychometric Scales

Descriptive statistics were studied for all three psychometric scales to understand the impact of the COVID-19 pandemic on the mental health of the students who participated in this study. The median scores of the FCV-19S, PHQ-9, and GAD-7 were found to be 22 (range 17-28), 5.5 (range 2-10.75), and 5 (range 0-9), respectively. The magnitudes of COVID-19 fear, symptoms of depression, and anxiety were graded according to their cutoff scores, as shown in Table 3. This study shows an alarming picture of the impact of the COVID-19 pandemic on the mental health of students, with 223 of 324 students (68.8%) having high fear of COVID-19, 93 students (28.7%) having moderate to severe depression, and 167 students (51.5%) having mild to severe GAD.

Table 3. Categorization of the severity of fear of COVID-19, anxiety, and depression among the participating students according to their scale cutoff scores (N=324).

Symptoms and severity	Value, n (%)
Fear of COVID-19	
High	223 (68.8)
Low	101 (31.2)
Depression	
Minimal	142 (43.8)
Mild	89 (27.5)
Moderate	46 (14.2)
Moderately severe	33 (10.2)
Severe	14 (4.3)
Anxiety	
Minimal	157 (48.5)
Mild	90 (27.8)
Moderate	38 (11.7)
Severe	39 (12)

Impact of Risk Factors on the Psychometric Scales

As revealed in Table 4, after multiple linear regression, we found no impact of any of the identified risk factors on the FCV-19S score. However, the table shows that having a family member infected with COVID-19 is significantly associated with GAD-7 and PHQ-9 scores, respectively. If any family member of a college student became infected with COVID-19, their GAD-7 and PHQ-9 scores increased by 2.4 and 3.6, respectively.

Table 4. Impact of sociodemographic characteristics on the psychometric scale scores. Multiple linear regression is statistically significant at *P*<.05.

Sociodemographic characteristics	FCV-19S[a,b]		PHQ-9[c,d]		GAD-7[e,f]	
	B (95% CI)	*P* value	B (95% CI)	*P* value	B (95% CI)	*P* value
Constant	23.464 (22.229-24.699)	<.001	6.5 (5.372 to 7.628)	<.001	5.54 (4.454 to 6.626)	<.001
Age[g] (years)						
22-25	–1.665 (–3.392 to 0.063)	.06	–0.343 (–1.921 to 1.235)	.67	–0.087 (–1.606 to 1.432)	.91
26-29	–4.435 (–9.787 to 0.916)	.10	–0.373 (–5.261 to 4.516)	.88	0.394 (–4.311 to 5.099)	.87
≥30	1.3 (–4.004 to 6.605)	.63	–2.739 (–7.584 to 2.107)	.27	0.618 (–4.046 to 5.282)	.80
Sex[h]						
Female	0.258 (–1.251 to 1.767)	.74	1.145 (–0.234 to 2.523)	.10	0.806 (–0.521 to 2.133)	.23
Degree enrolled[i]						
Master's	–1.288 (–3.685 to 1.109)	.29	–1.071 (–3.26 to 1.119)	.34	–0.364 (–2.472 to 1.743)	.73
PhD	–7.294 (–15.299 to 0.711)	.07	–4.098 (–11.41 to 3.215)	.27	–5.123 (–12.162 to 1.915)	.15
Diploma	–1.818 (–5.930 to 2.294)	.385	–2.548 (–6.304 to 1.208)	.18	–2.181 (–5.796 to 1.435)	.24
Family member infected with COVID-19[j]						
Yes	–0.659 (–3.016 to 1.699)	.58	3.689 (1.536 to 5.843)	.001	2.474 (0.401-4.546)	.02

[a]FCV-19S: Fear of COVID-19 Scale.
[b]R^2=0.050.
[c]PHQ-9: Patient Health Questionnaire-9.
[d]R^2=0.065.
[e]GAD-7: Generalized Anxiety Disorder-7 Scale.
[f]R^2=0.033.
[g]Reference category for the independent variable of age: 18-21 years.
[h]Reference category for the independent variable of sex: male.
[i]Reference category for the independent variable of degree enrolled: bachelor's degree.
[j]Reference category for the independent variable of family member infected with COVID-19: no.

Participants' Responses to the Psychometric Scales

FCV-19S Responses

In the survey, 207/324 respondents (63.7%) were found to be afraid of COVID-19. Watching COVID-19 stories and reports on social media seemed to have a major effect on the mental health of 183/324 students (56.3%), making them nervous or anxious. Among the 324 respondents, 71 (21.8%) stated that when they thought about COVID-19, they could not sleep properly due to fear of the disease, and 176 (57.2%) said they were uneasy when thinking about it. On the other hand, 128/324 students (39.3%) said that their hands did not become clammy and their heart did not race when thinking of COVID-19.

PHQ-9 Responses

Of the 324 students, 202 (62.2%) said they had no motivation or enjoyment when participating in activities, and 160 students (49.3%) reported feeling down, sad, or hopeless. Moreover, 162/324 respondents (50%) appeared to have difficulty falling asleep, slept for a long time, or slept too much, and they found it difficult to focus on activities such as reading or watching television. Of the 324 respondents, 92 (28.4%) had thoughts of being "better off dead" or hurting themselves.

GAD-7 Responses

Of the 324 students, 134 (41.3%) felt that they had become restless and irritable, and 169 students (52%) were afraid that something awful would happen to them for several days; 137 students (42.2%) agreed that they felt anxious, whereas 194 students (59.8%) worried too much.

Concurrent Validation of the FCV-19S

The FCV-19S was significantly associated with the GAD-7 and PHQ-9, respectively. The Pearson correlations of the FCV-19S with the PHQ-9 and GAD-7 were found to be r=0.474 and r=0.492, respectively (both *P*<.001; correlation was statistically significant at a *P* value of <.01 [2-tailed]). This moderately positive correlation of the FCV-19S scale with the PHQ-9 scale and GAD-7 scale helps to predict that an increase in fear of COVID-19 will ultimately increase the anxiety and depressive symptoms in students [21]. Therefore, the FCV-19S can give an overall idea of the levels of fear, depression, and anxiety among students caused by the COVID-19 pandemic.

Discussion

Principal Findings

This study aims to understand the impact of the COVID-19 pandemic on the mental health of students and to identify the risk factors that magnify mental health disorders in the current situation. This survey revealed a high prevalence of self-reported anxiety, depression, and fear of COVID-19 among college students in India. Among the risk factors, a family member contracting COVID-19 significantly increased the students' levels of anxiety and depression. This study also found a moderate positive correlation of the FCV-19S with the GAD-7 and PHQ-9, respectively.

In this study, we found that 223 of 324 students (68.7%) had high fear of COVID-19, which is almost double the proportion found by Parlapani et al [14] among general people in Greece (ie, 35.7%) but was consistent with that in a study by Gritsenko et al [22] that was conducted among Russian and Belarusian university students. This drastic difference in the fear of COVID-19 between students in India and the general public in Greece may be due to differences in the region, population category, and upsurge of COVID-19 cases, along with the government's effective measures to address mental health disorders among its residents. A study conducted in India by Sathe et al [23] reported that a moderate to severe level of fear of COVID-19 is prevalent in 49% of the general population, and Doshi et al [24] found that 48% of the general public in India indicated being afraid of COVID-19, which is a lower percentage compared to that of the college students in this study. Elemo et al [25] found average scores of 19.99 (SD 6.6) on the FCV-19S among international students in Turkey, which indicates a higher degree of anxiety due to COVID-19 [1]. These studies reveal a higher degree of fear of COVID-19 among students than in the general public in many countries.

The 2016 National Mental Health Survey reported a 2.7% prevalence of depressive disorder and a 3.1% prevalence of anxiety in the Indian population; however, in this study, we found alarming upsurges in the levels of anxiety and depression, mainly due to the COVID-19 pandemic [26]. It was found that 167 of 324 students (51.5%) had mild to severe anxiety symptoms, and 93 students (28.7%) had moderate to severe depressive symptoms. The results of this study were consistent with those of a study by Rehman et al [27], which was conducted during the first wave of the COVID-19 pandemic among students in India; however, the level of anxiety found in this study was lower than that in a study of college students in the United States, where 71% believed that their anxiety was increased by the COVID-19 outbreak [28]. A study conducted in Malaysia among university students found that anxiety was prevalent in 29% of the students, which is a lower percentage compared to the findings of this study [29]. When comparing our results with those of a survey conducted among university students in Bangladesh [30], the levels of anxiety were similar, but the level of depression was higher in the other study.

In contrast, a study conducted by Shah et al [31] among the global population to understand the impact of the COVID-19 pandemic on mental health found that 47% of students had depression due to the COVID-19 pandemic, but they had a similar level of anxiety compared to that in this study. A survey conducted by Aftab et al [32] among undergraduate and postgraduate students studying medicine worldwide found a prevalence of depression of 41.5% in these students, which is dramatically higher than that found this study; however, anxiety among those students was less prevalent than among those in this study. These studies reveal a higher degree of anxiety among college students during the COVID-19 outbreak, and web-based learning is an important cause of increased anxiety and depression [33-35].

Multiple linear regression showed that among the identified risk factors, infection of a family member with COVID-19 had a significant impact on anxiety and depression among students; however, there was no impact of any identified risk factor on the fear of COVID-19. These findings are consistent with studies conducted in India to assess fear of COVID-19, anxiety, and depression levels, as the same guidelines were implemented for the COVID-19 pandemic across the country [24,27]. Compared with international students, the findings of this study were consistent with the results of Islam et al [3], who conducted a study among university students in Bangladesh and reported no impact of age or gender on anxiety or depression levels, respectively; however, a study conducted among university students in France [30] reported an effect of gender on anxiety and depression. The multinational study conducted by Pramukti et al [36] among university students to understand the impact of the COVID-19 pandemic on anxiety and suicidal thoughts found a significant impact of gender on symptoms of anxiety, with a P value <.001; this is not consistent with the findings of this study [36]. However, a study conducted among university students in Malaysia [32] found no impact of age or gender on anxiety symptoms, which is similar to the findings of this study. The review of these studies reveals that the effects of sociodemographic factors on anxiety and depression differ according to the country and region.

The FCV-19S is a recently developed tool to understand the fear caused by the COVID-19 pandemic among the public. Various versions of this scale have been validated with other established psychometric scales used to understand anxiety, depression, stress, etc. This study also validated the English version of the FCV-19S with the GAD-7 and PHQ-9, respectively. The findings of this study are consistent with the concurrent validity of the Greek version of the FCV-19S with the PHQ-9, which reports a moderate positive correlation; however, our findings are inconsistent with the concurrent validity of the Greek version of the FCV-19S with the GAD-7 [21,37]. The Spanish version of the FCV-19S scale showed a weak positive correlation with the GAD-7 and PHQ-9 among males, whereas among females, it showed a moderate positive association with GAD-7 and a weak positive correlation with the PHQ-9 [38]. The validity of the Japanese version of the

FCV-19S with the GAD-7 was consistent with the findings of this study [39]. These studies reveal that the strength of the association differs when a different version of the FCV-19S is used.

Conclusion

This research indicates that fear of COVID-19 is very high among Indian students, along with anxiety and depression. Furthermore, among the identified risk factors, having a family member infected by COVID-19 significantly impacted anxiety and depression among students. This study also concludes that the FCV-19S has a moderate positive correlation with the GAD-7 and PHQ-9, respectively.

To mitigate the fear, anxiety, and depression caused by the COVID-19 pandemic, students should be encouraged to pursue healthier lifestyles during the pandemic. We also recommend developing and implementing various policies at the government level to reduce the effects of the COVID-19 pandemic on mental health.

Study Limitations

Some constraints are included in this report. First, there is an unequal distribution of respondents in this sample, and because it is a cross-sectional study, casual intervention cannot be performed. Second, there are very few diploma students; therefore, the survey results cannot be generalized to the whole student population. Third, the questionnaire was self-administered, so it is difficult to understand whether it was reasonably completed (ie, social desirability bias and semblance). Fourth, because the survey was internet-based, the study did not actively collect the responses of learners who are not linked to social media. Finally, this study adopted a cross-sectional study design; therefore, cause and effect relationships cannot be established.

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Conflicts of Interest

None declared.

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
FCV-19S: Fear of COVID-19 Scale
GAD: generalized anxiety disorder
GAD-7: Generalized Anxiety Disorder-7 scale
PHQ-9: Patient Health Questionnaire-9
SARS: severe acute respiratory syndrome
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Original Paper

A Full-Scale Agent-Based Model to Hypothetically Explore the Impact of Lockdown, Social Distancing, and Vaccination During the COVID-19 Pandemic in Lombardy, Italy: Model Development

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Abstract

Background: The COVID-19 outbreak, an event of global concern, has provided scientists the opportunity to use mathematical modeling to run simulations and test theories about the pandemic.

Objective: The aim of this study was to propose a full-scale individual-based model of the COVID-19 outbreak in Lombardy, Italy, to test various scenarios pertaining to the pandemic and achieve novel performance metrics.

Methods: The model was designed to simulate all 10 million inhabitants of Lombardy person by person via a simple agent-based approach using a commercial computer. In order to obtain performance data, a collision detection model was developed to enable cluster nodes in small cells that can be processed fully in parallel. Within this collision detection model, an epidemic model based mostly on experimental findings about COVID-19 was developed.

Results: The model was used to explain the behavior of the COVID-19 outbreak in Lombardy. Different parameters were used to simulate various scenarios relating to social distancing and lockdown. According to the model, these simple actions were enough to control the virus. The model also explained the decline in cases in the spring and simulated a hypothetical vaccination scenario, confirming, for example, the herd immunity threshold computed in previous works.

Conclusions: The model made it possible to test the impact of people's daily actions (eg, maintaining social distance) on the epidemic and to investigate interactions among agents within a social network. It also provided insight on the impact of a hypothetical vaccine.

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KEYWORDS

epidemiology; computational; model; COVID-19; modeling; outbreak; virus; infectious disease; simulation; impact; vaccine; agent-based model

Introduction

The first case of COVID-19 was detected in China [1], but one of the most serious outbreaks occurred in Italy at the end of January 2020 [2]. This epidemic witnessed a change in risk management: the use of mathematical modeling [3]. As mathematical modeling is complex [4], there are many approaches to solving these problems. One such approach is agent-based modeling [5], which in epidemiology has been used widely in the past. However, due to its computational limitations, approaches based on differential equations like SIR (susceptible-infected-recovered) models have often been preferred [6]. In particular, SIR models are typically mediated by ordinary differential equations (ODEs) [7] and have been used to model general populations worldwide [8,9], as well as the entire Italian population in particular [10]. However, ODE models often require many free parameters to be computed, and they cannot usually be derived directly from experimental data because these parameters are abstract quantities. Hence, the most common approach to ODE models in epidemiology is to fit all the free abstract parameters to experimental time series that will be explained by the model. However, it is difficult to test and quantify alternative scenarios with this approach since the parameters are very abstract.

To solve these problems, the latest advances in computer science and engineering, as well as the COVID-19 outbreak itself, have led to the use of agent-based models for simulating small community epidemic behaviors since in agent-scale simulations. The parameters, all of which involve the individual, are usually experimentally constrained and determined. Previous work by Gharakhanlou and Hooshangi [11] explored the COVID-19 outbreak using an agent-based model of approximately 750,000 inhabitants in the city of Urmia, Iran, with the movement of agents approximated by their location. Similarly, Son et al [12] used a transmission model with a subsampled population of 9000 people living in Daegu, South Korea. There are small-scale models as well, as shown by Cuevas [13]. Also worthy of mention is the model developed by the University of Palermo [14], which was based on the work of Muggeo [15].

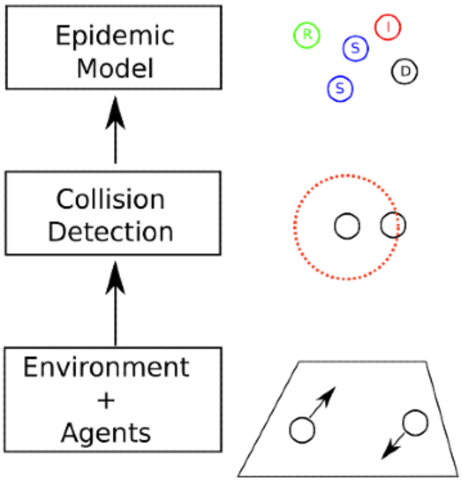
The aim of this study was to present a qualitative, full-scale agent-based model with the ability to reproduce the COVID-19 dynamics of Lombardy, Italy, modeling its outbreak and decline in cases, including as much real and open-access data as possible. Lombardy's population of 10.06 million makes this model very large scale compared to previous works. Secondarily, the study aimed to investigate several alternative scenarios in order to assess their impact at the time. Finally, a social interaction model, used in epidemiological simulations, was employed, per graph theory [16], to study the agents' interactions as a social network [17]. The results were used to draw several conclusions about the impact of people's habits during the COVID-19 outbreak.

Methods

The Model Structure

The key objective was to create a 3-layer model (Figure 1). The first layer was an agent-based particle model for Lombardy. Every agent is an inhabitant of the region, making this model a full-scale model of Lombardy. Therefore, we have 10.06 million agents who move according to the random walk theory [18]. The random walk behavior must be intended as an approximation of the actual motion of people during the day; this approximation was introduced to reduce the amount of information required to run the model and is widely used in many fields of science (eg, ideal gas theory) [18]. The large number of agents simulated is part of the novelty of this study because (to the best of the author's knowledge) it is the first to attempt to simulate such a large population individual by individual for this purpose.

Figure 1. The 3-layer structure of the model. The first layer, environment and agents, represents the motion of the inhabitants. The second layer represents social interaction between people in terms of collision detection. The third layer represents the virus dynamic in terms of epidemic behavior. S: susceptible, I: infected, R: recovered, D: deceased.



A collision detection algorithm was built within the agent-based model to detect whether 2 particles have a distance less than a fixed value. However, the large scale reached by the model required an ad hoc algorithm for this purpose; this challenging problem was solved via a square cells algorithm that permits the code to run in parallel (thereby decreasing the computational complexity of the task).

An epidemic model was built within the collision detection model, that is, a susceptible-infected-recovered-deceased (SIRD) model [19]. The model was filled with many experimental findings on COVID-19, and some fitting parameters were tuned on experimental findings. The whole analysis used as much open-access research as possible; moreover, the entire project was fully open source and is available on GitHub [20].

The model comprised three different layers:

1. The environment and agents model allows for the use of real data in agent movement, creating the first difference between the proposed model and ODE-based models [6] since this kind of model often only uses a few equations to describe large populations, which makes it difficult to take into account ensemble observations on single agents. On the other hand, the proposed model is suitable for a large number of agents, differentiating from previous contributions in this field [11,12].
2. The collision detection model, via 2-km–sided square cells, allows the code to run in parallel, making it possible to compute the epidemic spread of a population of 10 million people agent by agent.
3. The agent-based epidemic model, based on the Markovian process [19], makes it possible to use the experimental probability of infection measured directly from experimental data. This allows the model to be suitable for evaluating alternative scenarios in contrast to ODE-based models [6], which usually must be tuned to fit the time series observed.

The Agents Model

The agents model simulates the behavior of each inhabitant of Lombardy using the approximation of random walks [18]. The displacement of the particles follows the density of inhabitants in Lombardy (ie, publicly available data). Even if more accurate data on people displacement and movement could be used, privacy concerns may not permit the open-source and open-access distribution of this data. Per the random walk approach, every particle moves with a random vector at every step. The model runs at 6 frames per day, which is a good frame rate considering that the scale time for epidemic phenomena is usually months; however, this can be improved as discussed in the Conclusions section. The random walk approach can appear unrealistic, but this hypothesis has been shown to be appropriate to model very large-scale systems (eg, gas thermodynamics [21]). In addition to random walks, a weak velocity field with a dependence of $1/r^2$ was added, where r is the distance between 2 particles, as in a gravitational field, in order to aggregate the particles. The drift speed of the particles is constant and selected with a Weibull distribution [22] with a scale parameter of 6 and a shape parameter of 1.5. The particles' speeds were adjusted through a multiplicative constant in order to make the average path length of a particle in a day about 43 km, as suggested in a report by UnipolSai Assicurazioni [23].

The Environment Model

The setting of the simulation is Lombardy, making the environment model a closed 2D box with a boundary shape following Lombardy's borders. In order to keep the particles inside the region, a bouncing condition was introduced at the border, so that a particle that tries to cross the border bounces backward. This condition is very popular in gas thermodynamics [18]. The initial conditions of the particles in terms of position are distributed following the actual density of the population of Lombardy, extracted from UnipolSai Assicurazioni [23] via image analysis [24]; this is then intended as an approximation of the real data.

Collision Detection

Starting with the assumption that the algorithm has been designed to run on a commercial computer in parallel (the one used in the study has AMD 3900X 12-cores and 64 GB of RAM) and within reasonable time (about 20 minutes of calculation for

14 days of simulation), the collision detection algorithm played a central role in the implementation of the algorithm. In order to find all points with a distance less than a constant in a set of N points, a complexity order of N^2 is generally needed. In our model $N \approx 10^7$, the complexity order was 10^{14}, which is a large number.

Next, Lombardy was subdivided into a grid, 20 km in dimension. Collision detection was applied to every cell of the grid, and every cell was assigned to a separate parallel job to run the computation in parallel through the cells. This multiscale processing allowed for the speeding up of the code, reducing the RAM used simultaneously in computation, which made possible a simulation with 10 million particles at the same time. This approach neglects all the connections across the borders of the cells, but this is beyond the aims of this study.

The creation of this algorithm was a challenging aspect of this study. The idea was to use matrix optimization in order to speed up the computation. The territory was subdivided into 20-km–long cells, and the cells in every frame were completely independent, with the supposition that, on average, every cell contains m people. In order to compute the distance between all nodes in the network, we had to compute the order of N^2 pairwise distances.

With this scheme, we had to only compute the order of m^2 distances for each block multiplied by the number of blocks (which is about N/m) that is an order of Nm. Considering m small in comparison with N, it can be said that the scheme has a complexity near the order of N (for large N and small m). However, determining in which cell a person is located was also challenging because of the large size of the population. For these reasons, a simple grid scheme was used to locate nodes inside the cells. We used the following idea—supposing a segment from 0 km to L_C=2 km with N_c=4 cells:

1. From 0 km to 0.5 km
2. From 0.5 km to 1 km
3. From 1 km to 1.5 km
4. From 1.5 km to 2 km

If, for example, the point p=0.6 km needed to be located, the formula used to calculate this would be $id_p = ceil(N_c p / L_c)$. The result is 2, indicating the second cell. Applying this formula for the x-axis and y-axis allows the algorithm to locate people in the cells. Although this algorithm may appear to be simple, it requires few calculations to be computed, which can make a substantial difference when a large number of agents is concerned.

The Epidemic Model

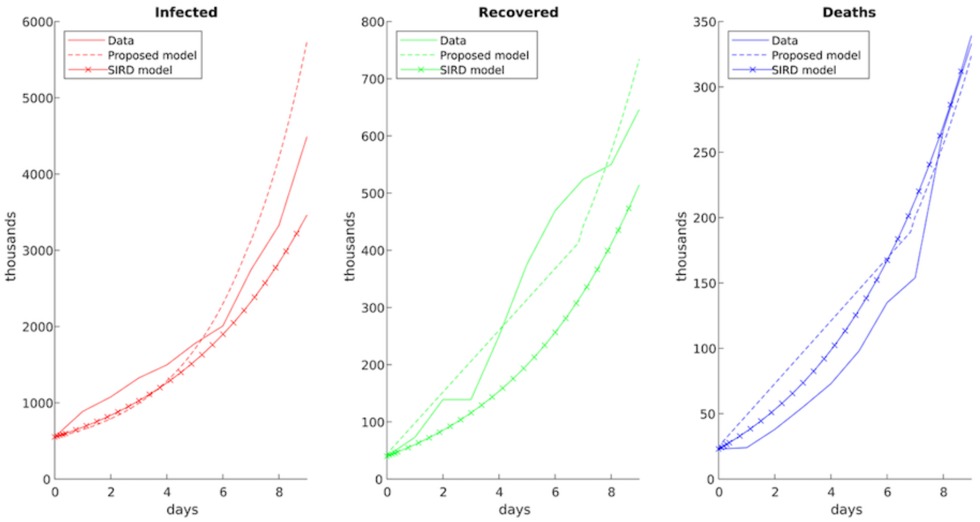
The epidemic model is an SIRD model [3]. Most of the models available up to now are called population models [25]. A population model is a model where every node is modeled by a set of differential equations; it models a subpopulation of a region. The number of people modeled by a single node can range from hundreds to millions. In our model, every node is a single person. The model is not an ODE model, but a stochastic agent-based model. Every node has four states:

1. Susceptible: a node that has not already contracted the disease. It can be become infected with a probability p_I for each contact with an infected node;
2. Infected: a node that is infected, which can then infect susceptible nodes. After E days, this node will change its state to recovered or to deceased, with a probability p_D to die and $1-p_D$ to recover;
3. Recovered: a node that has recovered from the disease and cannot contract it or infect susceptible nodes anymore;
4. Deceased: a node that has died and hence cannot infect other nodes.

Validation

The proposed model was compared with a classical SIRD model [26] fitted with a parameter exploration scheme on outbreak data (Figure 2). As seen in Figure 2, the results are comparable in terms of the rooted mean square error of the data: the SIRD model had an error of 150 for the infected, 71 for the recovered, and 18 for the deceased; and the proposed model exhibited an error of 535 for the infected, 58 for the recovered, and 34 for the deceased. This indicates that our model has comparable performance with the SIRD model (outperforming in the recovered), but it is not ODE mediated and is thus suitable for testing alternative scenarios. Moreover, in this paper, since most of the parameters are realistic, the model can be run for a general epidemic upon collecting the few parameters required (which in this case were all open access) and fitting the two parameters left. However, the model can be made more precise by adding additional realistic data, which most of the time are not fully open access; this, however, is out of the scope of this study.

Figure 2. Comparison between data on the outbreak, the proposed model, and a classical susceptible-infected-recovered-deceased (SIRD) model [26].



Results

All simulations are available in .avi format on GitHub [20], as well the MATLAB code, for reproducibility.

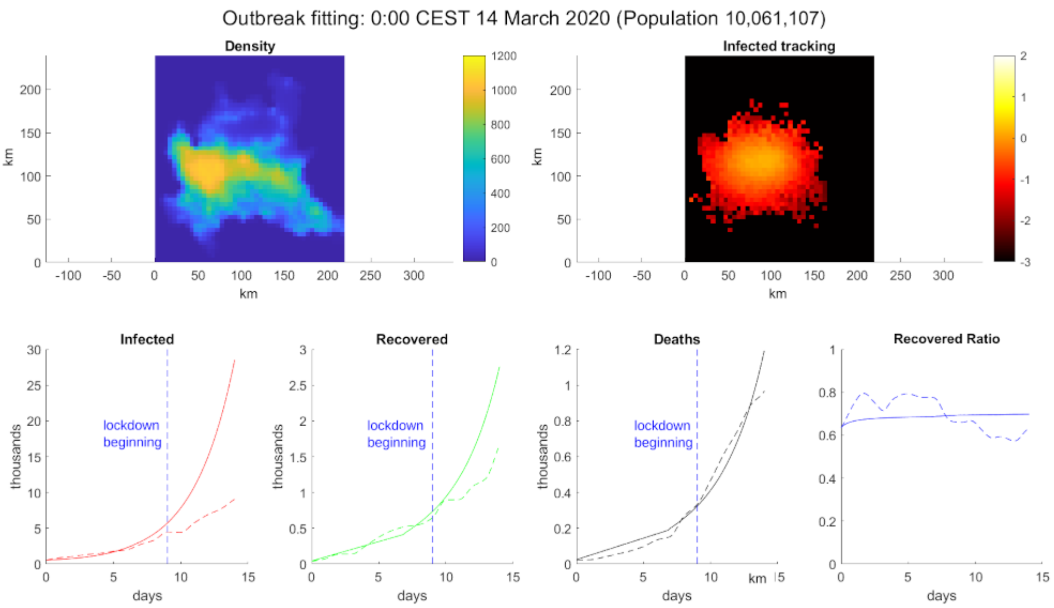
The Lombardy Outbreak

The first scenario was the Lombardy outbreak of March 2020 [2]. Our simulation began on February 29, 2020, and terminated on March 14, 2020. The main realistic parameters were p_I=1/40,500 (extracted from Bhatia and Klausner [27]) and p_D=0.3 (estimated from Worldometer [28], which has also been cited by Dhillon et al [29]).

The fitted parameters have a collision radius of 1 km. This can appear very large compared to the 1-m distance suggested by the World Health Organization [30]; however, when taken into account that there are 6 frames per day, then 1 km is the radius of the interaction of a person who remains in the same place for 4 hours and the duration of the disease (in days) E=7 (the Centers for Disease Control and Prevention suggests E<10 [31]).

The results of the simulations can be seen in Figure 3. The model was able to explain the experimental data until approximately March 9, 2020. On this day, the Decree of the President of the Council of Ministers (DPCM) implemented measures to contain the COVID-19 outbreak [32], which included the beginning of the lockdown in Italy. This discrepancy between the data and the model was the result of the collective effort of the Italian populace to protect itself against SARS-CoV-2. Therefore, the simulation serves to provide a warning about what could have happened.

Figure 3. COVID-19 outbreak simulation. Top-left: population density. Top-right: $\log_{10}$ of the infected percentage per cell. Bottom, from left to right: infected number, recovered number, deceased number, and recovered ratio (recovered/deaths). The solid line is the model simulation, the dotted line is extracted data from the Ministry of Health/Civil Protection Department [33] for Lombardy, and the vertical dotted blue line marks the date March 9, 2020 [32].



Impact of People's Habits

The second scenario was inspired by Chu et al [34], who showed that maintaining a 2-m distance between people halved the risk of contracting COVID-19. Thus, we aimed to simulate this kind of social distancing by halving p_I in the model. The results (Figure 4) showed that COVID-19 (in this scenario) was not contagious enough to spread as in the experimental data. This simulation demonstrated the striking role of a simple action like social distancing in fighting COVID-19 and highlighted the difference between a virus under control and a disease of epidemic proportions. This simple fact has already been observed in experimental findings in Germany [35], where a synthetic method was used to estimate the spread of the contagion without the use of masks.

We also performed a lockdown simulation, reducing the daily average kilometers traveled by a node from 43 km to 5 km and reducing the interaction distance from 1 km to 100 m. The results of this simulation can be seen in Figure 5. According to the model, these simple actions were enough to control the virus.

Figure 4. Social distancing simulation. Top-left: population density. Top-right: $\log_{10}$ of the infected percentage per cell. Bottom, from left to right: infected number, recovered number, deceased number, and recovered ratio (recovered/deaths). The solid line is the model simulation, the dotted line is extracted data from the Ministry of Health/Civil Protection Department [33] for Lombardy, and the vertical dotted blue line marks the date March 9, 2020 [32].

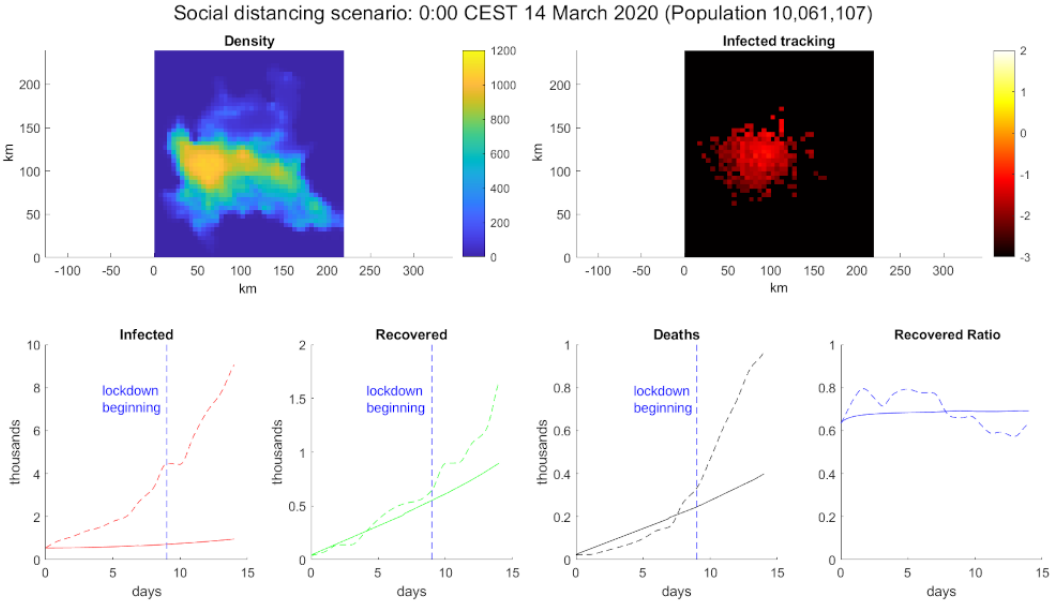
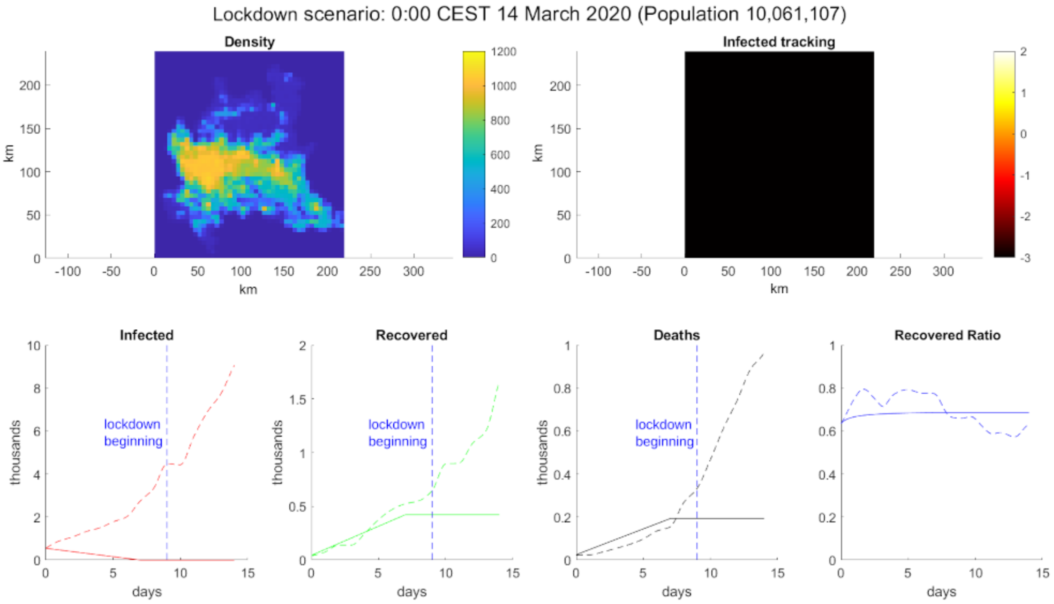


Figure 5. Lockdown simulation. Top-left: population density. Top-right: $\log_{10}$ of the infected percentage per cell. Bottom, from left to right: infected number, recovered number, deceased number, and recovered ratio (recovered/deaths). The solid line is the model simulation, the dotted line is extracted data from the Ministry of Health/Civil Protection Department [33] for Lombardy, and the vertical dotted blue line marks the date March 9, 2020 [32].



Network Topology

The impact of topology in an epidemic model is a popular topic [30,36] in the debate on social networks. Thus, we performed a test: 1000 particles were chosen and then tracked across all simulations to find the total number of connections (ie, contact between particles) made within the whole population. In graph theory, the number of connections of a node is called a degree [16]. This test allowed us to determine the degree distribution and the daily degree distribution (average degree per day) of this small group of people across time. However, only the final result is presented (the full simulation is available on GitHub [20]). The first scenario was the COVID-19 outbreak scenario (Figure 6).

It can be seen that the distribution has an evident left tail (in contrast with the right tail of the Barabási-Albert models [17]). This was probably due to the simulation time of 14 days (in contrast with human social networks, which usually take years to be built). The lockdown scenario was also interesting. In this scenario, we observed a decline in connectivity from thousands of average connections per day to hundreds (Figure 7). This shows the importance of lockdowns in COVID-19 containment.

Figure 6. COVID-19 outbreak simulation connectivity. Top-left: population density. Top-right: $\log_{10}$ of the group percentage per cell. Bottom-left: degree distribution of the test group. Bottom-right: daily degree distribution of the test group.

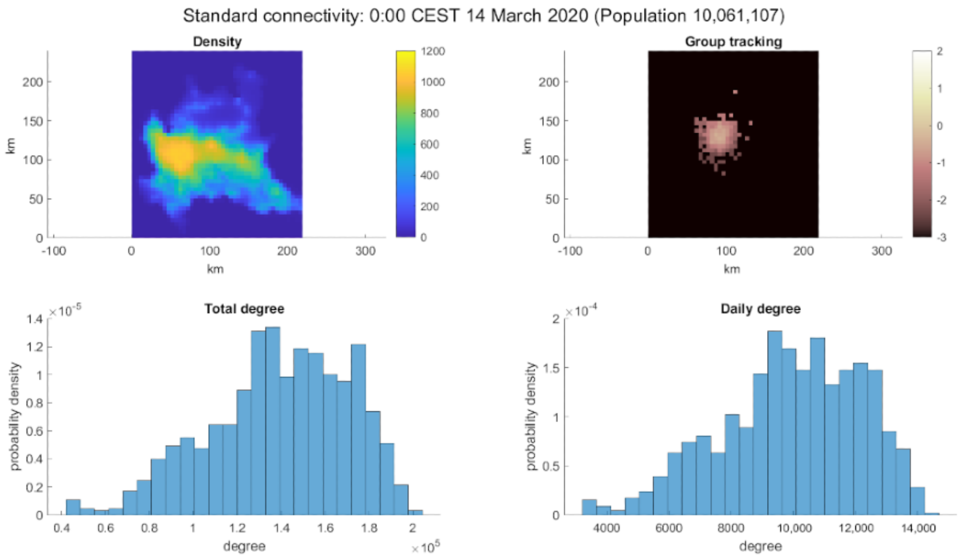
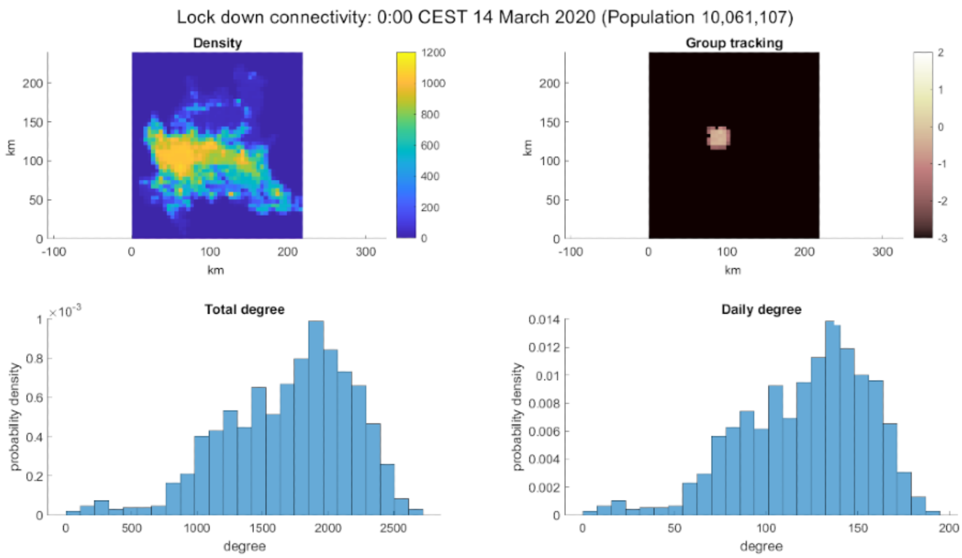


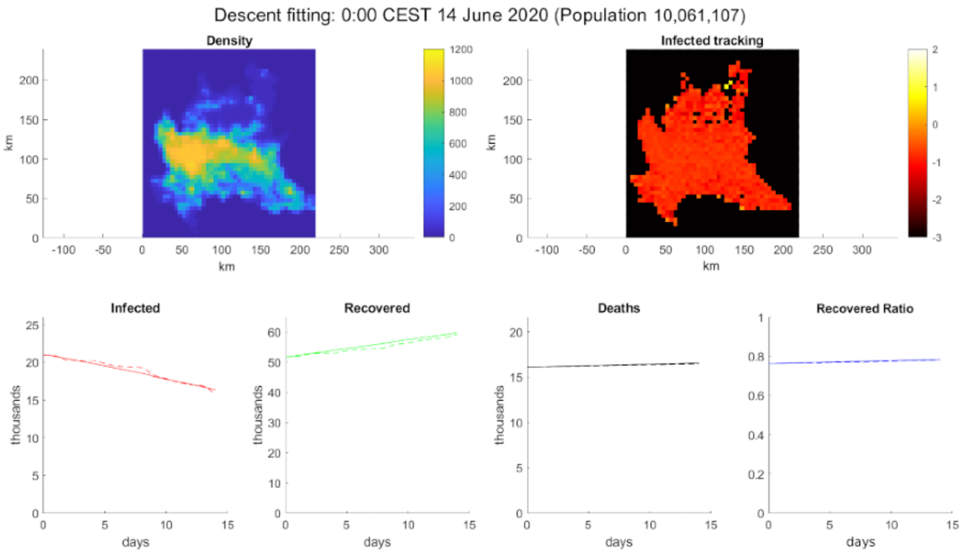
Figure 7. Lockdown simulation connectivity. Top-left: population density. Top-right: $\log_{10}$ of the group percentage per cell. Bottom-left: degree distribution of the test group. Bottom-right: daily degree distribution of the test group.



A Decline-in-Cases Scenario

This scenario took into account the period between May 31, 2020, and June 14, 2020. During this period, Italy concluded its lockdown, and the number of active cases was decreasing. For this simulation, the kilometers per day was set arbitrarily to 15 km because of the lack of additional information on mobility during this period. The probability of contracting the contagion was halved to account for social distancing. The radius of interaction and the duration of the disease were tuned to reproduce the experimental data. The value for the radius of interaction was 300 m and disease duration was 5 weeks (E=35). This value (which is higher in comparison to that of the outbreak) could be influenced by a clinical protocol more accurately and by the queue created by the large number of infected people, which could slow down the tests required to declare recovery. The qualitative fitting can be seen in Figure 8.

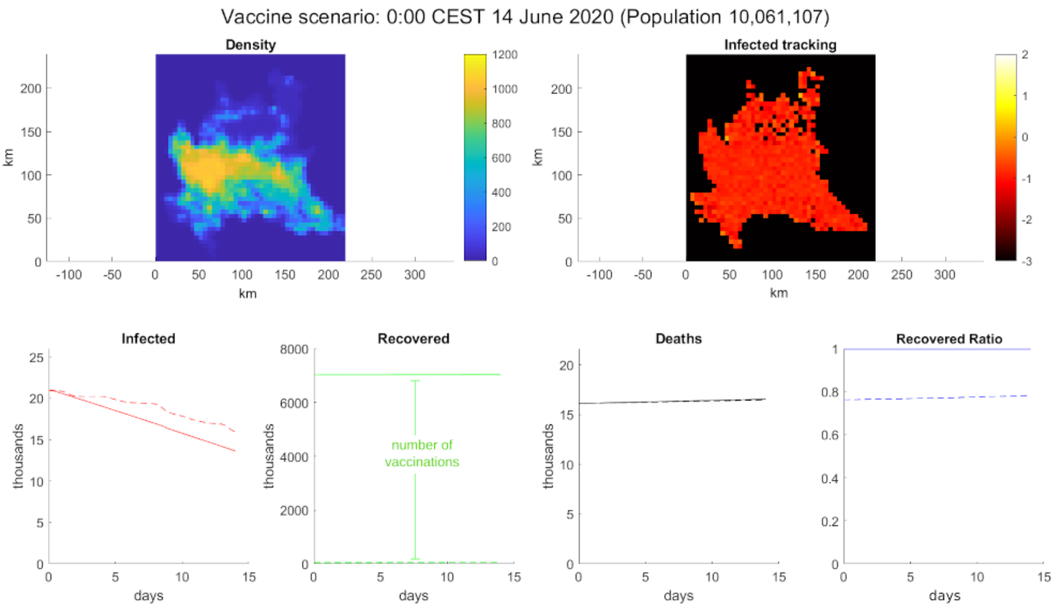
Figure 8. Simulation of a decline in cases. Top-left: population density. Top-right: $\log_{10}$ of the infected percentage per cell. Bottom, from left to right: infected number, recovered number, deceased number, and recovered ratio (recovered/deaths). The solid line is the model simulation and the dotted line is extracted data from the Decree of the President of the Council of Ministers [32] for Lombardy.



The Vaccine Scenario

Using the previous scenario of a decline in cases, we tested the impact of vaccinating 70% of the population, similar to the 62% suggested by Park and Kim [37]. The agent-based models are suitable for testing strategies like vaccination at the individual level. The result of the simulation was a strong decrease in infections, which was unexpected in a simulation of 14 days. The results are shown in Figure 9.

Figure 9. Simulation of vaccination. Top-left: population density. Top-right: $\log_{10}$ of the infected percentage per cell. Bottom, from left to right: infected number, recovered number, deceased number, and recovered ratio.



Discussion

Principal Findings

This model demonstrated the importance of people's actions in an epidemic setting. Indeed, the behavior of the virus was indicative of our own habits [17]. The agent-based model proposed here has shown great flexibility in simulating alternative scenarios; in contrast, although ODE models [6] are faster than the proposed model, they are not suitable for this task.

Limitations

The model proposed is more computationally expensive than ODE models, which require the calculation of few differential equations to simulate large populations. In general, such algorithms are also faster than agent-based models. The proposed model, however, allows for the interpretation of complex parameters.

Comparison With Prior Work

This study has explained the behavior of the COVID-19 outbreak in Lombardy and has validated the herd immunity threshold obtained with different techniques [37], even if the 62% proposed by Park and Kim [37] is less than the 70% proposed in this study. This contribution also provides a new methodology in social network analysis, where the graph theoretical approach is substituted by agents. It also paves the way to more realistic epidemic models, where hypothetical scenarios can be tested directly on the agents, without any ODE mediation.

Conclusions

This work provides a novel, efficient, and low-demanding (in terms of computational resources) population model. Many features remain to be introduced in the model, like an age-dependent virus model, the ability to introduce an age parameter in the model or a more precise spatial simulation based on big data, and the ability to simulate the habits of the population. In conclusion, future work could be done to increase the number of frames per day, thereby improving the performance of the agents.

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Conflicts of Interest

None declared.

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Abbreviations

DPCM: Decree of the President of the Council of Ministers
ODE: ordinary differential equation
SIR: susceptible-infected-recovered
SIRD: susceptible-infected-recovered-deceased

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Review

Use of Smartphone Apps for Improving Physical Function Capacity in Cardiac Patient Rehabilitation: Systematic Review

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Abstract

Background: Cardiac rehabilitation (CR) is an evidence-based approach for preventing secondary cardiac events. Smartphone apps are starting to be used in CR to give patients real-time feedback on their health, connect them remotely with their medical team, and allow them to perform their rehabilitation at home. The use of smartphone apps is becoming omnipresent and has real potential in impacting patients in need of CR.

Objective: This paper provides critical examinations and summaries of existing research studies with an in-depth analysis of not only the individual studies but also the larger patterns that have emerged with smartphone apps in CR as well as their significance for practice change.

Methods: A systematic review was conducted through broad database searches that focused on evaluating randomized controlled trials, in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) expectations. A total of 43 articles were evaluated, and 6 were chosen for this review. The dates of the articles ranged from 2014-2020, and the studies focused on the population of cardiac outpatients who needed CR after suffering a cardiac event, with interventions using a smartphone that incorporated the CR standards of the American Heart Association. The outcomes measured were directed at focusing on improved exercise function capacity, valued at a significance level of *P*<.05, for improved 6-minute walk test (6MWT) and peak oxygen uptake (PVO_2) results.

Results: In the evaluated articles, the results were inconsistent for significant positive effects of CR smartphone apps on cardiac patients' physical function capacity in terms of the 6MWT and PVO_2 when using a smartphone app to aid in CR.

Conclusions: Because evidence in the literature suggests nonhomogeneous results for successful use of smartphone apps in CR, it is crucial to investigate the potential reasons for this inconsistency. An important observation from this systematic review is that smartphone apps used in CR have better clinical outcomes related to physical function capacity if the app automatically records information or provides real-time feedback to participants about their progress, compared to apps that only educate and encourage use while requiring the participant to manually log their CR activities. Additional factors to consider during these studies include the starting health of the patients, the sample sizes, and the specific components of CR that the smartphone apps are using. Overall, more clinical trials are needed that implement smartphone apps with these factors in mind, while placing stronger emphasis on using biosensing capabilities that can automatically log results and send them to providers on a real-time dashboard.

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KEYWORDS

cardiac rehabilitation; physical capacity; exercise; smartphone apps

Introduction

Heart disease is still the leading cause of death in the United States; however, as medicine improves, survival rates for sudden and chronic heart complications are increasing, as indicated by a 34% drop in mortality rates from 2005-2015 and a predicted 27% further decline by 2030 [1]. There is now an increased need to manage these heart diseases in the long term [2]. However, we are now faced with the problem of high hospitalization reoccurrences of around 18% to 30%, which increases hospital expenses and the likelihood of mortality for patients [3]. Cardiac rehabilitation (CR) is a well-studied evidence-based secondary prevention method that has been found to decrease cardiac-related deaths by at least 26% for patients who have encountered a cardiac event, including surgery, coronary artery disease, myocardial infarction, and chronic heart disease [4,5].

There are several phases of CR, and depending on the hospital or clinic at which CR is initiated, its guidelines and definitions vary slightly. For the purpose of this review, it is stated that a full CR program typically lasts 3-8 months, depending on patient-specific goals [6]. The breakdown is as follows: Phase I of CR is considered the in-patient phase. This phase is entered after a cardiac event occurs, and it involves strengthening activities of daily living with therapists [7]. In Phase II of CR, the patient begins outpatient rehabilitation and develops a comprehensive treatment plan with health care providers; this plan often involves exercise and lifestyle modification, and it lasts approximately 3 to 6 weeks. This is crucial in the prevention of further cardiac events [7]. Phase III is the maintenance phase, where patients can decide to continue CR on their own; however, this phase is not required, nor does it have notable incremental benefits compared to Phase II [8,9].

Since 2016, it has been reported that even for eligible CR participants who were covered by Medicare, only 20%-25% used the service, and only 26% of those followed the rehabilitation program to completion [10].

In 2017, more than 250,000 patients were eligible for CR in the United States; however, less than 30% used the resource [4]. This is deemed unacceptable by the American Heart Association (AHA) [4]. Despite clinical trials and research that indicates CR programs are helpful in decreasing the occurrence of secondary coronary events, due to the patient-focused limitations of difficulty obtaining transportation to CR centers, lack of time, geographical barriers, and inability to drive, the participation in these programs is generally low [11-13].

The option of home-based focused CR has been discussed at length since 1995, with successful studies using the MULTIFIT program and the Healthy Heart Program; the AHA and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) assert that home-based CR is an equivalent option to in-person CR [4]. However, in the past, home-based CR has been difficult to implement because of the many different components to address and the limited number of physicians and nurses who can be physically present to conduct it. With known cardiac event prevention through CR, a goal was established by the Million Hearts Cardiac Rehabilitation Collaborative, comprising more than 100 organizations, to increase program participation of eligible CR patients to 70% from 2016 to 2022 because it is estimated that a million cardiac events could be prevented and save 25,000 lives in the United States alone [10].

Recently, technology and health care have reached an intersection. With increased communication and research between informatics and medicine, technology will be leveraged to support the American health care system and provide flexibility to patients for CR to combat problems such as geographical barriers and transportation. Studies are showing that smartphone apps can facilitate a higher volume of patients and can be used to better manage heart conditions at home, as communication is web-based.

A myriad of components of CR are outlined by the AHA and the AACVPR that are specific to CR in the United States; these include education on nutrition with diet modification guidelines, such as sodium restriction and lipid management using fasting lipid measurements; psychosocial support; hypertension treatment through exercise; smoking cessation; diabetes management; and exercise training [14]. With the expansion of technology, many of these CR components can now be managed through a smartphone app, which allows for remote monitoring, increased completion of CR, and better clinical outcomes.

One of the most influential components for preventing secondary heart-associated problems is physical activity [11]. Therefore, exercise capacity is the focal outcome addressed and can be measured through the 6-minute walk test (6MWT) and/or peak oxygen uptake (PVO_2). The 6MWT is a standardized way of measuring walking distance to determine exercise ability and capacity [3,11,15-17], and PVO_2 indicates exercise capacity through anaerobic respiration measurements during exercise [18]. Furthermore, with the rapid expansion of smartphone apps, the possibility of using them with home CR or alongside traditional CR is being explored.

Many randomized controlled trials (RCTs) have evaluated the use of smartphone apps in aiding compliance with CR programs, either in a traditional center or at home; however, not many have focused on examining clinical outcomes for patients who use apps in conjunction with home or traditional center–based CR [11]. The aim of this paper is to evaluate if smartphone apps significantly improve patient outcomes related to physical functional capacity during a CR program as opposed to lack of use of smartphone apps for cardiac outpatients who are using CR as a form of secondary prevention.

Methods

Search Strategy

A literature search was conducted through the University of Maryland's Health Sciences and Human Services Library (HS/HSL) and ResearchGate. The following search terms were used: "[MeSH]" "smartphone applications", OR [MeSH] "mobile app", OR [MeSH] "mobile phone [MeSH] OR Smartphone apps, OR [MeSH] "digital health" AND [MeSH] "cardiac rehabilitation" [MeSH] OR "cardiovascular rehabilitation," AND, "secondary prevention" AND "exercise". The original article inclusion criteria were as follows: articles published between 2014 and 2020, and a study population of cardiac outpatients who suffered a cardiac event and who needed a CR program. The outcomes measured included exercise improvement during the 6MWT and PVO_2. Peer-reviewed journal publications were included for completed RCTs in the English language. Due to the limited number of results, the search terms were expanded to include articles from 2014-2020 with the terms "mHealth" AND "mobile health" AND "telemonitoring" and to allow studies performed outside of the United States if they were compliant with AHA CR standards.

Database Search Results

The search results from University of Maryland HS/HSL and PubMed included 27 articles, of which 8 reported on the wrong intervention, 6 focused on the wrong population or country, 2 measured the wrong outcomes, 4 consisted of abstracts only, 2 did not contain published results, and 2 were qualitative sources. This left 3 articles for the review. A search of ResearchGate found 16 articles, or which 1 was a duplicate, 6 focused on the wrong intervention, 2 focused on the wrong population or country, 3 measured wrong outcomes, 1 was qualitative, and 3 were used in this review. Therefore, a total of 6 articles were incorporated into this literature review. See Multimedia Appendix 1 for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram.

Results

Individual Evidence From RCTs

An unblinded RCT performed by Varnfield et al [11] tested the effectiveness of a smartphone app (or website for those without a smartphone) using biofeedback from the smartphone app to aid in obtaining automatic patient progress reports, recording, and goal setting during CR for patients who had experienced a past heart attack. For the duration of 6 weeks, followed by a 6-month maintenance period, both the control group (n=60), which included traditional in-center cardiac rehabilitation (TCR), and the at-home CR program with the smartphone app/internet, called the Care Assessment Platform of Cardiac Rehabilitation (CAP-CR) (n=60), completed components of the CR program, including exercise monitoring, educational information, motivational messages, and weekly mentoring appointments, to improve their cardiac health in order to prevent reoccurring cardiac events. The results showed that both groups had significantly improved 6MWT results (CAP-CR: 60 minutes, TCR: 47 minutes, $P<.001$), and the CAP-CR intervention group experienced significant weight loss ($P=.02$), experienced significantly better quality of life (baseline median score on the EuroQol-5D dimensions scale=.84 compared to .92 at 6 weeks, $P<.001$) and showed better adherence (94%) to CAP-CR compared to TCR (68%) ($P<.05$). See Table 1 for details.

Widmer et al [3] conducted a randomized single blind controlled trial to determine if TCR with the use of a digital health intervention, in the form of an application via a smartphone or website, would help decrease the readmission rates for hospitals and emergency departments compared to TCR with no digital health intervention. In the span of 180 days, 34 participants were tested in the control group and 37 were given treatment in the intervention group. Readmission rates were recorded along with secondary measurements such as weight, blood pressure, blood glucose, physical activity, diet, and quality of life. The digital health intervention encompassed diet, exercise, and education tasks for the patients to complete. The results showed that there was no significant change in readmission rates between TCR and rehabilitation with the addition of the smartphone app or website ($P=.054$). Also, the difference in exercise/walking ability was not significant ($P=.35$). However, between the two groups, the digital health intervention group saw a significant reduction in weight and body mass index ($P=.02$) compared to the TCR group.

Maddison et al [18] used a mobile phone intervention, Heart Exercise And Remote Technologies (HEART), to study the effects of delivering text messages and videos to patients at home to increase exercise capacity through encouragement and reminders for an at-home exercise program. Although this was a good theory in practice, and the study had a large sample size of 171 participants, the intervention alone was not strong enough to create significant results, and it was determined that exercise capacity in the form of PVO_2 through respiratory gas analysis did not show significant changes during exercise before the program and after 24 weeks ($P=.65$).

In an 8-week-long study performed by Yudi et al [15], 168 acute coronary syndrome patients were tested for a program, of which 83 patients used a smartphone-based secondary prevention program with TCR compared to 85 patients using TCR alone. The smartphone app group had significant results for exercise capacity, as measured by the standard 6-minute walk test ($P=.02$). Additionally, compared to TCR alone, using a smartphone app facilitated program acceptance and mental well-being.

Table 1. Evidence summary.

Authors, Year	Objective	Evidence rating[a]	Design	Sample	Intervention	Outcome measurement	Result/recommendation
Lunde et al, 2020 [19]	Smartphone apps in CR[b] completion and follow-up for one year compared to traditional CR with no apps	II	Single-blind RCT[c]	113 participants at the end of and after CR with n=54 in the control group (no app) and n=48 in the intervention group (app)	Smartphone apps used with/after CR compared to traditional CR with no app	PVO_2[d], goals achieved, new exercise habits, exercise ability, BP[e], body weight, quality of life, lipid profile, triglycerides	Both traditional CR and CR with smartphone apps were significant in improving VO_2, goal achievement, and exercise ability
Maddison et al, 2015 [18]	To test the effectiveness of a mobile CR home exercise program	II	Parallel two-arm RCT	New Zealand patients with IHD[f] (N=171; control=86; intervention=85)	HEART[g], a mobile phone program that delivers automatic personalized text messages to increase behavior and motivation for exercise	Exercise capacity measured by PVO_2	Mobile phone program failed to increase exercise capacity in patients with IHD
Rosario et al, 2018 [16]	Smartphone app (STAHR[h] app) used between CR sessions to increase the completion rate of CR and help improve clinical outcomes for patients	II	Unblinded RCT	Australian patients in need of CR (N=66; control=33; smartphone app with medical equipment=33)	Smartphone app capable of automatically recording data from blood pressure cuff and weight scale while completing CR compared to CR group without app	Completion of CR, 6MWT[i], BP, heart rate, weight	Completion rates not significant between groups, but results for 6MWT were significant, and the intervention group improved significantly compared to the control group
Varnfield et al, 2014 [11]	To test smartphone app use and health impact during home CR	II	Unblinded RCT	Australian patients post-MI[j] (N=120; intervention=60; TCR[k]=60)	Effect of comprehensive smartphone app in home (CAP-CR[l]) on CR outcomes and use compared to TCR with no smartphone app	Modifiable factors: 6MWT for functional capacity, survey of diet, BP, heart rate, BMI, waist circumference, and lipid test, as well as general acceptability, adherence, completion	Both groups indicated significant improvement in 6MWT (TCR: 47 minutes, CAP-CR 60 minutes) with CAP-CR improving weight loss, diet, and emotional state. Home CR program using smartphone apps can improve post-MI CR use with positive clinical results
Widmer et al, 2017 [3]	Use of a smartphone app (or same program on the web) during CR can decrease ED visits and hospitalization	II	Single-blind RCT	US PCI[m] and ACS[n] patients (N=71; CR and app=37; just CR [control]=34)	Smartphone app (or website with same features) during CR compared to CR with no app or website	Number of ED[o] visits during study and number of walking minutes tolerated between the two groups	Overall failed to benefit patients, with no significant difference in exercise capacity or walking ability, but had significant weight loss and BMI improvement for patients. More studies should be conducted on larger scales.
Yudi et al, 2020 [15]	Use of a smartphone app intervention with traditional CR as secondary prevention for patients with ACS	II	Single-blind, two-arm, parallel RCT	New Zealand patients with ACS (N=168; control=85; smartphone app and TCR=83)	Smartphone app used with TCR compared to TCR alone	Exercise capacity by 6MWT	Results showed significant improvement for 6MWT with an increased distance in the smartphone app group, and the smartphone group was more likely to use CR. There was no difference for either group in smoking cessation.

[a]Evidence ratings for clinical studies: I=systematic review of randomized controlled trials, II=randomized controlled trial, III=quasi-experimental study not randomized, IV=qualitative study, V=systematic review of qualitative studies, VI=qualitative study, VII=expert opinion.

[b]CR: cardiac rehabilitation.

[c]RCT: randomized controlled trial.

[d]PVO_2: peak oxygen uptake.

[e]BP: blood pressure.

[f]IHD: ischemic heart disease.

[g]HEART: Heart Exercise And Remote Technologies

[h]STAHR: Smartphone Technology and Heart Rehabilitation.

[i]6MWT: 6-minute walk test.

[j]MI: myocardial infarction.

[k]TCR: traditional in-center cardiac rehabilitation.

[l]CAP-CR: Care Assessment Platform of Cardiac Rehabilitation.

[m]PCI: percutaneous coronary intervention.

[n]ACS: acute coronary syndrome.

[o]ED: emergency department.

A study completed in 2018 by Rosario et al [16] took a novel approach of creating a smartphone app that could wirelessly connect to a blood pressure cuff and weight scale, so that when the health technologies were used, information would automatically be downloaded to the app. Using 66 participants in a CR program (33 in the control group), this adjunctive smartphone technology was used between in-patient CR sessions to help patients record health information and keep up with the CR requirements at home to encourage active participation and decrease dropout rates. Apart from completion rates measured, the other main outcome was a 6MWT, which helped determine if using the automatic built-in pedometer and smartphone health monitoring equipment could achieve clinically significant results in exercise capacity. The experiment was shown to have significant results for completion and participants' exercise capabilities (*P*=.01).

A recent article, in 2020, by Lunde et al [19] focused on peak oxygen uptake and exercise ability in a maintenance period during and after CR, by way of a 1-year follow-up, of patients who used a smartphone app compared to TCR with no app. A single-blind RCT was performed with 113 participants, a control group (n=56) and an intervention group (n=57), with the intervention group receiving encouragement and personal goal-driven reminders on the app to complete CR activities a few times a week. The primary assessment, PVO_2, was significant for both groups, with *P*=.001 for the intervention group and *P*=.002 for the control group. Secondary assessments of goal achievement, new exercise habits, and exercise ability were significant for both groups (intervention group: *P*=.013; control group: *P*=.014). This study recommends the use of smartphone apps in aiding patients with CR and for the prevention of secondary coronary events.

Evidence Summary

Overall, from all the studies combined, the average age of participants was 57 years, with 536/709 males (75.6%) and 173/709 females (24.4%). Sample sizes varied from study to study, so caution should be used when applying these data to the entire cardiac outpatient population in need of CR. The number of study participants ranged from 6 to 171 [18], with a median number of 73 participants [3,16], 42 days [16] (with 6-month follow up) [11], 56 days [15], 168 days [18], 180 days [3], and 1 year [19].

Inclusion criteria for all study participants were as follows: received a referral for CR [11,16], English speaking [16,18,19], literate [18], clinically stable [16,18,19], age older than 18 years [15,16,19], and ownership of a smartphone [15,19]. Exclusion criteria were as follows: senses too impaired to use a smartphone [11], not owning a smartphone [15,18], terminal or unstable prognosis [15,18,19], and untreated ventricular tachycardia [15,19].

Table 2 provides a list of the interventions used in the smartphone CR programs.

Table 3 shows the main outcome measured, physical functional capacity either through the MWT or PVO_2 uptake, as well as other secondary outcomes.

There have been mixed outcomes regarding the use of smartphone apps in CR for improving exercise functional capacity. Overall, the use of smartphone apps and their acceptance in CR is gaining traction, even among older patients [20]; however, clinical outcome results are inconsistent.

Table 2. Comparison of important variables.

	Lunde et al, 2020 [19]	Maddison et al, 2015 [18]	Rosario et al, 2018 [16]	Varnfield et al, 2014 [11]	Widmer et al, 2017 [3]	Yudi et al, 2020 [15]
Usability/feasibility/utility		✓	✓	✓		✓
Adherence	✓			✓		✓
Cardiac rehabilitation education				✓	✓	✓
Exercise/walking prompts		✓				✓
Medication support						✓
Encouragement	✓	✓				✓
Dietary help				✓	✓	✓
Automatically sent data to physicians			✓			

Table 3. Exercise function capacity and contributing factors.

	Lunde et al, 2020 [19]	Maddison et al, 2015 [18]	Rosario et al, 2018 [16]	Varnfield et al, 2014 [11]	Widmer et al, 2017 [3]	Yudi et al, 2020 [15]
Exercise function capacity (6MWT[a]/compliance/ PVO_2[b])	+[c]	–[d]	+	+	–	+
Change in blood pressure/heart rate				+		–
Weight loss					+	
Usability/feasibility		✓[e]	✓	✓		✓
Lipid profile				+	–	
Hospital readmission or death occurred	✓				✓	✓
Cardiac rehabilitation phase[f]	III	II/III	N/A[g]	N/A	II	I/II

[a]6MWT: 6-minute walk test.

[b]PVO_2: peak oxygen uptake.

[c]+: significant improvement for intervention group.

[d]–: no significant improvement in intervention group.

[e]✓: measured.

[f]Phase I: in-patient phase; Phase II: patient begins outpatient rehabilitation and develops a comprehensive treatment plan; Phase III: maintenance phase.

[g]N/A: not applicable.

Discussion

Principal Findings

Currently, the results are mixed for studies on the use of smartphone apps in CR to improve physical functional capacity. However, a key observation that should be noted is that some of the distinguishing differences between clinically failed smartphone CR and improvements in patient outcomes were associated with apps that included an automaticity component for recording progress (such as an automatic step counter) [11-13], providing real-time feedback on progress, automatic logging of information, or correctional goal setting [11,12,16,17]. Conversely, the apps that were not as successful at creating clinical outcomes for exercise capacity were the apps that constantly required patients to record their data, placed the patients in CR too soon after the cardiac event, and focused on only one intervention aspect of CR [18].

CR smartphone apps that implement correctional feedback and/or automatic recording during exercise programs and portions of CR yielded positive results for increased exercise capacity and compliance [11,16]. A contributing factor in this finding may be that motivational level is often overlooked with these programs; patients want to get better, but sustaining motivation can be difficult with boring tasks, such as manually recording data every few hours. Additionally, being able to see one's performance in real time is a motivating factor, as discovered by Varnfield et al [11] and Rosario et al [16], who had success with exercise compliance and improvement when patients could see their step count through the app's accelerometer and the information was automatically logged. Rosario et al [16] found that the most accepted CR management component was the smartphone app's near-field communication abilities (ie, downloading the blood pressure results and weight results automatically to the phone app as well as the built-in pedometer for recording steps).

The unsuccessful CR smartphone outcomes were obtained for the apps that heavily relied on self-reporting surveys and patient-recorded progress and were overall unable to increase the patient's exercise capacity during CR [3,18]. Behavioral motivation is a substantial component of patients who use a CR program for secondary prevention of cardiac events. This is a difficult aspect to address, and although some articles, such as that by Maddison et al [18], did attempt to encourage use of a CR program by text messaging encouragement, this intervention alone is not strong enough to enable motivational behavior change. In addition, Rosario et al [16] reported that questionnaires that collected data were only completed by 22 out of 66 participants (33%), and this was the least successful intervention to keep participants engaged in CR. Finally, another good example of how self-reporting data and surveys create an ambivalent patient experience on improved results was reported by Vuorinen et al [21], who obtained unsuccessful results for decreasing myocardial infarction readmission rates. Their CR program and smartphone app did not specifically address any exercise component; however, they discovered that data collection via patient report in the app was inaccurate because many of the patients stopped recording results for interventions, such as blood pressure and medication adherence [21]. Patients had a tendency to falsify reports and felt anxious while constantly recording their results because it made them hyperaware of their heart condition. It was suggested that automatic data transfer be used to accommodate these issues.

Another factor to consider when patients participate in a CR program with a smartphone app is to evaluate what phase of CR they are performing, because the starting health and clinical stability of patients differs between phases. It has been noted that for Phase I of CR with smartphone apps, patients are more likely to have higher hospitalization rates, deaths, and cardiac exacerbations because they are less stable at the start of the program [13]. However, this is a sad paradox because the patients who need CR the most are the ones who are the sickest and least stable, and so it is suggested that further research and brainstorming should be aimed at creating alternatives to reach this population.

One demerit to the current body of research is that some of the sources had small sample sizes [3,11], which can skew data and lead to biased interpretations due to a nonrepresentative sample. Another drawback to using smartphone apps is that overall, they are poorly regulated and easily misguided. iTunes alone claims to offer 43,000 wellness apps, but many of these are mislabeled [22]. Moreover, of the 710 cardiac apps, only a few are intended for CR [22]. Therefore, the smartphone apps chosen for this review were consciously picked for their evidence-based approach related to CR.

Overall, there is a lack of evidence-based literature to support the notion that smartphone apps have clinical impact related to exercise in cardiac disease management via acting as, or with, a CR program compared to the traditional in-person rehabilitation or at-home CR with no app support. Although many articles suggest that there is potential for these apps, to date, the overwhelming focus has been on determining if there is interest in a smartphone app for CR rather than if it is clinically effective. Large-scale scientific testing in the United States is the next step, and there are numerous protocols suggesting that RCTs are in the process of being conducted; however, the results of these studies have yet to be published.

Another problem is that in the available research regarding completed RCTs, some of the current apps in telehealth focus on the exercise portion of CR and ignore the other important interventions set by the AACVPR and AHA, such as individual assessment, nutrition, management of blood pressure, lipids, diabetes, exercise education, psychosocial support, and medication compliance. Studies that only focused on one CR component did not show improved cardiac patient health [18]. To combat cardiac illnesses, a multitiered approach is recommended because the heart is a complicated organ. Therefore, it is appropriate for smartphone app interventions to include more than one component of CR. However, a drawback of this approach is that it is difficult to test and to determine the effects of individual interventions on a certain outcome due to the possibility of confounding variables.

Conclusions

The quality and safety implications of using smartphone apps include the ability to monitor the health status of patients from a remote location [13], increased communication with professionals from the medical team [12,13], and increased motivation for patients to take control of their own health [12]. Additionally, in the health care setting, language barriers can often create miscommunications and hinder the level of care given. Smartphone apps can be presented to patients in multiple languages; therefore, better-quality care can be administered [12]. Currently, the research for using smartphone apps with CR is not strong enough for cohesive translation into practice. Suggestions can be made for future studies based on current trends. For example, it should be recommended that CR app developers keep the starting health of their patients in mind because the physical/mental ability to use an app determines compliance in app use [13]. Furthermore, better coordination between health care professionals and app developers should occur for content creation to ensure that the workflow and CR program improves patient health rather than hindering it. It has also been suggested that as advocates for CR, physicians can prescribe CR apps for patients in rural areas or when there are transportation difficulties. However, because there are numerous apps on the market, these apps should be researched further to ensure that they aid in achieving better patient outcomes [22]. The apps that had the most impact were the ones that used remote sensing technologies to monitor some aspects of the patients' health and gave real-time feedback for appropriate goal setting related to the individual's needs for their CR program [11]. More research is required on smartphone apps, but as technologies are quickly advancing and telehealth is becoming more prevalent, a new direction of research should also include analysis of newer technologies that pair with smartphone apps, such as watches, with biosensing capabilities that can now detect alarming arrhythmias [13,20].

A key finding from this literature review is that there was a positive correlation between automatic biosensing capabilities and feedback apps when used in a multi-factorial CR approach and the physical functional capacity of cardiac patients. These current trends in the literature suggest smartphone apps can be used to aid CR if the key CR components are used in conjunction with biosensing abilities. However, other components, such as simple texting, self-logging information, and unstable health prior to CR, are ineffective in supporting rehabilitation efforts.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram.

[DOC File , 60 KB - xmed_v2i3e21906_app1.doc]

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Abbreviations

6MWT: 6-minute walk test
AACVPR: American Association of Cardiovascular and Pulmonary Rehabilitation
AHA: American Heart Association
CAP-CR: Care Assessment Platform of Cardiac Rehabilitation
CR: cardiac rehabilitation
HEART: Heart Exercise And Remote Technologies
HS/HSL: Health Sciences and Human Services Library
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVO_2: peak oxygen uptake
RCT: randomized controlled trials
TCR: traditional in-center cardiac rehabilitation

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Original Paper

Technologies to Support Assessment of Movement During Video Consultations: Exploratory Study

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Abstract

Background: Understanding and assessing patients' body movements is essential for physical rehabilitation but is challenging in video consultations, as clinicians are frequently unable to see the whole patient or observe the patient as they perform specific movements.

Objective: The objective of this exploratory study was to assess the use of readily available technologies that would enable remote assessment of patient movement as part of a video consultation.

Methods: We reviewed the literature and available technologies and chose four technologies (Kubi and Pivo desktop robots, Facebook Portal TV, wide-angle webcam), in addition to help from a friend or a simple mobile phone holder, to assist video consultations. We used 5 standard assessments (sit-to-stand, timed "Up & Go," Berg Balance Test, ankle range of motion, shoulder range of motion) as the "challenge" for the technology. We developed an evaluation framework of 6 items: efficacy, cost, delivery, patient setup, clinician training and guidance, and safety. The coauthors, including 10 physiotherapists, then took the roles of clinician and patient to explore 7 combinations of 5 technologies. Subsequently, we applied our findings to hypothetical patients based on the researchers' family members and clinical experience.

Results: Kubi, which allowed the clinician to remotely control the patient's device, was useful for repositioning the tablet camera to gain a better view of the patient's body parts but not for tracking movement. Facebook Portal TV was useful, but only for upper body movement, as it functions based on face tracking. Both Pivo, with automated full body tracking using a mobile phone, and the wide-angle webcam for a laptop or desktop computer show promise. Simple solutions such as having a friend operate a mobile phone and use of a mobile phone holder also have potential. The setup of these technologies will require better instructions than are currently available from suppliers, and successful use will depend on the technology readiness of patients and, to some degree, of clinicians.

Conclusions: Technologies that may enable clinicians to assess movement remotely as part of video consultations depend on the interplay of technology readiness, the patient's clinical conditions, and social support. The most promising off-the-shelf approaches seem to be use of wide-angle webcams, Pivo, help from a friend, or a simple mobile phone holder. Collaborative work between patients and clinicians is needed to develop and trial technological solutions to support video consultations assessing movement.

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KEYWORDS

tele-rehabilitation; video-consultations; assessment of movement; eHealth; technology; desktop robots; wide-angle webcams; physical health; rehabilitation; remote; assessment; assistive technology; evaluation; framework; webcam; telehealth; robots

Introduction

The COVID-19 pandemic has focused attention on remote consultations, and although there is evidence supporting the feasibility and acceptability of telephone and video-based rehabilitation for patients and practitioners [1,2], challenges remain. Relatively little work has been published on the remote assessment of movement as needed in the rehabilitation of people with a physical disability, including those recovering from COVID-19. Understanding and assessing patients' body movements is essential for physical rehabilitation but is challenging in video consultations, as clinicians can only see the patient on a 2D screen; thus, they are frequently unable to see the whole patient or see the patient performing specific movements or functional activities. Although anecdotally, various technologies may have been discussed, there is little advice available for clinicians to address this issue. A recent review ([3], forthcoming) included 11 primary studies, 3 reviews, and 9 guidance documents, and it was noted that (1) telerehabilitation guidance was not specific to movement-related assessment and (2) most research studies provided neither guidance nor training of movement-specific assessment to practitioners.

In our recent survey of 247 UK-based health [4] and social care practitioners, over half of those who carried out video consultations for movement assessments [4] reported concerns regarding the validity and reliability of remote physical assessments. Central to these concerns were technology-related issues (including poor internet connections and hardware issues, resulting in poor audio and visual quality) and physical examination restrictions, including a limited view of the patient, not being able to "feel" movement, and difficulty gaining an accurate assessment of the many aspects of mobility (eg, range, velocity, quality, endurance) that are important in rehabilitation. One concern for many respondents, specific to video consultations that assess movement, was difficulties positioning the camera. For example, one physiotherapist in the field of neurology said, "The camera angle does not give you a true image of the range of movement." Ensuring a good field of view was perceived as centrally important for a successful video consultation. A consultant in rehabilitation medicine said, "My top three tips? Position of camera, position of camera, position of camera!" Difficulties with camera angles, limited field of view, and tracking movement are common obstacles experienced by clinicians working in telehealth [5,6].

Video consultations are typically undertaken with clinicians using a laptop and patients using either a laptop, tablet, or mobile phone via software such as Attend Anywhere [7]. Telepresence robots, videocall technologies embedded in robots controlled by the caller to give the sense of "being there," have often been suggested as the future direction for remote home care, and there has been considerable investment in their development and evaluation [8,9]. Although the cost of commercial telepresence robots has decreased considerably over recent years (eg, Giraff cost £5000 [US $6940] in 2013, while Padbot cost £900 [US $1249] in 2020), as of March 2021, they were not yet ubiquitous or affordable for mass use in telerehabilitation. However, much of the sophistication and hence the cost of telepresence robots lies in their motor and guidance capabilities. Therefore, we postulated that desktop robotics in which the camera on the device can be rotated or angled to follow movement might be sufficiently affordable, effective, and feasible to use remotely, such as when required during a pandemic lockdown.

We were aware of two potential desktop robot devices, Kubi and Pivo. To check for other suitable technologies or approaches, we reviewed the literature, searching three bibliographic databases (Web of Science, MEDLINE, and CINAHL) for published literature from 2017 (Multimedia Appendix 1). We identified two papers [10,11] of relevance.

Wu et al [10] investigated the usability of the Kubi desktop telepresence robot in older people with self-reported mobility impairments. They studied 5 people and reported that the Kubi movement speed, controls, and user interface were a limitation of this device. This work was published in 2017; therefore, we thought Kubi warranted further inclusion in our investigations. However, we had also identified a newer and less expensive but similar device: Pivo. We therefore included Kubi and Pivo (£600 [US $833] and £85 [US $118], respectively; March 2021) (Multimedia Appendix 2) as devices that could potentially track a patient's movement. The manufacturers of Kubi describe it as "desktop robotics" (Table 1). Currently (March 2021), Kubi allows the clinician to remotely control the position of a tablet using an interface on their tablet or laptop (Table 1). The Pivo Pod is a small cylindrical and wireless device, and it could equally be called a "desktop robot." It is approximately 3 inches tall, with a mount attached to the top that can hold a smartphone and rotate 360 degrees, automatically following the user (either their head or whole body). The smartphone (both IOS and Android) requires the Pivo Meet app and uses Bluetooth to pair the Pivo Pod to the phone. Pivo Meet is a 1-1 video chat application that supports video consultations, during which the automatic tracking of the Pod will follow any movement.

Table 1. 7 new permutations of the 5 technologies assessed.

Technology	Permutations	Image
Kubi Plus	• This desktop robotic device can be remotely controlled by the clinician during the appointment; the setup also includes a 10-inch tablet computer (Lenovo Group Limited).	
Pivo	• Using Pivo Pod software, this device tracks the patient around a room. The patient records and sends the video. • Using Pivo Meet software, the same procedure as above is performed, but in real time during a video call.	
Wide-angle webcam	• We tested the Brio Stream Webcam (Logitech International SA), but we also include a brief review of other possible devices in Multimedia Appendix 3.	
Facebook Portal TV	• This device, with millions of users globally, includes a wide-angle webcam with software that tracks the user around the room (to some degree). It uses Facebook Messenger or WhatsApp video (owned by Facebook).	
Mobile phone	• The mobile phone (eg, iPhone) is operated by a friend. • The mobile phone is operated by the patient but with use of a stand.	

In considering devices (Kubi and Pivo) that moved to track patients' movement, webcams that could automatically track participants or had sufficiently wide angles so that participants could be seen at all times seemed relevant to consider. Venkateraman et al [11] studied gait in 42 ambulant veterans, evaluating the reliability and validity of the Tinetti Performance-Oriented Mobility Assessment gait scale (POMA-G) using a single fixed laptop or tablet camera [11]. Recorded video footage of patients conducting the assessment was compared to in-person assessments, and no significant differences were found in reliability and validity between video assessments and in-person POMA-G assessments. However, it was necessary to have both front and lateral views of the patient. Therefore, we also tested a generic wide-angle webcam and Facebook Portal TV (which includes a tracking webcam).

In summary, the aim of this exploratory study was to assess technology-supported methods for video consultations in which movement is assessed. We assessed Kubi, Pivo, Facebook Portal TV, and a wide-angle webcam, as well as help from a friend or family member with a mobile phone or a simple holder for a mobile phone, for their potential to undertake a video consultation assessing movement.

Methods

Ethics

Ethical permission was neither needed nor sought. All trials were conducted by the co-authors, who acted as either the clinician or the simulated patient.

Assessment Challenge

While recognizing the complexity of movement as a construct, we needed a "typical" physical assessment challenge that might be experienced within a video consultation. We based this challenge on 5 standardized and validated physical tests, which we selected because they are commonly used measures within the face-to-face rehabilitation environment: (1) sit-to-stand in 30 seconds [12], (2) timed "Up & Go" test [13], (3) Berg Balance Test [14], (4) visual estimation of ankle range of motion [15], and (5) visual estimation of shoulder range of motion [16] (Multimedia Appendix 4).

Assessment Framework

The first criterion was feasibility and efficacy; could the clinician complete the assessment challenge using this equipment? This was then extended, and an assessment framework was developed using ideas from the work of Tyson and Connell [17]. They noted that although there were many tools that measured mobility, nearly all had been developed for use in research and were impractical or inadequately developed for everyday clinical use. Their systematic review recommends the best measures to use with neurological and stroke patients in the clinical setting. They developed criteria and a scoring system for clinical utility based on four questions: (1) What is the time taken to administer, analyze, and interpret the measure? (2) What is the cost? (3) Does the measure need specialist equipment and training to use? (4) Is the measure portable?

We built on these four ideas for video consultations involving assessment of movement. "Time" evolved to become (1) the elapsed time to send equipment to the patient, (2) the time and setup process required of the patient and/or their family member or friend, (3) the time for the clinician to set up the equipment and become experienced in using it (initial setup) and then to set up for each subsequent patient. “Cost” was divided into (1) capital cost for equipment (considering life expectancy and obsolescence of equipment) and (2) revenue cost in getting equipment to and from patients. “Training” was combined with usability, as in, “How difficult is this technology to use for clinicians? Do they need guidance or training? How long would it take clinicians to get set up for each patient once they were familiar with the equipment?” “Portability” was combined with the time and setup process required of patients; this also considered whether patients required their own equipment as part of the setup. Another criterion, perhaps assumed to be “dealt with” in face-to-face consultations, is patient safety. This is important in considering telerehabilitation both from the point of view of physical safety, for example from falling or from infection prevention and control through to data safety, when comparing to face-to-face consultations. Safety was added as a sixth element of the assessment framework.

The assessment framework therefore became:

1. Efficacy: can you carry out the assessment?
2. Capital or licensing cost: what is the current cost of the technology for the National Health Service (NHS)?
3. Delivery: for people with limited mobility and those in rural areas with no nearby post office, and for all during the pandemic, what is the best option? (Courier delivery and collection appeared to be the best option. We cited prices from couriers based on a 30-mile journey for various package sizes.)
4. Patient setup: what are the time and challenges involved for patients in getting the equipment set up and ready for video consultations?
5. Clinician training and guidance: how difficult is the use of this technology for clinicians? Do they need guidance or training? How long will it take clinicians to get set up for each patient once they are familiar with the equipment?
6. Safety: How physically safe are patients when using this equipment at home? How safe are any data that may be transmitted from the point of view of data security and confidentiality?

Finally, Tyson and Connell [17] had a specific patient group in mind for their review; we considered which patient groups might be suitable for different technology scenarios. We discuss these as a whole rather than individually for each technology, and we consider both the patient’s technological readiness and clinical condition.

Technology Options and Specifications

We examined 7 new permutations of 5 technologies against the 6 criteria of the assessment framework. The 5 technologies were Kubi, Pivo (either for the patient alone on their own time or “live” during video consultation), wide-angle webcam, Facebook Portal TV, and mobile phone (either held by a friend or by the patient on their own using a stand or with no additional hardware) (Table 1). We were aware that technology specifications change rapidly and, for example, use of a mobile phone with a low-specification camera and processor will perform very differently from a “cutting-edge” phone with high-end specifications. Furthermore, broadband and Wi-Fi network speeds may have a major influence on technology performance. We aimed to trial the technologies in a number of settings and to carefully document the technologies used. Full specifications (March 2021) are given in Multimedia Appendix 4.

Environment

We tested the technologies in a range of environments, including people’s homes with less or more spacious rooms, and in sunlight and artificial light.

Usability and User Instructions

All technologies came with manufacturer instructions for setup; however, reference to web-based help and user group commentaries as well as help desk user guidance was often also required. However, it is reasonable to posit that clear and easy-to-follow instructions can be written, and we present our results based on the assumption that the technology would be used with clear installation and user guidance.

Participants

Members of the author team took on the roles of clinician and patient, and they also discussed the use of the technologies with family members. Nine members of the author team were practicing clinicians using remote consultations/telerehabilitation, and one member was a student clinician. Other coauthor participants were staff members from a center for health technology.

Results

Technology Assessment

The baseline assessment was use of a mobile phone and no additional hardware or help. The patient used Attend Anywhere or other video consultation software, and they were required to find a way to balance the phone on a piece of furniture to allow the clinician to see them in full view of the camera. This is possible if the patient is resourceful, is physically capable, and has sufficient space. As with all options using the patient’s mobile phone, a key limitation is poor image quality as a result of Wi-Fi or telephone network availability, lighting, or the quality of the camera on the mobile phone. Safety concerns about the patient’s home space and maneuvering around environmental obstacles while undertaking the requested movements apply to this and all scenarios.

Neither Kubi, Pivo, nor Facebook Portal TV were rated as being easy to set up; all users in this assessment challenge had to seek web-based help and help desk user guidance. Further results (summarized in Table 2) were obtained once the technology was set up. Capital costs are presented at current prices for one item, assuming the NHS must buy and provide the device. Marginal costs would be zero if the patient already owned the device. If the device was NHS owned, it would be used by many patients sequentially over the life of the device. Costs also assume that the patient has Wi-Fi service.

Table 2. Summary of findings for the 7 new scenarios and 6 assessment criteria.

Technology/assistance in addition to "normal" video consultation	Assessment criteria					
	Efficacy	NHS[a] capital cost	NHS delivery cost	Patient setup	Clinician training and guidance	Safety[b]
Kubi + tablet	Good for outcome measures that did not require tracking; tracking poor due to time lag	£437[c] for Kubi plus £110 for Lenovo tablet	£40	Issues with device not holding charge, on/off button, Wi-Fi connection, instructions	Simple; the clinician calls the patient and can easily go from one patient to the next	Unable to view patient when not tracking; potential to lose sight of loss of balance/falls. Data security not an issue, as this approach involves continued use of standard software
Pivo						
Recorded	Good for all outcome measures; patient must transfer data file	£85	£26	Issues with connection, instructions	Simple	Data security unknown; more exploration needed
Live	Good for all outcome measures, but patient contacts clinician	£85	£26	Issues with connection, instructions	Patient must call clinician; issues with instructions	Data security unknown; more exploration needed
Wide-angle webcam	Good for all outcome measures, but only works for laptop or personal computer	£190	£26	Only works for laptop or personal computer, but simple	Simple	Data security not an issue, as this approach involves continued use of standard software
Facebook TV Portal	Only works for upper body (feet not in picture); unable to effectively track faster walking; only usable in patient's TV room	£140	£26	Requires Wi-Fi–connected smart TV; issues with instructions	Simple; the patient can be added to the clinician's mobile contacts to make a WhatsApp call	Data security—some concerns related to using WhatsApp
Mobile phone						
Friend using mobile phone	Good for all outcome measures if a friend is available	£0	£0	Need to be able to call a friend	Simple	Data security not an issue, as this approach involves continued use of standard software
Mobile phone holder	Patient may leave field of view during tracking	£26	£26	Simple	Simple	Data security not an issue, as this approach involves continued use of standard software

[a]NHS: National Health Service.

[b]All technologies have safety considerations regarding space and collision with furniture.

[c]1 British pound=US $1.39.

Kubi

Efficacy (Assessment Challenge)

For operation, the system was rated as easy to use, although "a bit clunky"; moreover, clinicians were required to accustom themselves to the "loading bar" movement in relation to the space of the patient's room. Kubi worked well to capture outcome measures that required repositioning or did not require tracking of the patient (eg, opening a conversation in one part of the room, followed by the clinician repositioning the tablet angle when the patient moved to another area for movement assessment or to view body parts, such as feet). It was possible to complete a Berg Balance Test, assess range of movement, and undertake a sit-to-stand test at a distance of >2 m from the Kubi. However, assessing the quality of the movement was more challenging due to the low picture quality/time lag and "jerkiness" of the Kubi image. When tracking (ie, following someone's walking/movement with rotation of the tablet), the Kubi did not respond quickly, the user interface was cumbersome, and the tracking speed was fixed. As a result, the patient was lost from view, which was problematic for walking and turning assessments. Clinicians were often unable to observe the movement unless the patient positioned the Kubi far enough away to make the whole person visible on the screen; this was challenging when considering environmental constraints such as space and furniture.

Patient Setup

An issue was encountered with the batteries in Kubi devices not holding a charge. This led to connection problems, creating confusion during setup when trying to follow instructions on pairing the Kubi devices with partner tablets. Other issues raised were a problematic on/off button and problems connecting to the Wi-Fi network. The authors who trialed Kubi thought that despite being "tech savvy" and having the manufacturer's instructions, they needed numerous "work-arounds" and much time to set up. It is unclear if well-written instructions and instructional videos would overcome this problem.

Clinician Training and Guidance

Clinician setup of the software on their laptop was relatively simple. In clinical practice, when dealing with a number of patients, the software would typically be loaded and "ready to go" on the clinician's laptop or desktop computer. Although we tested Kubi using Zoom, it could be used with Attend Anywhere or other video consultation software. The clinician could move between patients quickly with the next patient's Kubi ID number and Attend Anywhere link.

Safety

The inability to track patients effectively raised safety concerns; clinicians could lose sight of walking patients who were becoming unsteady or falling, and the clinicians were thus unable to provide instructions or prevent the fall. There were particular challenges when the physical environment involved restricted space, as patients inevitably needed to move closer to the camera, thereby preventing the clinician from seeing the whole person. Data security with Kubi is good; it allows the user to run NHS-approved software such as Attend Anywhere and therefore does not have the data security concerns of some other technologies.

Pivo (Recorded)

Efficacy (Assessment Challenge)

Pivo Pod allows for either facial or head-to-toe artificial intelligence (AI) tracking. With tracking speeds from slow to "frenzy," the Pivo easily tracks the patient's movements from side to side. The Pivo also automatically zooms and focuses during the video. All 5 assessment challenges were achieved with this device. The Pivo would be a valuable tool for recording short video clips in the home environment, such as standing up and moving from a chair or wheelchair, lifting and carrying objects, impact of fatigue through the day, and gait in the home environment.

Patient Setup

If the Pivo is sent complete with a mobile phone, it is necessary to connect the Pivo to a Wi-Fi or mobile network. If the patient uses their own mobile phone, they will need to download and install software via the app and sign in via an email or Pivo account. There are a number of Pivo apps, which creates potential for confusion. Depending on the patient's technical literacy, they may require assistance with the initial video operation and selection of features, such as AI tracking. Transferring the file may also be challenging. A 2-minute video is 225 MB in size, which is too large for most email servers; thus, an alternative file sharing platform is required, which adds complications for the patient.

Clinician Training and Guidance

The clinician needs to access the video files from a file sharing platform; however, this is time-efficient for clinicians, as they can go from one patient file to another.

Pivo (Live)

Efficacy (Assessment Challenge)

In Pivo Meet (live call), clinicians were able to complete all assessments. Patients remained in view of the automatic tracking, with 2 m distance from the camera required for full body view. Auto-tracking was better for side-to-side movements than for forward-and-back movements. In addition to auto-tracking, clinicians could control the movement of the Pivo. Tracking was responsive and smooth; however, vertical (up-down) adjustments to the camera angle could not be made.

Patient Setup

Physical setup simply involved placing a phone onto the Pivo holder. Downloading and setting up the Pivo Meet app was more difficult, but it should be possible to simplify this process.

Clinician Training and Guidance

The clinician cannot initiate the consultation and must wait for the patient to send them a call link; therefore, for efficient use of clinician time, a health care assistant or an administrator should perhaps receive the Pivo call and keep the patient waiting for the clinician.

Wide-angle Webcam

Efficacy (Assessment Challenge)

A wide-angle webcam proved to be a simple solution, provided there was sufficient room (at least 3 m from the camera) to allow a full-body view. In one trial, there were some problems with lighting in the patient's home; however, this could occur with any device. In a room where overhead lighting or lighting behind the camera was possible and there were no environmental obstacles, the patient's movements and actions were fully visible at all times, and it was possible to effectively complete all 5 outcome measures. Care may be needed in choosing webcams with automatic light adjusting software.

Patient Setup

In theory, setup of a webcam should be "plug and play"; however, in practice, further checks are needed. This is only relevant for patients who have laptop computers, desktop computers, or a device that requires an additional webcam. It is not applicable for patients who only have tablets or mobile phones.

Facebook Portal TV

Efficacy (Assessment Challenge)

Users reported no significant lag time (using a WhatsApp video link). However, the AI tracking is based on facial recognition tracking, which creates challenges in keeping the patient in the full field of view. Additionally, it was not possible in any position to see below the patient's knees. For this reason, it was not possible to safely conduct the timed Up & Go test, Berg Balance Test, or sit-to-stand test. Faster walking speeds also resulted in the patient leaving the field of view momentarily. The TV portal is confined to a TV room, which may make walking assessments challenging.

Safety

Concerns exist around using Facebook products and services regarding personal data [18,19]. Over the last decade, Facebook has received numerous fines for their mishandling of user data [20]. Facebook's business model is based on their use of data [21], and their pixel software allows tracking of users across the internet even if they have not logged into a Facebook service. However, current NHS policy on use of Facebook platforms such as WhatsApp (used for Facebook Portal TV) is that "It is fine to use...to communicate with colleagues and patients/service users...where there is no practical alternative and the benefits outweigh the risk" [22].

Mobile Phone and a Friend or Carer

Efficacy (Assessment Challenge)

Use of WhatsApp with another person holding the camera enabled the clinicians to undertake a complete assessment using all 5 outcome measures. With clear instructions from the clinician, the friend was able to offer multiple fields of view of the patient.

Delivery

A cost may be associated with the friend or carer being at the patient's house.

Safety

There are some safely considerations related to the assisting friend bumping into or tripping over furniture while tracking the patient with the camera rather than watching where they are going. Data security was identified as an issue, although guidance from the NHS's digital health technology unit, NHSX, seems to be more liberal given the COVID-19 pandemic [23,24].

Mobile Phone and a Flexible Hose Stand

Efficacy (Assessment Challenge)

The flexible hose allows the patient to be guided by the clinician to achieve the appropriate field of view. At a distance of 3 m, the patient is in full view of the camera, and it was possible to complete all 5 assessment challenges.

What Type of Consultation or Patient Group Would These Technologies Be Useful For?

The spectrum of "technology readiness" of the patient and their relative or friend is critical in determining suitable options. For a patient with no smartphone, no Wi-Fi access, and no relatives or friends using such technologies, video consultations that require assessment of movement would be inaccessible. This would not be the case for a digitally well-connected patient. The clinical condition will also pose specific challenges, irrespective of the technology at hand [25]. We created some "hypothetical patients," that is, "mental constructs" that we established by taking the technology use and skills, various disabilities and physical limitations, and other characteristics of family members of the authors and "mentally" combining these with typical clinical conditions encountered by the therapists in the team. Table 3 gives examples of these hypothetical patients and how the combination of technology and their clinical condition might affect their choice of technology.

Table 3. Technology options for patients at different levels of technology readiness and with different clinical presentations.

Hypothetical patient[a]	Clinical condition drawn from clinical experience	Likely choice of technology
The patient owns an iPad and has Wi-Fi access. The patient uses email and FaceTime but does not have a mobile phone, is nearly blind, and has very limited hearing. They are technologically dependent on family members to set up apps or maintain technology.	Frail, difficulties with balance when standing and walking, regular falls	Although this patient could participate in a FaceTime call, the camera angle would be difficult and setting up any new technology would be difficult; hence, a friend or family member with a smartphone would be the best option.
The patient regularly uses a laptop computer, Skype, and Facebook Portal TV (via smart TV), which they use to stay in contact with family. They also use a tablet and laptop computer and although they have and use a smartphone, they tend to use the larger "fixed" technologies. The patient lives in an isolated location and would not want to involve a family member or friend in the consultation.	Pain and stiffness in shoulder	Using technology the patient is used to, Facebook Portal TV (the clinician does not need to see the patient's feet) would work well. The next option might be the wide-angle webcam, which would fit their laptop. Pivo as a third option would be possible but would take more time to set up.
Same person as above but with a different clinical condition.	Knee and ankle pain and stiffness; independent walking with mild unsteadiness	A wide-angle webcam would be the first choice, as the clinician needs to see the patient's feet. Pivo would be the second option.
The patient has a smartphone, laptop computer, Facebook Portal TV, tablet, and Wi-Fi access, but sometimes struggles with technology. They live with a partner who is a technology enthusiast. They would be willing for their partner to help with the consultation.	Neck pain with poor posture	The first choice is the partner using a smartphone, as no setup or delivery of equipment is required. If the partner was not available, the patient would probably opt for a wide-angle webcam with a simple USB connection.
Same person as above but with a different clinical condition. Although a household Facebook TV portal is available, the patient struggles to use it.	Pelvic girdle pain	The patient may prefer not to share this consultation with their partner, but the partner would be able to set up the Facebook TV portal before leaving the room. If the partner is not available, a wide-angle webcam is the easiest "plug and play" option.
The patient is a "digital native" smartphone user living in accommodations with relatively limited space.	Gait problems as a result of multiple sclerosis	Pivo would be the first option, as the patient does not have a device for the easy plug and play option of a wide-angle webcam. A simple mobile stand might be a second option.

[a]The technology use of the hypothetical patients is based on that of family members of the therapists.

Discussion

Principal Results

The COVID-19 pandemic has resulted in rapid uptake of the use of video consultations; however, in physiotherapy and rehabilitation, this uptake has been hampered by the difficulty of assessing movement. We identified three main technology approaches to address this problem: various rotating devices, sometimes described as desktop robots (Kubi and Pivo), stationary lenses that are either wide-angled or track the focus (wide-angle webcams and Facebook Portal TV), use of simple mobile holders, or assistance from other people. We tested the use of these approaches with coauthors taking the role of either the clinician or patient, and then we applied our understanding to "hypothetical patients." There is no "one size fits all" approach in the use of video consultations [26], and similarly, the interplay of technologies in place, patient confidence, skills and support, and clinical conditions will determine the best technology to support assessment of movement in a video consultation. In relation to older people using assistive technologies, Greenhalgh et al [27] described the idea of bricolage, pragmatic customization, and combination of devices by the participant or friend or family. The same idea of "whatever works" applies to video consultations involving assessment of movement.

The two mechanical tracking devices, Kubi and Pivo, had significant differences in cost (Kubi £437 [US $600], Pivo £85 [US $118]). Our experience indicated that the Kubi would be of use when clinicians can move the camera angle to obtain a good angle when movement takes place within that new field of view; however, it proved difficult to effectively track movement, mainly because of the speed of response of the device. Kubi, however, was viewed as useful for "looking around" the home environment to observe possible safety hazards, but it was considered expensive for that modest role. The Pivo is, in our opinion, the better device to mechanically track the patient's movements, as it provided a rapid response and did so automatically. Potential problems that we experienced with Pivo were that the Pivo Meet software required the patient to contact the clinician (rather than the clinician initiating contact with the patient) and that tracking was only enabled in the horizontal plane. Also, the video call must be conducted using the Pivo Meet software, whereas Kubi uses parallel software to control movement of the device while the video call can still be conducted using the service provider's preferred video call software. Both devices require further work to develop easy patient setup routines and to test these with real patients.

Based on our experience, the use of a wide-angle webcam is likely to be the easiest to set up for patients who have a laptop or desktop computer. Facebook Portal TV, for those patients who already have it installed, could play a useful role provided that the clinician does not need to see the patient's feet. The technologically simplest approach is to get another person to use a mobile phone to "film" the patient during the videoconference, but not every patient has access to another person, and they may not wish to share their consultation for reasons of confidentiality and privacy. The possible addition of a simple adjustable stand (£25, US $35) may be sufficient to enable patients to angle their phones or tablets to enable the clinician to have a better view of the movement.

An internet-based goniometer has demonstrated good to high validity and reliability of telerehabilitation in orthopedics and stroke when assessing joint range of motion of upper limb joints [28-32]. Similarly, adaptation of existing movement sensor technology (such as the Microsoft Kinect [33]) or other apps such as Coach's Eye [34] could improve the accuracy of recording of joint range. However, these adaptations risk adding further layers of complexity to an already technologically challenging scenario. Other simple devices include a large "paper protractor" or asking permission from the patient to take a screenshot in order to use a program such as Microsoft Paint or Adobe Photoshop to perform goniometric calculations. However, processing these data accurately requires awareness of, and compensation for, issues such as parallax. Given the increased awareness of the need for effective remote monitoring systems, data sets are being gathered to address these challenges, meaning that this is an area that is likely to develop significantly moving forward [35].

The practical barriers of using devices such as Pivo or a wide-angle webcam may be related to the delivery and retrieval by the health provider and to the setup by the patient. Some health informatics services, such as those supporting people with chronic obstructive pulmonary disease at home, have been successfully using courier services to deliver simple-to-install equipment and have then been providing telephone support to patients in setting up this equipment (R Jones, personal communication). Further exploration of the feasibility and long-term cost of delivering and collecting different technologies by courier is needed.

Across all technologies, clear setup instructions are required, ideally coproduced with service users, and available in different formats, such as paper, electronic, or instructional videos. Setup has been an issue with normal video consultations [36], and our experience of the included instructions for Kubi, Facebook Portal TV, and other devices was that they were not as "usable" as they need to be. Instructions for clinicians and patients need to be professional in appearance, concise, and clear, with a comprehensive step-by-step guide, including for software installation. Also included should be a troubleshooting section, such as what to do if the Wi-Fi is switched off and how to increase the volume. Establishing the right settings and options for both clinician and patient is critical; hence, there is a need for inclusion of this information in the user instructions. If a user instruction video is produced, it should be subtitled (for people with hearing impairment), but there should also be a written guide. If the NHS becomes a major purchaser of such technologies, it could use its purchasing power to encourage manufacturers to produce easier and better-explained technology setups.

Consideration of the technology selected and the confidence of the user is particularly important and, where possible, there is a need to "bootstrap" from the known technologies in use by an individual. It is particularly important to consider issues such as cognition, anxiety, and sensory impairments such as vision or hearing. Once the clinician is experienced, they should also be able to give assistance over the telephone if the patient is struggling with setup. Alternatively, students or other community support organizations (eg, in Cornwall, the Cornwall Rural Community Charity [37], or nationally, the Good Things Foundation [38] or Digital Eagles [39], may be able to support patients using their existing technologies.

Outpatient consultations were resumed during the COVID-19 pandemic for many but not all services, and not to all patients. A risk/benefit judgement was made if patients were highly vulnerable or shielding. Conducting face-to-face consultations was feasible following the latest guidance on infection prevention and control with full personal protective equipment. However, this approach does not eliminate all risks. Patient choice is central to this decision. Face-to-face consultations can be difficult for many patients who have trouble travelling to the local hospital owing to both feasibility and cost issues.

Getting a family member or friend to hold the mobile phone or tablet for the video consultation, ensuring that the patient is "in shot," may be more reliable than using these technologies and may be safer as well. There is evidence from our national survey [5] that this is currently occurring: "Our clients generally do not carry out video consultations on their own, they would normally have some support from a carer or family member" (Occupational Therapist, Neurology). This approach provides some advantages with regard to safety, although it does not completely resolve the issue when standby or hands-on assistance is needed (for example, with a standing balance task) given the requirement to hold the device. This approach is also problematic if the friend of family member is requested to assist in moving the limbs of a patient at the same time they hold the camera. Another disadvantage is that such assistance is likely to be required at each consultation; in contrast, technological alternatives might enable greater patient autonomy and privacy. In our survey [4], practitioners reported that family members provided a number of different types of support in video consultations, including technical support (setting up the technology, positioning the camera), physical support (helping to move or guide the patient, standby assistance for safety), and psychological support (reassuring the patient, clarifying instructions). However, this is not without difficulties: "It can be hard for patients/family members to get the right technique [for positioning the camera]" (Physiotherapist, Musculoskeletal/Rheumatology).

Technology is advancing rapidly. Two lines of current research that may help in assessing movement remotely are use of patient-wearable technologies [6,40] and more intuitive clinician interfaces, including use of wearable headsets [41]. Aggarwal explored the use of "smart socks" [42], which may be able to transmit data about foot pressures and balance to clinicians, and such technologies may prove to be useful additions to improve visual data.

The technology that is sometimes used in addition to technology for video consultations may raise concerns about data privacy and security for both patients and clinicians. This is a rapidly changing environment both for the technology and advice given by relevant bodies. For example, we originally thought that Facebook Portal TV was unlikely to receive approval for use by NHS trusts because of data security concerns; however, views on balancing data security concerns versus access during the pandemic indicate that opinions seem to be shifting. Advice from the NHSX Information Governance team [23,24] states that it is acceptable to use video conferencing tools such as Skype, WhatsApp, and FaceTime as well as commercial products designed specifically for this purpose, particularly as a short-term measure. Although NHSX states that any video consulting tool can be used provided there has been an appropriate local risk assessment [24] and, for example, Healthwatch seems to assume that Zoom may be used [43], some trusts still restrict use of video consultations to Microsoft Teams or Attend Anywhere.

The most promising approaches that we explored were use of wide-angle webcams, Pivo, a simple stand to hold a mobile phone, and obtaining help from another person with a mobile phone. Further testing and observational studies with patients within a clinical context are now needed. Equipment loans are integral to standard NHS practice; hence, it is appropriate to explore whether this should be extended to the loan of assistive devices to enhance the effectiveness of video consultations.

Limitations

Our study was a preliminary exploration of currently available technologies with the use of role-play by clinicians. Technology development is rapid; by the time of publication, the devices reviewed may have progressed significantly, and new devices may have become available. However, our study provides guidance on potentially productive lines of inquiry and further research. Our exploratory study has been conducted by just one team, and further work by others would help validate our approach and conclusions. Furthermore, our work was carried in the United Kingdom; these results may not easily be generalized to resource-limited environments and developing countries.

Comparison With Prior Work

We were only aware of one previous study of devices to assess movement in video consultations. Wu et al's study [10] of 5 older people with self-reported mobility impairments reported limitations of using the Kubi device but did not investigate other technologies**.**

Conclusions

Our findings suggest that the "technology readiness" of the patient and clinician, the clinical condition, and the availability of support from another person are important factors to consider when implementing technologies, such as those we have reviewed, to remotely assess movement as part of video consultations. The most promising off-the-shelf approaches seem to be use of wide-angle webcams, Pivo, a simple mobile phone holder, and obtaining help from another person with a mobile. Comparative clinical trials of these approaches, perhaps in the form of a preference trial, would be worthwhile.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Literature search details.
[DOCX File , 91 KB - xmed_v2i3e30233_app1.docx]

Multimedia Appendix 2
Hardware specifications at the time of the study.
[DOCX File , 35 KB - xmed_v2i3e30233_app2.docx]

Multimedia Appendix 3
Notes on other devices that were not tested.
[DOCX File , 36 KB - xmed_v2i3e30233_app3.docx]

Multimedia Appendix 4
Clinical instructions for the technology assessment.
[DOCX File , 35 KB - xmed_v2i3e30233_app4.docx]

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Abbreviations

AI: artificial intelligence
EPIC: eHealth Productivity and Innovation in Cornwall

NHS: National Health Service
POMA-G: Tinetti Performance-Oriented Mobility Assessment gait scale

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Original Paper

Utility of the ROX Index in Predicting Intubation for Patients With COVID-19–Related Hypoxemic Respiratory Failure Receiving High-Flow Nasal Therapy: Retrospective Cohort Study

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Abstract

Background: The use of high-flow nasal therapy (HFNT) to treat COVID-19 pneumonia has been greatly debated around the world due to concerns about increased health care worker transmission and delays in invasive mechanical ventilation (IMV). Herein, we analyzed the utility of the noninvasive ROX (ratio of oxygen saturation) index to predict the need for and timing of IMV.

Objective: This study aimed to assess whether the ROX index can be a useful score to predict intubation and IMV in patients receiving HFNT as treatment for COVID-19–related hypoxemic respiratory failure.

Methods: This is a retrospective cohort analysis of 129 consecutive patients with COVID-19 admitted to Temple University Hospital in Philadelphia, PA, from March 10, 2020, to May 17, 2020. This is a single-center study conducted in designated COVID-19 units (intensive care unit and other wards) at Temple University Hospital. Patients with moderate and severe hypoxemic respiratory failure treated with HFNT were included in the study. HFNT patients were divided into two groups: HFNT only and intubation (ie, patients who progressed from HFNT to IMV). The primary outcome was the value of the ROX index in predicting the need for IMV. Secondary outcomes were mortality, rate of intubation, length of stay, and rate of nosocomial infections in a cohort treated initially with HFNT.

Results: Of the 837 patients with COVID-19, 129 met the inclusion criteria. The mean age was 60.8 (SD 13.6) years, mean BMI was 32.6 (SD 8) kg/m², 58 (45%) were female, 72 (55.8%) were African American, 40 (31%) were Hispanic, and 48 (37.2%)

were nonsmokers. The mean time to intubation was 2.5 (SD 3.3) days. An ROX index value of less than 5 at HFNT initiation was suggestive of progression to IMV (odds ratio [OR] 2.137, *P*=.052). Any further decrease in ROX index value after HFNT initiation was predictive of intubation (OR 14.67, *P*<.001). Mortality was 11.2% (n=10) in the HFNT-only group versus 47.5% (n=19) in the intubation group (*P*<.001). Mortality and need for pulmonary vasodilators were higher in the intubation group.

Conclusions: The ROX index helps decide which patients need IMV and may limit eventual morbidity and mortality associated with the progression to IMV.

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KEYWORDS

respiratory; medicine; nasal therapy; COVID-19; mechanical ventilation; ventilators; mortality; morbidity; intubation

Introduction

December 2019 was marked by a cluster of acute respiratory illnesses now known as COVID-19, caused by the novel coronavirus SARS-CoV-2. The virus has infected more than 8.7 million people worldwide with more than 460,000 reported deaths, resulting in a worldwide health care crisis [1,2]. The majority of morbidity from COVID-19 seems to arise from severe hypoxemic respiratory failure. As the pandemic spreads to the farthest reaches of the globe, health care centers have become overwhelmed, quickly exhausting their supply of ventilators and personnel who are trained to manage these critically ill patients. There is ongoing controversy concerning the optimal mode of respiratory support to treat COVID-19–associated hypoxemic respiratory failure.

The timing and adequacy of noninvasive forms of oxygen support (ie, high-flow nasal therapy [HFNT], simple face mask usage, etc) versus invasive mechanical ventilation (IMV) is not known. IMV has been associated with significant morbidity and mortality. In some case series, a mortality rate greater than 90% has been reported [3-6]. Case series from China, Italy, and New York, United States, have reported intubation rates ranging from 20.2% to 88% [4,6-9]. Early utilization of IMV has been greatly influenced by concerns for viral aerosolization and subsequently health care transmission through the use of noninvasive forms of oxygen support [10]. In addition, rapid progression of hypoxemic respiratory failure from mild dyspnea to acute respiratory distress syndrome (ARDS) within 48 to 72 hours has been noted in early studies [9,11]. Consequently, some centers decided to preemptively intubate patients with oxygen requirements as low as 6 L/min via nasal cannula for prolonged periods [3].

HFNT, in contrast to IMV, is a noninvasive oxygen system that delivers humidified air-oxygen blends and a titratable fraction of inspired oxygen (FiO_2) as high as 60 L/min and 100% FiO_2, respectively. Despite proven efficacy in other disease processes, the utilization of HFNT has been limited, and its use has not been widely recommended for patients with COVID-19–related pneumonia and hypoxemic respiratory failure. Limitations to the adoption of this mode of high-flow oxygenation include concerns about the rapid progression of the disease as well as fear of the aerosolization of SARS-CoV-2, resulting in increased transmission to health care providers [12-14].

However, HFNT has been successfully used in severe viral respiratory illnesses, including influenza A and H1N1 [15]. HFNT reduces the need for IMV rates compared to other modalities, with some studies also showing reduced 90-day mortality rates [16-19]. By decreasing the incidence of invasive ventilation, HFNT has the potential to decrease complications associated with IMV such as the incidence of ventilator-associated pneumonia.

Moreover, compared with noninvasive ventilation and conventional oxygen therapy, the use of HFNT has also been shown to reduce reintubation rates due to postextubation respiratory failure and has much better tolerability than noninvasive ventilation [20,21]. The Surviving Sepsis Guidelines for COVID-19 also recommends using HFNT in patients with acute hypoxemic respiratory failure due to COVID-19 [22].

The ROX index, defined as the ratio of oxygen saturation as measured by pulse oximetry (SpO_2)/FiO_2 to respiratory rate (RR) in breaths per minute, is a validated measurement that predicts outcomes when using HFNT to treat hypoxemic respiratory failure. An ROX index <4.88 after 12 hours predicts the need for IMV in patients with pneumonia [23].

Herein, we analyzed the utility of the ROX index to predict the need for and timing of IMV in a retrospective analysis of 129 patients with COVID-19–associated, moderate to severe hypoxemic respiratory failure treated with HFNT. In addition, mortality and rates of intubation, length of stay, and nosocomial infection in the cohort treated with HFNT are also reported.

Methods

Ethical Approval and Consent to Participate

The study was approved by the Temple University Institutional Review Board (TU-IRB protocol number: 27051). A waiver of consent was granted due to the acknowledged minimal risk to the patients.

Patient and Public Involvement

Neither patients nor the public was involved in the design, conduct, reporting, or dissemination plans of our research.

Design

A retrospective observation study of 1397 consecutive patients admitted to Temple University Hospital in Philadelphia, PA, from March 10, 2020, to May 17, 2020, was performed. Initial screening included patients who were either positive for COVID-19 using nasopharyngeal real-time reverse transcriptase–polymerase chain reaction (RT-PCR) or had high clinical suspicion based on high-resolution computerized tomography (HRCT) of the chest (typical peripheral nodular or ground-glass opacities without alternative cause) [24] with a typical inflammatory biomarker profile, but had a negative RT-PCR.

Thereafter, only patients with moderate and severe hypoxemic respiratory failure who were treated with HFNT at any point during their hospitalization were included in the study. Moderate and severe hypoxemic respiratory failure was defined as hypoxemia requiring more than 6 L/min of oxygen via nasal cannula. Absence of HFNT use during hospitalization was an exclusion criterion. Treatment protocols used at our hospital are described in Multimedia Appendix 1.

Data Collection

Demographics, including age, sex, comorbidities, BMI, and smoking status (current smoker, nonsmoker), were collected. In addition, laboratory biomarkers on admission, including complete blood count with differential, ferritin, fibrinogen, lactate dehydrogenase (LDH), D-dimer, and C-reactive protein (CRP), were analyzed.

Respiratory metrics at the initiation of HFNT included RR, pulse oximetry, and FiO_2. The same parameters were collected on days 1, 2, 3, and 5 after HFNT initiation. Parameters were recorded at the lowest FiO_2 and highest pulse oximetry reported for the day. For patients who required IMV prior to the conclusion of data collection, respiratory parameters on the day of intubation were reported. Days on HFNT therapy, time to intubation (in days), average flow rate on HFNT, and the presence of hospital-acquired pneumonia or ventilator-associated pneumonia were also collected.

Outcomes

The primary outcome was the ability of the ROX index to predict the need for IMV. Secondary outcomes included mortality, hospital length of stay, and hospital- or ventilator-acquired pneumonia. Hospital- and ventilator-acquired pneumonia was defined based on the presence of sputum positivity and treatment with antibiotics.

Data Analysis

Our patients were divided into two groups for analysis: (1) HFNT support as a bridge to recovery (HFNT group) and (2) HFNT with progression to IMV (ie, intubation group). Comparisons were made between demographics, baseline laboratory values, and outcomes within the two groups. Changes in ROX index and concomitant changes in the clinical parameters of heart rate were also analyzed.

A multivariable prediction model for intubation for our cohort based on the above parameters was created. ROX index, comorbidities, and clinical and laboratory data were used to identify parameters that could predict the need for intubation. A receiver operating characteristic (ROC) curve was generated to determine the accuracy of the model.

Statistical Methods

Continuous variables are presented as mean (SD) and categorical variables as counts and percentages. Continuous variables were compared with the use of the two-sample *t* test or the paired *t* test for categorical variables using the Pearson chi-square test. Laboratory data were nonparametric and were compared using the Wilcox rank-sum test. Kaplan-Meier analysis was estimated for survival and compared by the log-rank test.

To build a predictive model for intubation, multivariable logistic regression was performed to determine the adjusted associations of the variables with intubation. The initial model included all the variables associated with intubation in univariate analyses for $P<.10$. The final model optimized the balance of the fewest variables with good predictive performance. Assessment of model performance was based on discrimination and calibration. Discrimination was evaluated using the C-statistic, which represents the area under the ROC curve (AUC), where higher values represent better discrimination. Calibration was assessed by the Hosmer-Lemeshow test, where a *P* value greater than .05 indicates adequate calibration.

All statistical tests were two-tailed, and $P<.05$ was considered to indicate statistical significance. All statistical analyses were performed using Stata 14.0 (StataCorp).

Availability of Supporting Data

The supporting data will be made available upon request.

Results

Demographics

A total of 1397 patients who were admitted to Temple University Hospital between March 10, 2020, and May 17, 2020, were screened. Of these, 837 patients had tested positive for COVID-19 by nasopharyngeal RT-PCR or were treated due to high clinical suspicion based on typical HRCT imaging and an inflammatory biomarker profile. Overall, 388 patients had hypoxemic respiratory failure, and 129 (15.4%) patients met our inclusion criteria of being on HFNT with moderate to severe hypoxemic respiratory failure (Figure 1). The mean age was 60.8 (SD 13.6) years, mean BMI was 32.6 (SD 8) kg/m², 58 (45 %) were female, 72 (55.8%) were African American, 40 (31%) were Hispanic, and 48 (37.2%) were nonsmokers. The major comorbidities reported (in descending incidence) were hypertension, diabetes, lung disease, heart disease, chronic kidney disease, malignancy, and psychiatric illness (Table 1). There were no differences in age, BMI, and gender between the groups. The proportion of nonsmokers was higher in the intubation group (22/40, 55% vs 26/89, 29.2%), as well as a trend toward a higher incidence of lung disease, chronic kidney disease, malignancy, and psychiatric disorders.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram for screening. HFNT: high-flow nasal therapy, IMV: invasive mechanical ventilation.

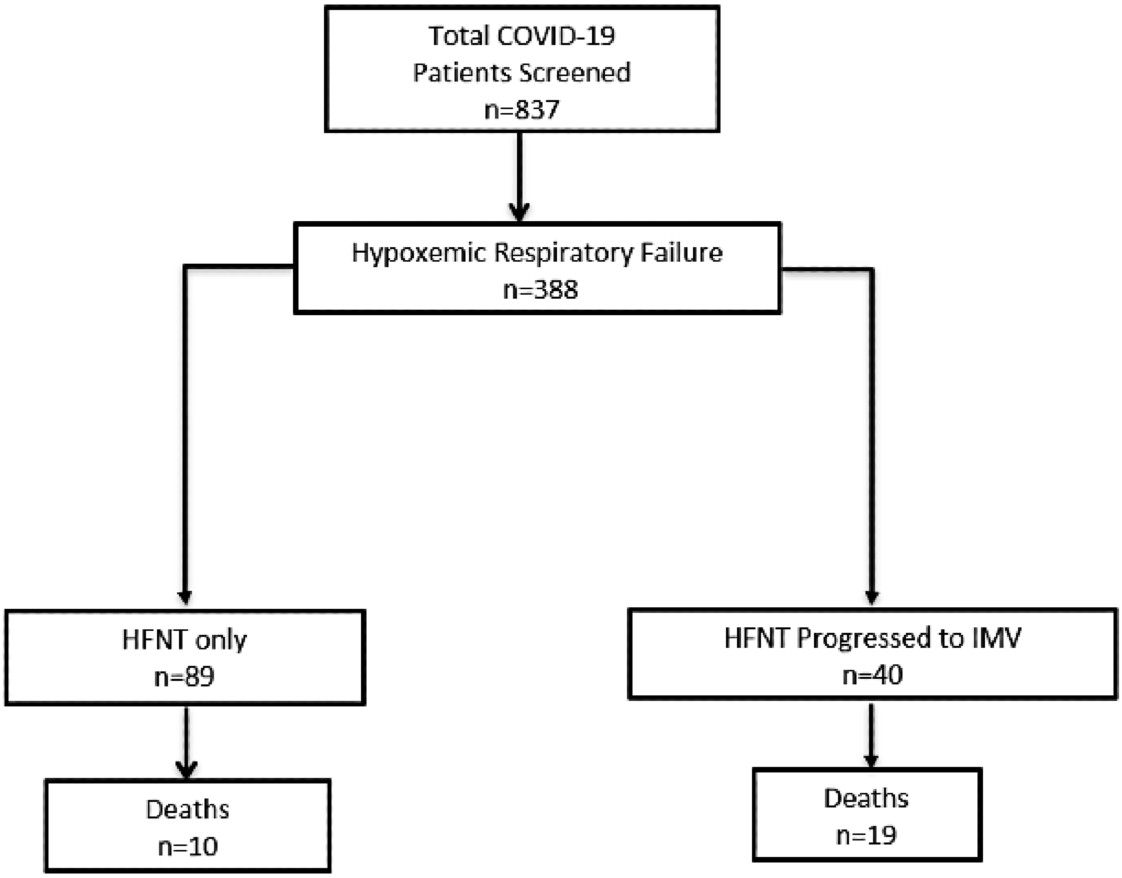


Table 1. Baseline demographics comparing the high-flow nasal therapy (HFNT) group and the intubation group (ie, HFNT with progression to invasive mechanical ventilation).

Characteristic	Total (N=129)	HFNT only (n=89)	Intubation (n=40)	*P* value
Demographics				
Age (years), mean (SD)	60.8 (13.6)	60.7 (14.0)	61.2 (12.9)	.86
BMI (kg/m^2), mean (SD)	32.6 (8.0)	32.7 (8.0)	32.3 (8.0)	.80
Gender, n (%)				.25
Female	58 (45.0)	43 (48.3)	15 (37.5)	
Male	71 (55.0)	46 (51.7)	25 (62.5)	
Race, n (%)				.09
African American	72 (55.8)	51 (57.3)	21 (52.5)	
Caucasian	12 (9.3)	5 (5.6)	7 (17.5)	
Hispanic	40 (31.0)	28 (31.5)	12 (30.0)	
Other/unknown	5 (3.9)	5 (5.6)	0 (0)	
Smoking status, n (%)				.006
Smoking	72 (55.8)	58 (65.2)	14 (35.0)	
Nonsmoker	48 (37.2)	26 (29.2)	22 (55.0)	
Smoker	9 (7.0)	5 (5.6)	4 (10.0)	
Unknown	—[a]	—	—	
Comorbidities, n (%)				
Lung disease	38 (29.7)	23 (26.1)	15 (37.5)	.19
Hypertension	85 (65.9)	59 (66.3)	26 (65.0)	.89
Heart disease	33 (25.6)	22 (24.7)	11 (27.5)	.74
Diabetes mellitus	59 (45.7)	44 (49.4)	15 (37.5)	.21
Chronic kidney disease	23 (17.8)	13 (14.6)	10 (25.0)	.15
Psychiatric illness	10 (7.9)	4 (4.6)	6 (15.0)	.04
Malignancy	15 (11.7)	4 (4.5)	11 (27.5)	<.001
Treatments, n (%)				
Remdesivir	11 (8.5)	7 (7.9)	4 (10.0)	.69
Sarilumab	61 (47.3)	49 (55.1)	12 (30.0)	.008
Anakinra	17 (13.2)	13 (14.6)	4 (10.0)	.47
Tocilizumab	24 (18.6)	14 (15.7)	10 (25.0)	.21
Etoposide	2 (1.6)	0 (0)	2 (5.0)	.03
Intravenous immunoglobulin	38 (29.5)	21 (23.6)	17 (42.5)	.03
Pulse steroids	111 (86.0)	75 (84.3)	36 (90.0)	.39
Hydroxychloroquine	11 (8.5)	6 (6.7)	5 (12.5)	.28
Gimsilumab	13 (10.1)	7 (7.9)	6 (15.0)	.21
Plasma	15 (11.6)	9 (10.1)	6 (15.0)	.42
Azithromycin	73 (70.2)	53 (73.6)	20 (62.5)	.25
Admission laboratory markers, mean (SD)				
Ferritin (ng/ml)	1193.5 (2490.9)	939.8 (1232.6)	1751.8 (4043.6)	.22
C-reactive protein (mg/dl)	11.4 (8.0)	10.9 (7.4)	12.5 (9.0)	.30
Lactate dehydrogenase (U/L)	425.3 (254.7)	401.4 (255.4)	478.5 (248.2)	.11
D-dimer (ng/ml)	4719.6 (14,244.6)	3465.7 (10,618.9)	7509.5 (19,998.8)	.23

Characteristic	Total (N=129)	HFNT only (n=89)	Intubation (n=40)	*P* value
Fibrinogen (mg/dl)	519.6 (185.0)	532.1 (158.1)	492.5 (233.4)	.34
Absolute lymphocyte count (K/mm^3)	1.4 (2.9)	1.1 (0.8)	2.2 (5.1)	.17
Interleukin 6 (pg/ml)	743.1 (5026.8)	34.7 (45.9)	1634.2 (7526.2)	.25
Interleukin 1 (pg/ml)	2.6 (3.9)	2.1 (0.5)	3.4 (6.0)	.30
Aspartate aminotransferase (U/L)	58.5 (71.9)	49.5 (35.3)	79.0 (117.1)	.14
Alanine aminotransferase (U/L)	41.8 (35.0)	40.0 (24.2)	45.9 (51.8)	.49
Total bilirubin	0.9 (1.1)	0.8 (1.1)	1.2 (0.9)	.03
Platelet (K/mm^3)	215.4 (97.9)	219.5 (103.2)	206.1 (84.9)	.48
Blood urea nitrogen (mg/dl)	29.1 (26.2)	26.3 (24.9)	35.3 (28.2)	.07
Creatinine (mg/dl)	2.5 (3.9)	2.1 (3.9)	3.3 (3.8)	<.001
Glomerular filtration rate (ml/min)	60.1 (32.7)	66.6 (31.6)	45.4 (30.5)	<.001
Triglycerides (mg/dl)	166.7 (165.1)	143.2 (87.0)	213.8 (253.8)	.10
Respiratory parameters, mean (SD)				
HFNT use (days)	5.6 (5.1)	6.6 (5.5)	3.2 (3.1)	<.001
HFNT flow rate	33.5 (11.7)	31.5 (9.7)	38.2 (14.6)	.012
S/F[b] ratio at admission	294.7 (131.6)	313.3 (125.6)	252.2 (136.8)	.015
S/F at HFNT initiation	121.1 (38.4)	124.4 (38.8)	113.8 (37)	.15
ROX[c] at HFNT initiation	5.1 (2)	5.4 (2.1)	4.5 (1.6)	.02
Pulmonary vasodilators	46 (35.7)	25 (28.1)	21 (52.5)	.007
Ventilator use (days)	10.2 (7.6)	—	10.2 (7.6)	—
Tracheostomy	11 (27.5)	—	11 (27.5)	—

[a]Not applicable.

[b]S/F: SpO_2/FiO_2 ratio.

[c]ROX: ratio of oxygen saturation.

Treatments

Azithromycin (n=73, 70.2%) and steroids (n=111, 86%) were the most frequently utilized therapies. Immunomodulator therapy, including sarilumab, anakinra, intravenous immunoglobulin, and tocilizumab, was the next most commonly used therapies. There was a higher usage of gimsilumab, hydroxychloroquine, intravenous immunoglobulin, tocilizumab, and etoposide in the intubation group, while azithromycin was higher in the HFNT-only group. Steroid usage and other immunomodulators were similar across the groups.

Laboratory Markers

Elevated inflammatory markers (ie, ferritin, CRP, D-dimer, fibrinogen, LDH, interleukin 6 [IL-6]), transaminitis, and lymphopenia were observed in all patients. There was a trend toward higher inflammatory markers (ie, ferritin, CRP, LDH, D-dimer, IL-6, interleukin 1), triglycerides, and transaminases in the intubation group. Significantly higher creatinine and lower glomerular filtration rate (GFR) were seen in the intubation group.

Respiratory Parameters

The mean S/F (SpO_2/FiO_2) ratio at admission was 294.7 (SD 131.6) and was statistically different between the groups (mean 313.3, SD 125.6 vs mean 252.2, SD 136.8). The S/F ratio at high flow initiation was 121.1 (SD 38.4) overall, with no statistically significant differences between the groups (HFNT group: mean 124.4, SD 38.8 vs intubation group: mean 113.8, SD 37). The mean corresponding P/F (PaO_2/FiO_2) ratio at the start of HFNT was ~100.

Initial HFNT settings were 33.5 (SD 11.7) L/min of flow, while FiO_2 was 84.1% (SD 20.3%). The intubation group had a statistically higher flow rate than the HFNT group. The average use of HFNT in our population was 5.6 (SD 5.1) days. The minimum settings on HFNT were 10-L flow and a FiO_2 of 30%, while the maximum settings were 60-L flow and a FiO_2 of 100%. The major complication with the use of HFNT was progression to IMV, which was seen in 40 (31.0%) patients. Average ventilator use in days was 10.2 (SD 7.6), and 10 (27.5%) patients received a tracheostomy. Overall, 46 (35.7%) patients required pulmonary vasodilators, with statistically higher usage in the intubation group.

Outcomes

ROX Index Trends

The mean ROX index value for the total cohort was 5.1 (SD 2.0) at HFNT initiation, and 5.9 (SD 2.5), 6.9 (SD 3.9), 8.1 (SD 4.1), and 10.3 (SD 5.9) on days 1, 2, 3, and 5, respectively. The mean ROX index consistently improved from initiation to day 5 in the HFNT group, while staying nearly constant in the intubation group (Figure 2). At each time interval, the ROX index was significantly higher in the HFNT group compared to the intubation group. The ROX change per day was also statistically different between the groups (HFNT group: mean 1.2, SD 1.3 vs intubation group: mean 0.3, SD 1.2). The ROX before intubation was lowest at 3.4 (SD 1.0) (Table 2).

Figure 2. Average ROX (ratio of oxygen saturation) index progression of the high-flow nasal therapy (HFNT) group and the intubation group (ie, HFNT with progression to invasive mechanical ventilation [IMV]).

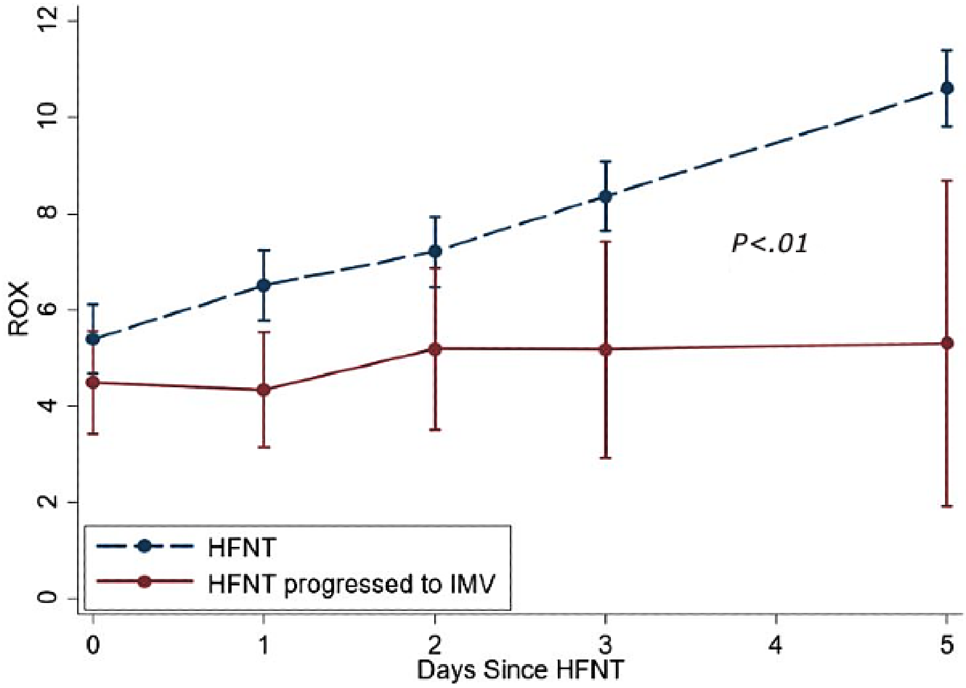


Table 2. ROX (ratio of oxygen saturation) trends comparing the high-flow nasal therapy (HFNT) group and the intubation group (ie, HFNT with progression to invasive mechanical ventilation [IMV]).

Variable	Patients, N	Total ROX, mean (SD)	HFNT only, mean (SD)	Intubation, mean (SD)	*P* value
ROX at HFNT initiation	129	5.1 (2.0)	5.4 (2.1)	4.5 (1.6)	.02
ROX at day 1	119	5.9 (2.5)	6.5 (2.4)	4.3 (1.8)	<.001
ROX at day 2	101	6.9 (3.1)	7.2 (3.2)	5.2 (2.1)	.02
ROX at day 3	98	8.1 (4.1)	8.4 (4.2)	5.2 (1.9)	<.001
ROX at day 5	78	10.3 (5.9)	10.6 (5.9)	5.3 (2.0)	.08
ROX at IMV	40	3.4 (1.0)	—[a]	3.4 (1.0)	—
Mean ROX change per 24 hours	129	0.7 (1.5)	1.2 (1.3)	–0.3 (1.2)	<.001
ROX change per 24 hours	129	0.5 (0 to 1.5)[b]	1.2 (0.3 to 1.7)[b]	0 (–0.5 to 0.1)[b]	<.001

[a]Not applicable.

[b]Median (IQR).

Secondary Outcomes

Overall, mortality at our institution was 6.06% for patients positive for COVID-19 infection. However, in this cohort of severe hypoxemic respiratory failure, the mortality was 22.5% (n=29), with 11.2% (n=10) in the HFNT group and 47.5% (n=19) in the intubation group. Figure 3 shows the Kaplan-Meier curve between the two groups for survival. Of the 10 deaths in the HFNT group, 6 patients were in hospice care while the remaining were categorized as “do not resuscitate/intubate.” Average length of stay was statistically higher in the intubation group (HFNT group: 11.1 days vs intubation group: 19.5 days) (Table 3). The overall incidence of hospital-acquired pneumonia was significantly higher in the intubation group (25% [n=10] vs 1.1% [n=1], *P*<.001).

Figure 3. Kaplan-Meier comparing survival in the high-flow nasal therapy (HFNT) group and the intubation group (ie, HFNT with progression to invasive mechanical ventilation [IMV]).

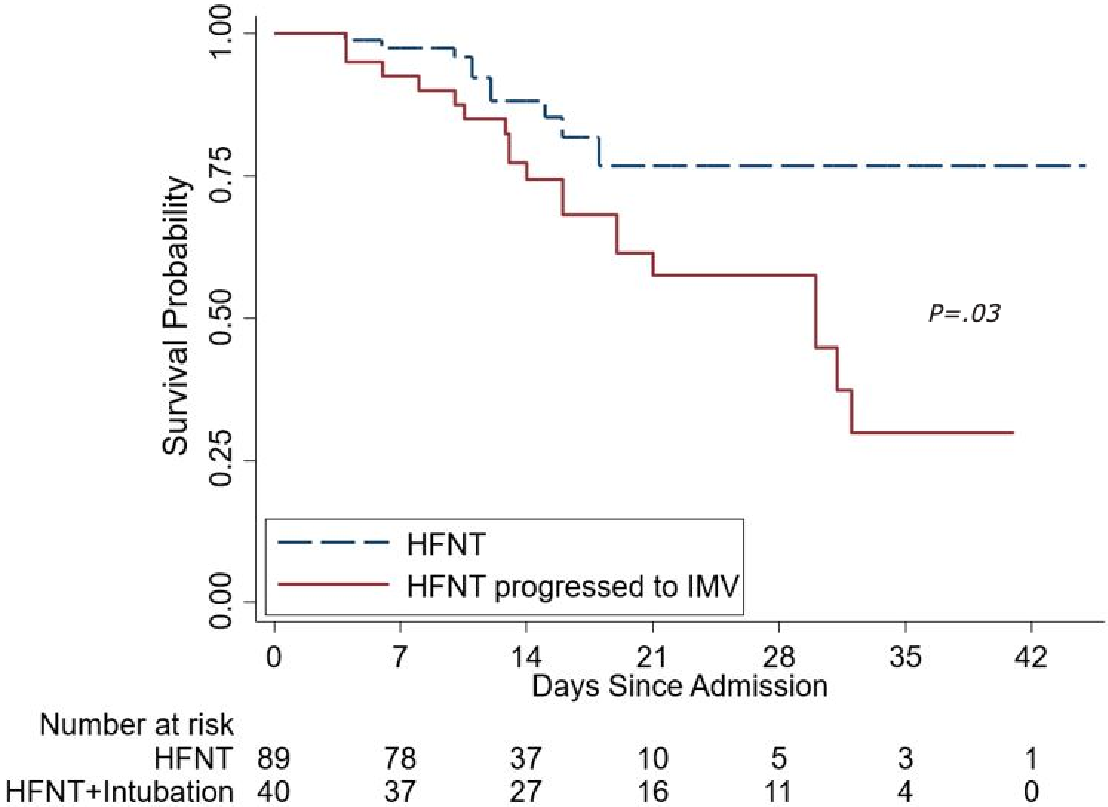


Table 3. Comparison of the high-flow nasal therapy (HFNT) group and the intubation group (ie, HFNT with progression to invasive mechanical ventilation [IMV]) for other outcomes.

Variable	Total (N=129)	HFNT only (n=89)	Intubation (n=40)	*P* value
Days to IMV				—[a]
Mean (SD)	2.5 (3.3)	—	2.5 (3.3)	
Median (IQR)	1 (1.0-3.0)	—	1 (1.0-3.0)	
Mortality, n (%)	29 (22.5)	10 (11.2)	19 (47.5)	<.001
Length of stay, mean (SD)	14.0 (8.0)	11.1 (4.7)	19.5 (9.9)	<.001
HAP[b]/VAP[c], n (%)	11 (8.6)	1 (1.1)	10 (25.0)	<.001

[a]Not applicable.

[b]HAP: hospital-acquired pneumonia.

[c]VAP: ventilator-acquired pneumonia.

Prediction Model

At HFNC initiation, an ROX of <5 was nearly predictive of intubation (odds ratio [OR] 2.137, *P*<.06). Any change in ROX of less than or equal to zero (decrease or no change) after HFNT initiation over 24 hours was also predictive of intubation (OR 14.67, *P*<.001). A decrease in ROX by 1 over 24 hours regardless of the ROX index value was strongly predictive of intubation (OR 5, *P*<.001) (Table 4). Figure 4 shows intubation-free survival based on ROX change (≤0 versus >0) per 24 hours. In the univariate analysis, smoking, history of malignancy, admission LDH >500, peak D-dimer >4000, peak ferritin >1000, peak CRP ≥10, peak LDH >500, an ROX decrease as described above, admission triglycerides >200, and a GFR <60 were all predictive of intubation (Table S1, Multimedia Appendix 2). In the multivariate model, unchanged and/or decreased ROX over 24 hours, peak D-dimer >4000, and GFR <60 were predictive of intubation (Table 4). Figures 5 and 6 show the ROC curve for ROX change over 24 hours (AUC=0.77) and the multivariate model (AUC=0.86), respectively.

Table 4. A logistic regression model for predicting the need for invasive mechanical ventilation.[a]

Variable	Odds ratio	*P* value
ROX[b] at HFNT[c] initiation		.05
≤5	2.137	
>5	1	
ΔROX from baseline (any 24-hour period)		<.001
Decreased by 1	5	
Increased by 1	1	
ΔROX change per day		
≤0	14.671	<.001
>0	1	<.001
Pulmonary vasodilators		.008
Yes	2.83	
No	1	
Final multivariate model		
ΔROX change per day (≤0 vs >0)	13.17	.001
Peak D-dimer (≥4000 vs <4000)	4.47	.003
GFR[d] (≤60 vs >60)	3.29	.02

[a]Univariate model in Multimedia Appendix 2.

[b]ROX: ratio of oxygen saturation.

[c]HFNT: high-flow nasal therapy.

[d]GFR: glomerular filtration rate.

Figure 4. Kaplan-Meier estimator showing intubation-free survival probability by ROX (ratio of oxygen saturation) change per 24 hours. HFNT: high-flow nasal therapy.

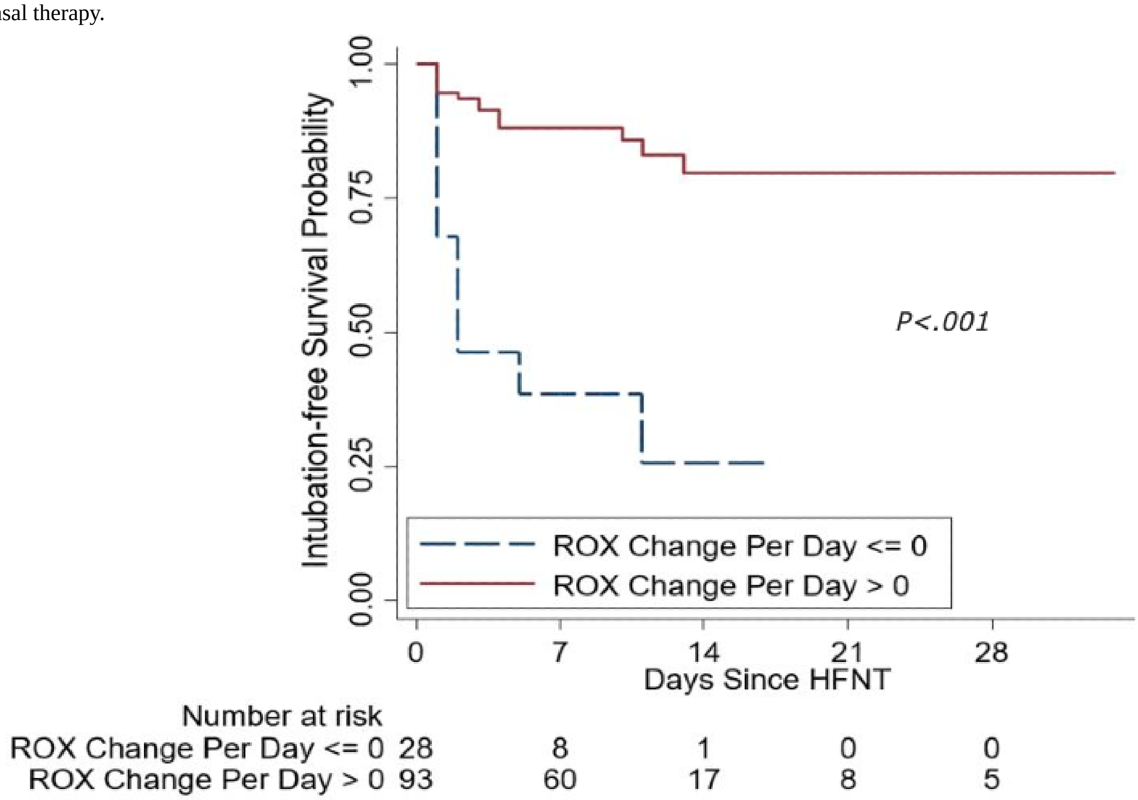


Figure 5. Receiver operating characteristic (ROC) curve predicting need for invasive mechanical ventilation using change in ROX (ratio of oxygen saturation) per 24 hours.

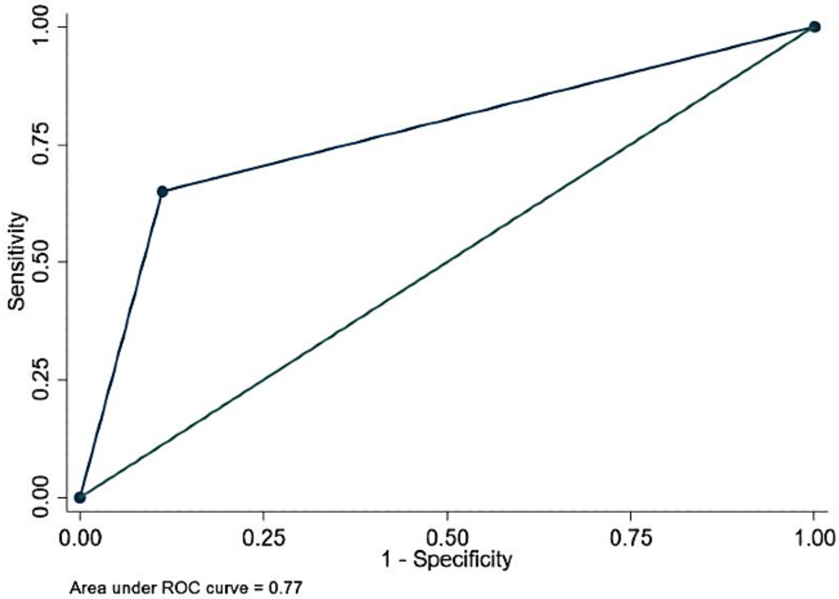
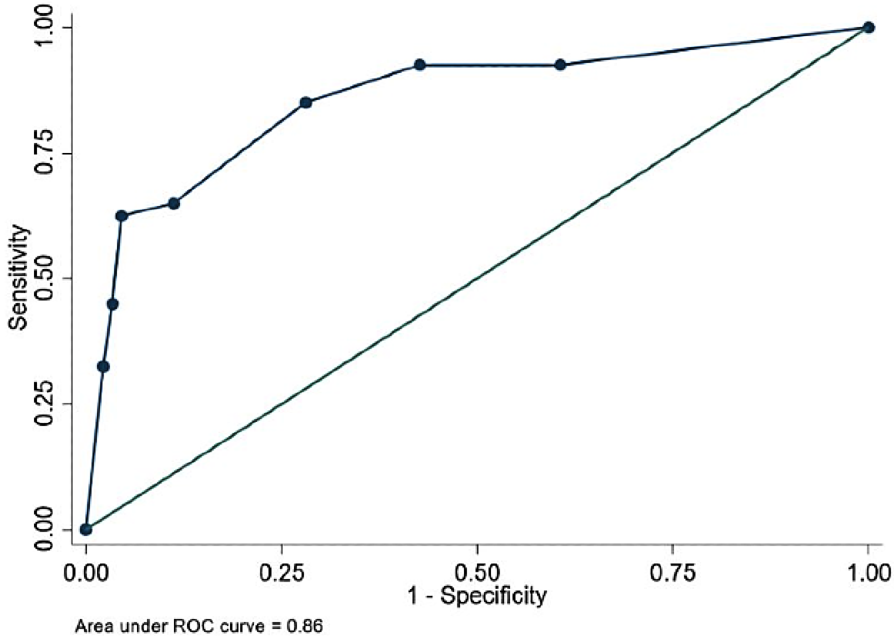


Figure 6. Receiver operating characteristic (ROC) curve of the multivariate model of change in ROX (ratio of oxygen saturation), D-dimer, and glomerular filtration rate to predict need for invasive mechanical ventilation.



Discussion

Principal Findings

In this retrospective review of patients with acute hypoxemic respiratory failure secondary to COVID-19 pneumonia, 129 patients were initially treated with HFNT. Out of this cohort, 89 patients remained on HFNT while 40 patients eventually required IMV. The 89 patients who were successfully treated with HFNT as a bridge to recovery experienced significant improvement in ROX from initiation of HFNT and at all recorded time points. In contrast, the ROX value for patients who ultimately required intubation remained steady or decreased over time. There were no associated deaths peri-intubation despite the presence of significant hypoxemia. There were no reported cases of failure to intubate resulting in an adverse outcome. Overall, the intubation group had a higher incidence of lung disease, chronic kidney disease, smoking, and malignancy.

HFNT is an important oxygen delivery modality that can help reduce intubation as seen by our overall institution intubation rate of 10%, which is significantly lower than what has been reported in the literature [4,6,7]. Moreover, there may be survival benefits to HFNT therapy among COVID-19 cases as seen in prior acute hypoxemic respiratory failure studies [13,25]. Despite our patient population having a higher incidence of lung disease and nicotine exposure than that reported in previous studies, the mortality rate was 22%, which is lower than prior reports [4,6,11].

Gattinoni and colleagues [26,27] proposed that patients with COVID-19 fall into two distinct groups or phenotypes. The "type L" or "non-ARDS type 1" phenotype has low elastance and high compliance. These patients often present with profound hypoxemia and low lung recruitability. The "type H" or "ARDS type 2" phenotype has high elastance and low compliance, requiring traditional management strategies of higher positive end-expiratory pressure (PEEP) and lower tidal volumes [26,27]. A significant number of patients with COVID-19 present with silent hypoxemia. As HFNT provides a modest PEEP effect (ie, 3-5 cm H_2O at flow rates of 30-50 L/min with the mouth closed) [28], patients with predominant type L physiology may benefit from the oxygenation support that HFNC can provide noninvasively. HFNT also leads to a high oxygen reservoir by reducing anatomical dead space in the nasopharynx [29]. Often, higher tidal volumes are employed in the type L phenotype, which can lead to ventilator-associated lung injury (VILI). VILI can cause inflammatory cytokine release in patients with ARDS, including IL-6, both in critically ill people [30,31]. IL-6 in particular is one of the pathologic mechanisms for lung injury in COVID-19 [32,33]. Thus, the use of HFNT should not be overlooked in patients with severe COVID-19 respiratory failure.

Patient self-induced lung injury (P-SILI) has been cited as a theoretical contraindication to noninvasive methods of oxygenation. To date, however, P-SILI remains a conceptual model concept compared to VILI [34,35].

Optimal timing of IMV remains a point of debate, especially in patients previously supported with noninvasive forms of oxygen support, especially with regards to COVID-19. Based on our results, any decrease in the ROX index over a 24-hour period from baseline ROX at HFNT initiation is a strong predictor of intubation, irrespective of the total number of HFNT days. We chose to designate ROX change as ≤0 vs >0 for ease of use in the acute care setting.

Roca et al [23,36] previously used an ROX index of <4.8 at 12 hours to successfully identify patients at high risk for intubation among a cohort of 191 patients treated with HFNC for acute hypoxemic respiratory failure secondary to pneumonia [23,36]. Our analysis further supports their findings in the setting of viral pneumonia as opposed to predominantly bacterial pneumonia as was reported in their study. Our ROC analysis yielded similar results to initial studies. Thus, using serial measurements, we can identify patients on HFNT therapy in whom IMV should be considered based on changes in ROX [37].

Theoretically, the ROX can easily identify patients shifting from the type L to type H phenotype (lower S/F ratios and higher respiratory drive), thus minimizing subsequent risks of P-SILI. Another advantage of using the ROX index is its noninvasive nature based on readily available clinical parameters. The ROX index can be calculated remotely, thus preserving personal protective equipment and limiting health care exposure. When combined with a decreasing ROX index, a GFR <60 and D-dimer >4000 stratifies high-risk patients with increased accuracy. Kidney dysfunction makes patients susceptible to even small fluid shifts, thus worsening hypoxemia. D-dimer levels >4000 might possibly be a sign of microthrombi in pulmonary circulation, which has been described among COVID-19 cases [38].

Viral transmission through aerosolization by noninvasive forms of oxygenation such as HFNT remains controversial and is much debated. During the SARS (severe acute respiratory syndrome) outbreak in 2003, transmission to health care workers was reported in only 8% of HFNT patients [39]. This was demonstrated in further studies that proved that bacterial environmental contamination was not increased in the setting of HFNT use [40]. An in vitro study mimicking clinical scenarios including HFNT with mannequins only revealed proximal dispersion of secretions to the face and nasal cannula itself [41,42]. A recent study with healthy volunteers wearing high-flow nasal cannulas at both 30 L/min and 60 L/min of gas flow did not report variable aerosolization of particles between 10 to 10,000 nm, regardless of coughing, when compared with patients on room air or oxygen via regular nasal cannula [43]. At an institution with dedicated COVID-19 wards, only 1 of 80 staff members in our department had suspicion of health care transmission while directly caring for patients with COVID-19, thus re-emphasizing that HFNT did not present an increased risk of transmission to health care personnel.

Strengths and Limitations

Our study has several strengths. It is the largest reported cohort utilizing HFNT in patients with COVID-19 thus far. The ROX index was able to successfully predict bridge to recovery or progression to IMV without demonstrable adverse effects from delaying the implementation of mechanical ventilation. In a high-risk, urban population with multiple comorbidities, the use of HFNT resulted in a lower rate of intubation, and suggests a possible mortality benefit while maintaining a low risk of health care transmission.

Our study has several limitations as well. First, it is a retrospective review, thus making it susceptible to unintended biases. However, developing a prospective study during a pandemic situation was impractical. Second, although this is the largest HFNT study, the total sample size is limited and representative of a single center's experience. Lastly, we were unable to provide consistent details on the presence and degree of hypercapnia for our cohort due to our institutional policy to minimize staff exposure to COVID-19 infection.

Conclusion

In conclusion, the ROX index serves as an accurate risk stratification tool in patients with moderate and severe hypoxemic respiratory failure secondary to COVID-19 pneumonia. HFNT can be safely and successfully implemented while utilizing the ROX index to predict the need for IMV. Monitoring ROX trends may allow clinicians to avoid any significant delays in escalating the level of care or implementing IMV. The use of HFNT not only reduces intubation rates but also has the potential to reduce mortality and morbidity associated with IMV.

Authors' Contributions

MP is the corresponding author and guarantor for the manuscript. MP, MG, JC, and GC formulated the overall study design. HZ, NP, MP, AG, RM, JC, NM, ZD-S, IY, LT, and JG assisted in data collection, consolidation, and analysis. MP, JC, PR, RG, GD, NM, and MG drafted the manuscript. GC and MG revised and reviewed the manuscript.
Members of the Temple University Research Group have been included in Multimedia Appendix 3.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Treatment protocols.
[DOCX File , 16 KB - xmed_v2i3e29062_app1.docx]

Multimedia Appendix 2
Univariate analysis predicting the need for invasive mechanical ventilation.
[DOCX File , 16 KB - xmed_v2i3e29062_app2.docx]

Multimedia Appendix 3
List of Temple University Research Group collaborators.
[DOCX File , 23 KB - xmed_v2i3e29062_app3.docx]

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Abbreviations

ARDS: acute respiratory distress syndrome
AUC: area under the receiver operating characteristic curve
CRP: C-reactive protein
GFR: glomerular filtration rate
HFNT: high-flow nasal therapy
HRCT: high-resolution computerized tomography
IL-6: interleukin 6
IMV: invasive mechanical ventilation
LDH: lactate dehydrogenase
OR: odds ratio
P-SILI: patient self-induced lung injury
P/F: PaO_2/FiO_2 ratio
PEEP: positive end-expiratory pressure
ROC: receiver operating characteristic
ROX: ratio of oxygen saturation
RT-PCR: reverse transcriptase–polymerase chain reaction
S/F: SpO_2/FiO_2 ratio
SARS: severe acute respiratory syndrome
VILI: ventilator-associated lung injury

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