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Lessons learned in analytics from the COVID-19 pandemic

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Lessons learned in analytics from the COVID-19 pandemic

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Ryan White HIV/AIDS Part B and AIDS Drug Assistance Programs during COVID-19: safety net public health programs' challenges and innovations

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Introduction: We characterized the challenges and innovations of states' Ryan White HIV/AIDS Program (RWHAP) Part B programs, including AIDS Drug Assistance Programs (ADAPs), during the COVID-19 pandemic. In the United States, these are important safety net programs for HIV healthcare, providing essential medical and support services, and medications, to people with HIV with low incomes who are uninsured/underinsured.

Methods: Data were collected via the 2021-2022 NASTAD National RWHAP Part B and ADAP Monitoring Project Report, a cross-sectional survey of state, district, and territorial programs through a mixed method study design. For quantitative data, we used descriptive statistics. Qualitative responses were coded and analyzed using content analysis.

Results: Forty-seven RWHAP Part B and ADAPs responded (92% response rate). The majority of respondents reported that maintaining client eligibility (78%) and working remotely (70%) were the most challenging aspects of the pandemic, particularly in regards to implementing new telehealth and e-certification platforms. In response to COVID-19, programs introduced enrollment "grace periods" (19%), bolstered client outreach (11%), allowed more than a 30 day supply of medications (79%), and supported medication home delivery for clients (80%).

Discussion: Despite the challenges of the COVID-19 pandemic, RWHAP Part B and ADAPs implemented several operational innovations in order to continue providing essential medicines and services. Other public health programs may adopt similar innovations, including digital innovations, for greater public health benefit. Future studies should assess the retention of policy innovations over time, their impact on the individual client level satisfaction or health outcomes, and what factors may improve the acceptability of telehealth and e-certification platforms.

KEYWORDS

AIDS Drug Assistance Program, HIV, COVID-19, Ryan White HIV/AIDS Program, public health practice

1. Introduction

In the United States (US), Ryan White HIV/AIDS Program (RWHAP) state Part B programs and state AIDS Drug Assistance Programs (ADAPs) are key pillars of the HIV healthcare delivery safety net. State RWHAP Part B programs support core medical and support services in all 50 states, the District of Columbia, and US territories (1). RWHAP Part B also include ADAPs, which provide free medications, including antiretroviral therapy, or subsidized insurance plan coverage to people with HIV with low incomes who are uninsured/underinsured (2). In 2020, the COVID-19 pandemic upended the economy and led to record unemployment (3). The demand on income eligibility-based safety net programs, such as RWHAPs and ADAPs, may surge when economic disruptions occur (4, 5). Thus far, HIV and COVID-19 have been co-located in geographic areas with greater poverty and unemployment, highlighting how adverse social determinants can amplify disease burden and attenuate public health responses in these communities (6–9). Because RWHAP Part B and ADAPs are a "payer of last resort," they work in tandem with other health coverage programs (10). Therefore, the federal and state expansion of broader safety net programs in response to COVID-19 directly impacted how Part B programs and ADAPs could respond. For example, the federal requirement that state Medicaid programs provide continuous coverage during the Public Health Emergency (PHE) (11) undoubtedly sustained medication access for many people with HIV and likely led to less of a surge in need for ADAP support.

Recently, the Kaiser Family Foundation surveyed directly-funded RWHAP medical provider grantees during the COVID-19 pandemic and reported on additional aspects of the impact of COVID-19 on HIV care (12, 13). They found that while many RWHAP medical provider grantees had operating challenges, grantees adjusted in many ways including by using telehealth and offering COVID-19 testing. Despite this work, the experience of state RWHAP Part B programs and ADAPs during COVID-19 has not been described in the published literature. ADAPs are in a unique position as a safety net public health program based at state health departments. Additionally, while ADAPs are federally mandated, they are funded by a combination of federal and state funds, and most implementation decisions are made at the state level (5, 14). RWHAP Part B program implementation also has a lot of flexibility at the state level. Our objective was to explore how RWHAP Part B and ADAPs responded to the COVID-19 pandemic, what challenges they faced, and what innovations were developed to overcome barriers and maintain service delivery.

2. Materials and methods

2.1. Data collection

Data were collected as part of the 2021–2022 National Alliance of State & Territorial AIDS Directors (NASTAD) National RWHAP Part B and ADAP Monitoring Project Report, an annual cross-sectional survey of state and territorial programs (15). The survey reports on utilization, expenditures, and client outcomes. Data on programs' practices during the COVID-19 pandemic to-date were collected between May and July 2021. This study was reviewed by the University of Virginia Institutional Review Board and was determined to be non-human subject research.

To understand the impact of COVID-19, questions were added to the 2021–2022 Monitoring Project survey. They included: 7 Likert-style questions assessing the impact of COVID-19-related challenges for ADAPs, 3 Likert-style questions regarding specific innovations ADAPs implemented to address the challenges, and 3 open-ended, text-entry based questions for both programs to detail challenges and innovations that affected their specific programs (Supplementary material 1). State program leaders were asked to complete the questions. NASTAD and University of Virginia staff assessed data quality to ensure response accuracy.

2.2. Quantitative data analysis

We calculated overall response rates for each question and reported at the national and regional level. Regions were defined according to the US Census Bureau: Northeast, Midwest, West, and South (16). At the regional level, we evaluated differences in categorical responses by calculating proportions and applied Fischer's exact test. Data were analyzed using R Studio (17). P values <0.05 are reported in the text.

2.3. Qualitative data analysis

Text responses were transcribed verbatim. We used both an inductive and directed coding approach to guide the qualitative analysis using content analysis (18). An initial codebook was developed using an open coding approach and constant comparison to describe phenomena of interest described from the program's experience. We assessed the richness and quality of the data concurrently throughout the iterative development and refinement of the codebook. We maintained field notes to document the iterations and refinements. The codebook was then applied in a directed approach independently by two reviewers. The initial applications were compared by calculating inter-rater agreement (Krippendorff's alpha) (19). Codes and descriptions applied inconsistently by reviewers were revised and resolved by consensus.

Due to the nature of the interview questions prompting discussion of difficulties and allowances made during the pandemic, codes were grouped conceptually into two topics: challenges and innovations. Each topic contained codes, related sub-codes, code application frequency, code presence frequency, and exemplar quote(s). To maintain rigor, decisions regarding the analysis (re-parenting or merging codes) were open to all members of the study team (20). All aspects of the codebook development and application were managed using Dedoose (21).

Quantitative and qualitative results are described together topically in results. We created a situational map that depicts codes present in >5% of responses. Based on responses and reviewer interpretation, interconnected sub-codes are represented using lines. Arrows were added when reviewers interpreted a relational connection.

3. Results

Forty-seven programs responded to the COVID-19 Likert-style questions as part of the Monitoring Project survey yielding a national response rate of 92%. Regionally, the sample consisted of 11 Midwest (92%, response rate), 9 Northeast (100%), 15 South (88%), and 12 West

(92%) jurisdictions. Quantitative findings are in Tables 1, 2. Forty-five programs answered the open-ended questions yielding a national response rate of 88%. The initial codebook applications achieved a Krippendorff's alpha of 0.82, indicative of strong agreement. For the qualitative analysis, codes, presence, frequency, and representative quotes are in Supplementary Table 1 (challenges) and Supplementary Table 2 (innovations). In addition, codes and sub-codes are depicted in a situational map (Figure 1). The topics of challenges and innovations are described in five codes: (1) Eligibility and Enrollment, (2) Administrative, (3) Medical, (4) Ancillary Services, and (5) Policy.

3.1. Challenges – eligibility and enrollment

Until recently, ADAPs were required to recertify ADAP eligibility every 6 months, which required collection of income documentation and client signatures. ADAPs reported challenges with enrolling and ensuring eligibility of their clients during the first year of the COVID-19 pandemic. The majority of ADAPs indicated the maintenance of client eligibility was the most challenging issue, with 38 ADAPs (81%) describing it as 'very' or 'somewhat' challenging (Table 1). However, nearly half of the Midwest jurisdictions found maintaining eligibility to be 'not challenging' (45%). One Northeast program described the challenge stating, "Case managers being unable to meet with clients in person to obtain/explain documents. Loss of employer insurance and challenges related to getting unemployment information from clients" (Supplementary Table 1).

Churning refers to the transition of clients on and off RWHAP Part B and ADAP services. Churning on and off was identified as 'very' or 'somewhat' challenging among 64% of ADAPs, while others rated clients churning within ADAP programs (example: from full pay to/from subsidized insurance) similarly (62%). Churning can be caused by a number of factors, including onerous application and re-determination systems that make it hard to stay enrolled in coverage even when individuals are eligible. Churning on or off ADAP can also be due to changes in life circumstances that affect eligibility for certain programs such as abrupt loss of employer-sponsored insurance necessitating enrollment in ADAP, or a loss of income causing movement out of ADAP and into Medicaid. The majority of programs (60%) found that technical issues that hindered client's ability to transmit eligibility documentation were 'very' or 'somewhat' challenging. Additionally, the majority (60%) were not challenged by technical issues related to Health Insurance Portability and Accountability Act (HIPAA).

3.2. Challenges – administrative

As public health safety net programs operating within state health departments, RWHAP Part B and ADAPs were impacted by the workforce response to the pandemic. Seven programs (16%) noted a decrease in staffing due to re-allocation as part of the public health response to COVID-19, as well as due to quarantine requirements (4%). Interestingly, twenty (43%) ADAPs found that maintaining adequate staffing was 'not challenging' while twenty (43%) found it to be 'very' or 'somewhat' challenging. Programs found working remotely 'very' or 'somewhat' challenging (70%), with some programs stressing the difficulty establishing rapport with clients (11%) and the limited interpersonal assistance they could provide (16%). Programs also noted the burden to staff's mental health (9%), with one stating, "The program was acutely aware of and responsive to behavioral health and trauma informed considerations related to workforce staff and patients" (South program). Lastly, 5 (11%) programs described the operational challenges tied to increased program expenditures related to increased demand for services including food delivery, telehealth, and emergency financial assistance.

3.3. Challenges – medical

RWHAP Part B programs described the difficulties providing medical services for clients. Closures of facilities following stay-at-home advisories were noted by 9 programs (20%). The implementation of telehealth platforms enabled practitioners to provide routine care while negating transmission risk, but some programs reported diminished benefits due to poor accessibility of these platforms (16%) and the lack of technology-focused educational resources (13%). One Midwest programs described the challenges: "Telehealth provided an avenue to organizations; however, it presents its own challenges and barriers. The technology is new to most service providers, some of whom did not have the bandwidth to quickly adapt. Also, there are many different platforms, some are prohibitively costly for small sized community-based and AIDS Service Organizations to afford. Thus, most of these providers relied on telephonic contact with clients, which was not ideal." Following the implementation of telehealth platforms and the re-opening of clinics, some programs noted a delay in laboratory services, with a South program adding "Data is stating [*sic*] to reveal overdue labs now that we are more than 12 months into the pandemic." Five programs experienced issues related to medication access (11%), with some specifying the delays in mail delivery of medications (4%).

3.4. Challenges – ancillary services

In addition to disrupting medical care, the COVID-19 pandemic introduced barriers for clients accessing vital ancillary services. Lack of access to transportation services was noted by 5 programs (11%), particularly for clients in "rural areas" (South program) and because, "clients had fear using public transportation for ANY service appointment" (South program). Lack of access to housing services were described among 9% of program, with a West program reporting that "Early on in the pandemic there were a lot of incidents of homeless RW patients requesting hotels, as to avoid congregate settings, especially when winter hit. These incidents clashed with program rules and limited funding for EFA [Emergency Financial Assistance]." Lastly, two programs reported issues with access to dental services due to clinic closures (4%).

3.5. Challenges – policy

The Coronavirus Aid, Relief and Economic Security Act -P.L. 116–136 (CARES Act) provided emergency funding for programs to enable uninterrupted service for their clients (22). While appreciative of the funding, some reported challenges with spending the money (7%), with two programs noting contradictory

TABLE 1 Challenges during first year of the COVID-19 pandemic for AIDS drug assistance programs, overall and by region, 2020.

Challenges	Total (n = 47)		Region								
			Midwest (n = 11)		Northeast (n = 9)		South (n = 15)		West (n = 12)		
	n	%	n	%	n	%	n	%	n	%	p*
Maintenance of eligibility											0.4
Very challenging	15	32%	3	27%	2	22%	5	33%	5	42%	
Somewhat challenging	23	49%	3	27%	6	67%	8	53%	6	50%	
Not challenging	9	19%	5	45%	1	11%	2	13%	1	8%	
Not applicable	0	0%	0	0%	0	0%	0	0%	0	0%	
IT issues – document sharing											>0.9
Very challenging	10	22%	1	9%	2	22%	4	27%	3	27%	
Somewhat challenging	18	39%	5	45%	3	33%	6	40%	4	36%	
Not challenging	16	35%	5	45%	3	33%	5	33%	3	27%	
Not applicable	2	4%	0	0%	1	11%	0	0%	1	9%	
IT issues – HIPAA-specific											0.8
Very challenging	6	13%	0	0%	1	11%	3	20%	2	17%	
Somewhat challenging	12	26%	5	45%	2	22%	3	20%	2	17%	
Not challenging	28	60%	6	55%	6	67%	9	60%	7	58%	
Not applicable	1	2%	0	0%	0	0%	0	0%	1	8%	
Staff turnover											0.06
Very challenging	9	20%	1	9%	4	44%	1	7%	3	27%	
Somewhat challenging	11	24%	4	36%	1	11%	6	40%	0	0%	
Not challenging	20	43%	6	55%	3	33%	7	47%	4	36%	
Not applicable	6	13%	0	0%	1	11%	1	7%	4	36%	
Remote work/telework											0.5
Very challenging	9	19%	0	0%	2	22%	5	33%	2	17%	
Somewhat challenging	24	51%	8	73%	4	44%	5	33%	7	58%	
Not challenging	14	30%	3	27%	3	33%	5	33%	3	25%	
Not applicable	0	0%	0	0%	0	0%	0	0%	0	0%	
Churning on and off ADAP											0.12
Very challenging	5	11%	3	27%	0	0%	0	0%	2	17%	
Somewhat challenging	25	54%	5	45%	5	56%	7	50%	8	67%	
Not challenging	15	33%	3	27%	4	44%	7	50%	1	8%	
Not applicable	1	2%	0	0%	0	0%	0	0%	1	8%	
Churning within ADAP programs											0.8
Very challenging	5	11%	2	18%	1	11%	1	7%	1	8%	
Somewhat challenging	24	52%	6	55%	4	44%	6	46%	8	67%	
Not challenging	15	33%	3	27%	4	44%	6	86%	2	17%	
Not applicable	2	4%	0	0%	0	0%	1	100%	1	8%	

* Fisher's exact test.

Missing response: Missing responses: IT issues Document Sharing (1), Staff Turnover (1), Churning on and off ADAP (1), Churning within ADAP programs (1).

and time-consuming reporting requirements (4%). One program summarized: "The CARES Act resources were greatly appreciated, needed and well used to improve responsiveness in meeting service needs of People Living with HIV. However, this separate funding stream required additional specific administrative burden at multiple levels, from providers having to code and report on additional service category codes, additional line items to be processed during invoicing and monitoring and added reporting requirements. This higher level of administrative burden was especially challenging considering the COVID-19 context. Yet, the additional resources assisted people with HIV with high needs and were valued at all levels" (South program).

TABLE 2 Innovations and allowances enacted by state AIDS drug assistance programs during first year of the COVID-19 pandemic, overall and by region, 2020.

Innovations/allowances	Total ($n = 47$)		Region								
			Midwest ($n = 11$)		Northeast ($n = 9$)		South ($n = 15$)		West ($n = 12$)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*p**
More than 30 days of medications											0.8
Did offer	37	79%	9	82%	7	78%	10	67%	11	92%	
Did not offer	6	13%	1	9%	1	11%	3	20%	1	8%	
Considered/considering	3	6%	1	9%	0	0%	2	13%	0	0%	
Not applicable	1	2%	0	0%	1	11%	0	0%	0	0%	
E-certification for eligibility											0.4
Did offer	29	62%	7	64%	3	33%	10	67%	9	75%	
Did not offer	12	26%	3	27%	2	22%	4	27%	3	25%	
Considered/considering	2	4%	0	0%	2	22%	0	0%	0	0%	
Not applicable	4	9%	1	9%	2	22%	1	7%	0	0%	
Newly started to mail medications											0.05
Did offer	11	23%	2	18%	0	0%	2	13%	7	58%	
Did not offer	9	19%	1	9%	2	22%	4	27%	2	17%	
Not applicable	27	57%	8	73%	7	78%	9	60%	3	25%	

*Fisher's exact test.

3.6. Innovations – eligibility and enrollment

As the challenges of the pandemic grew, programs developed innovative strategies to minimize service gaps and provide flexibility to clients. The majority of ADAPs introduced e-certification (completing certification and re-certification entirely electronically) to facilitate client eligibility (62%) while 12 (26%) elected not to offer this service (Supplementary Table 2). Regionally, offering e-certification was more infrequent among Northeast jurisdictions (33%) compared to the Midwest (82%), South (78%) and West (92%). Some programs streamlined the e-certification process for clients through online document sharing platforms (20%). Furthermore, 36% of programs streamlined enrollment with self-attestation for income and residency status and used verbal or text-based signatures. Nine programs chose to introduce grace periods and waivers (20%) to provide flexibility during enrollment: "ADAP staff would get permission over the phone and assist clients with their online application and provide one month of temporary coverage until the client or case manager could provide all documentation" (Midwest program).

3.7. Innovations – administrative

Following the initial stay-at-home advisories, programs adapted their workforce model to primarily telework-based. Four programs highlighted how these changes helped to increase organizational structure (9%), with one stating, "ADAP set up internal secure folder structure for daily operational needs for ADAP staff that became very efficient after initial staff training and use" (South program). Others noted how this structure negated physical paperwork and expedited documentation processing for clients (4%). Five programs found that the new model helped case managers maintain client engagement by increasing outreach (11%) with 3 noting how the changes led to increased check-ins (7%). As the pandemic continued, some programs recognized the emotional trauma to staff and clients, and introduced pandemic stress and trauma programming for staff and clients (4%).

3.8. Innovations – medical

In response to the pandemic, programs employed a series of measures to minimize gaps in HIV care. Thirteen programs (29%) highlighted new telehealth platforms for facilitating virtual check-ins, particularly following the success of user training (9%) and for jurisdictions who were developing their platform prior to the pandemic (9%). To increase medication access, the majority of ADAPs allowed clients to obtain more than 30 days of medications (60 or 90 day fills) (79%). Almost all West programs (92%) offered this innovation. While over half of ADAPs already had a mechanism for mailing clients their medications (57%), 11 (23%) began offering this service during the pandemic, particularly in the West (58%, $p < 0.05$). Some programs allowed clients to obtain refills early (11%). One Northeast program summarized their innovations in service delivery: "The [program] have implemented steps to further streamline enrollment, and changes to both pharmacy and primary care formularies allow for extended supplies, early refills, telehealth options, and other methods to assist in minimizing exposure to COVID-19 for participants while allowing for uninterrupted access to care."

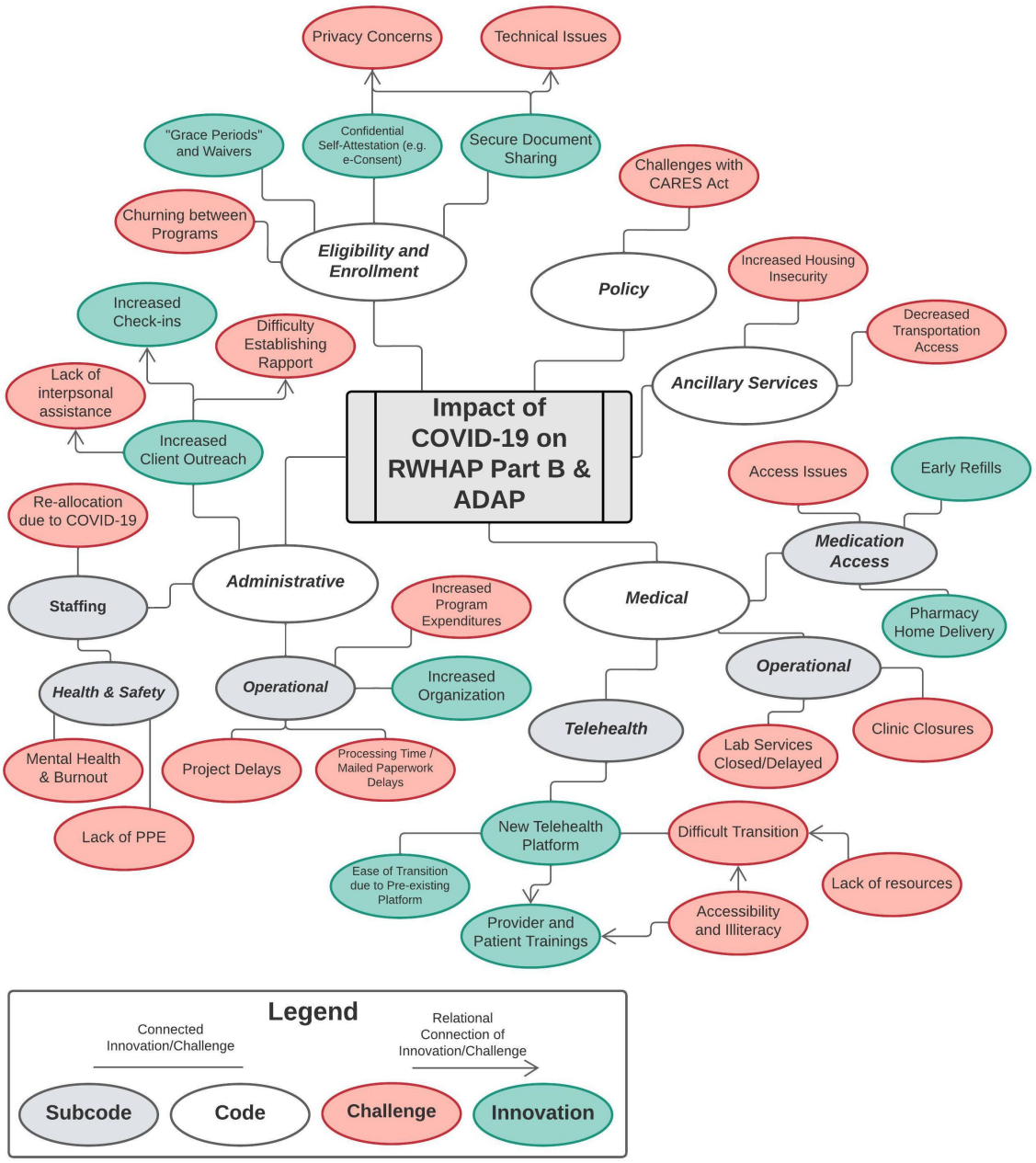

FIGURE 1
Situational map of codes and sub-codes, describing the challenges of COVID-19 and subsequent innovations implemented by ryan white HIV/AIDS program Part B and AIDS drug assistance programs.

4. Discussion

Our study highlights the breadth of challenges to state RWHAP Part B and ADAPs during the initial phases of the COVID-19 pandemic, and the innovations they developed in order to continue providing prescription drug assistance and medical care. For ADAPs, the maintenance of client eligibility was identified as the most challenging issue, and the majority allowed clients to obtain more than 30 days of medication. One-fifth to one-quarter of RWHAP Part B programs noted challenges with clinic closures and delayed lab services, and one-third described the implementation of an innovative telehealth platform. Our analysis reflects that during the first year of the pandemic the majority of programs employed flexible, innovative policies in response to ongoing challenges.

During the initial months of the pandemic, the Health Resources and Services Administration (HRSA) provided guidance to programs that clarified enrollment and service delivery policy and introduced changes as the pandemic progressed. In September 2020, HRSA released comprehensive documents interpreting existing policy requirements (23) in the context of the pandemic, and encouraged programs to exercise flexibility in determining eligibility, promoting remote documentation processes, and recertification (24, 25). By October 2021, HRSA introduced additional flexibilities by eliminating

the 6 month recertification requirement and continuing to allow programs to confirm eligibility in accordance with their policies and procedures (26). Further research is warranted to assess how these policies impact client outcomes, and if any can be permanently adopted to optimize care and prevention into the future.

Our findings detailing the program's perspectives are similar to what has been found for providers of the RWHAP. Kaiser Family Foundation's survey of directly funded RWHAP medical provider grantees found similar service delivery innovations during the pandemic (12). Nine out of 10 RWHAP clinicians reported offering multi-month ART prescriptions (12) while we found that 8 out of 10 ADAPs allowed ART prescriptions for more than 30 days. Almost 40% of RWHAP clinicians reported a change in payer mix, primarily an increase in clients who were uninsured, and this is in line from a programmatic perspective with more than half of ADAPs reporting that clients churning on and off ADAP was 'very' or 'somewhat' challenging. In contrast, while 61% of ADAPs reported an increase in total expenditures for over $200 million between 2019 and 2020 (15), we only found 11% of programs noting this trend in the open-ended responses. As RWHAP Part B programs and ADAPs are vital in ensuring continued access to HIV care, the identification and uptake of innovative policies and practices to prevent coverage gaps is critical and will be particularly relevant as Medicaid's continuous coverage requirement is repealed as the PHE concludes.

Since the completion of our study, the 2023 National RWHAP Part B and ADAP Monitoring Project Report was published and provides additional insight regarding COVID-19 innovations that were implemented in 2020 and 2021, particularly in the digital public health sphere (27). Of the 37 states who utilized e-consent as of 2022, 33 programs (89%) indicated they were 'somewhat likely' or 'very likely' to continue its use. Regarding the use of secure document sharing for enrollment and recertification, 45 states (98%) were 'very likely' to continue, and only one state (2%) indicated they were 'very unlikely' to continue. The high level of continuation of these digital public health tools seems to signal that programs found this beneficial. While both of these digital tools have a clear utility and high acceptance among these safety net programs, it is critical to recognize and minimize the barriers to access for communities negatively affected by social determinants of health (28). Safety net programs need to adapt and innovate on digital public health tools so that they adequately serve and address the needs of their key populations.

The strengths of this work include that it is a national sample with a high response rate, and the study was conducted close to the time period in question so recall bias was likely minimal. Furthermore, a study from a national scope has not been published to date. The limitations include the possibility of non-response bias (29) as participating programs may differ from those that did not respond. Additionally, the response rate for the open ended questions was lower than for the quantitative survey questions. Finally, because it was a cross-sectional design, we could not identify dynamic challenges and innovation as the COVID-19 pandemic unfolded. Future work in this area is needed.

Overall, our findings characterize the measures RWHAP Part B programs and ADAPs took to provide clients with essential services during the first year of the COVID-19 pandemic. Other public health programs may learn from these HIV programs and adopt similar innovations, particularly the digital public health tools including secure document sharing via an online platform and e-certification for eligibility. Future studies should evaluate the impact these innovations had for patients, what potential barriers inhibit their widespread use for programs and patients, and what adopted flexibilities can be sustained to optimize service delivery during later phases of the pandemic and post-pandemic.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: some of the data in this study are publicly available: https://nastad.org/partb-adap-2021-2022-report. Additional data was accessed through a data use agreement with NASTAD. Interested parties can contact NASTAD to discuss data access with a data use agreement. Requests to access these datasets should be directed to https://nastad.org/.

Author contributions

KM, AmS, AnS, AK, TH, AH, JK-M, contributed to the conception and design of the study. KM, AmS, ZA, AnS, contributed to the acquisition of the data. KM, AnS, ZA, ES, JK-M contributed to the statistical analysis, interpretation, and visualization of data. KM, AnS, AK, AnS, AH, JK-M wrote sections of the manuscript and provided revisions. All authors read and approved the submitted version.

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Conflict of interest

KM reports previous stock ownership in Gilead Sciences, Inc. KM also reports unpaid leadership positions: member of the Ryan White Medical Providers Coalition Steering Committee and Chair of the Advisory Committee to Virginia Medication Assistance Program. AK reports being a paid consultant for NASTAD and JSI, working on RWHAP Part B/ADAP technical assistance, and a paid consultant for the HRSA HIV/AIDS Bureau for their Division of State HIV/AIDS Programs. AS reports stock ownership in Merck & Company.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1172009/full#supplementary-material

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Scoping review of the methodology of large health surveys conducted in Spain early on in the COVID-19 pandemic

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Background: The use of health surveys has been key in the scientific community to promptly communicate results about the health impact of COVID-19. But what information was collected, where, when and how, and who was the study population?

Objective: To describe the methodological characteristics used in large health surveys conducted in Spain early on in the COVID-19 pandemic.

Methods: Scoping review. Inclusion criteria: observational studies published between January 2020 and December 2021, with sample sizes of over 2,000 persons resident in Spain. Databases consulted: PubMed, CINAHL, Literatura Latinoamericana y del Caribe en CC de la Salud, Scopus, PsycINFO, Embase, Sociological Abstracts, Dialnet and Web of Science Core Collection. We analyzed the characteristics of the literature references, methodologies and information gathered in the surveys selected. Fifty five studies were included.

Results: Sixty percentage of the studies included had mental health as their main topic and 75% were conducted on the general adult population. Thirteen percentage had a longitudinal design, 93% used the internet to gather information and the same percentage used non-probability sampling. Thirty percentage made some type of sampling correction to reduce coverage or non-response biases, but not selection biases. Sixty seven percentage did not state the availability of their data.

Conclusions: Consistent with the extensive use of non-probability sampling without any bias correction in the extraordinary setting created by COVID-19, quality population frameworks are required so that probability and representative samples can be extracted quickly to promptly address other health crises, as well as to reduce potential coverage, non-response and particularly selection biases by utilizing reweighting techniques. The low data accessibility despite the huge opportunity that COVID-19 provided for Open Science-based research is striking.

KEYWORDS

COVID-19, surveys and questionnaires, mental health, non-probability surveys, reweighting

Introduction

Health surveys are a fundamental support tool for decision-making in health planning. They provide information on magnitude, distribution and trends in health, the social factors that determine them and the use of social services from the population's perspective. They permit identification of the main challenges for prioritizing activity, designing and developing intervention strategies, evaluating and allocating resources, and the main risk groups in terms of health, lifestyles, and access to health services (1).

The highly significant role of surveys for Public Health was greater still with the COVID-19 pandemic due to the urgent requirement for its health impact outcomes to be conveyed (2). This context led the scientific community, regardless of location or area of expertise, to gather information about the pandemic quickly, and here surveys were the key tool. This resulted in the publication of an extremely large number of scientific articles mainly relating to population lockdown and restrictions on mobility (3–9); measures that brought changes and adaptations to the methods and techniques for collecting information through surveys.

In this respect, non-probability surveys conducted with volunteers via the internet proliferated: for example, via websites, mobile apps, and publicity on social media. These types of survey enable statistics to be accessed more rapidly and at the same time provide an inexpensive means of compiling data, although they are subject to selection and coverage biases. This does not happen with probability surveys, often used by health statistics services such as Gold Standard, since they enable valid inferences to be made about the population without having to include hypotheses in models (10, 11). Furthermore, sampling theory based on distribution of probability arising from sample design enables any potential sampling errors in the estimators concerned to be determined and controlled (11).

Prior statistical reweighting is therefore necessary in non-probability sampling in order to obtain valid and precise estimates that eliminate, or at last reduce, these biases (12, 13). In sum, the survey methodology used to compile and analyze information has a direct effect on the quality of the results obtained.

Finally, the use of health surveys has been key in the scientific community to promptly communicate results about the health impact of COVID-19. But what information was collected, where, when and how, and who was the study population? This research question justified the study objective of this work as the performance of a scoping review to describe the methodological characteristics of large health surveys conducted in Spain at the beginning of the COVID-19 pandemic.

Methods

We performed a scoping review (14) using the methodological framework developed by Arksey and O'Malley (15) and the Joanna Briggs Institute (16), and reported in line with PRISMA-ScR guidelines (17). We based our scoping review following the Population, Concept and Context (PCC) format as the research review question (18). Thus, the research review question for the Population was "Spanish surveys," for the Context was "COVID-19," and for the Concept was "Survey Methodology."

TABLE 1 Search terms (PubMed search strategy).

1. ("surveys and questionnaires" [MeSH Terms] OR "health surveys" [MeSH Terms] OR "healthcare survey" [Text Word] OR survey* [Text Word] OR questionnaire* [Text Word] OR interview* [Text Word])
2. ("COVID-19" [All Fields] OR "COVID-19" [MeSH Terms] OR "COVID-19 vaccines" [All Fields] OR "COVID-19 vaccines" [MeSH Terms] OR "COVID-19 serotherapy" [All Fields] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 nucleic acid testing" [All Fields] OR "COVID-19 nucleic acid testing" [MeSH Terms] OR "COVID-19 serological testing" [All Fields] OR "COVID-19 serological testing" [MeSH Terms] OR "COVID-19 testing" [All Fields] OR "COVID-19 testing" [MeSH Terms] OR "sars cov 2" [All Fields] OR "SARS-CoV-2" [MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2" [All Fields] OR "ncov" [All Fields] OR "2019 ncov" [All Fields] OR (("coronavirus" [MeSH Terms] OR "coronavirus" [All Fields] OR "cov" [All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))
3. "Spain" [Text Word]
4. 1 AND 2 AND 3

The following databases were consulted: PubMed, CINAHL (Ebscohost), Literatura Latinoamericana y del Caribe en CC de la Salud (LILACS), Scopus, PsycINFO (Proquest), Embase (Elsevier), Sociological Abstracts (Proquest), Dialnet and Web of Science Core Collection. We selected biomedical and multidisciplinary databases because most of the surveys during the pandemic were related to social services and according to the following criteria:

- Databases with large coverage and large numbers of journals included: Pubmed, Scopus, Embase.
- Databases with Spanish journals and articles in Spanish included: LILACS, Scopus, Dialnet.
- Databases specializing in health literature: Pubmed, CINAHL, Embase.
- Databases specializing in socio-sanitary literature: PsyINFO, Sociological Abstract, WOS, Scopus.

This search was complemented with gray literature information sources: OpenGray (unpublished literature), Gray Literature Report, the University of Oxford Global Directory for COVID surveys (https://supertracker.spi.ox.ac.uk/surveys/) and open searches in Google. The searches were developed between January 2020 and December 2021. These coverage dates of the databases were given by the novelty of the subject, COVID-19. There were no language restrictions. The search strategy was conducted through a combination of controlled terminology (MeSH/Emtree) and free language representative of the concepts COVID-19, surveys, and Spain, and was adapted to the different databases consulted (Table 1).

The results were transferred to a Mendeley database, subsequent to which we identified and classified articles on the Rayyan web platform, eliminating duplicate references (19). Initial selection was performed by peers (ACL, EM, AO, CSC, and DY) through screening titles and abstracts for eligibility. In the event of disagreement, a third researcher was asked to arbitrate.

Inclusion criteria were observational studies published between January 2020 and December 2021, with a total effective sample of $\geq$2,000 persons resident in Spain, published in English and Spanish. Exclusion criteria were studies that did not collect any information on perception of physical or mental health, qualitative,

intervention or experimental studies and studies based on records. In the event of several articles stemming from the same survey, the one providing the most information about the survey was selected.

Data were extracted independently (by CSC and DY) using a standardized, predefined form that included variables relating to characteristics:

- Literature references: link to publication, first author institution of work, date of publication, language, name of journal, type of publication (scientific article, report, review, comment, letter), open access (yes/no), impact factor and position (highest quartile) (20).
- Survey: geographical area, study population, study design, sampling design, effective sampling size, sample weighting and other corrections, survey type, date information collected, response rate, waves or measurements, analyses performed, availability of microdata (Tables 1, 2).
- Information collected: objective of study, primary topic [defined as mental health (43), lifestyle habits (27), wellbeing (76), quality of life (29), life satisfaction (42), perceived risk of infection (56), resilience (45) and working conditions (22)], information blocks, scales/composite variables, conclusions, observations (Supplementary Tables 1, 2).

The variables of the second paragraph (survey characteristics) were selected from the STROBE (50) list, given that the studies in this review are observational.

Results

A total of 3,095 articles were identified following the search strategy described above. Two thousand nine hundred twenty-four articles were identified using scientific literature databases and 171 using gray literature. A full-text check was performed on 225 of them, i.e., 6.4 and 21.6%, respectively, for scientific literature databases and gray literature. Finally, 55 references were included for the analysis (Figure 1).

Table 2 shows the methodological characteristics of each survey selected. The majority were signed by first authors from Spanish institutions (88%), 76.4% focused on Spain, 10.9% were conducted in smaller geographical units such as Autonomous Communities or municipalities, and 12.7% in various countries (in addition to Spain).

Almost half of the surveys selected published their results in 2020 (45%) and all of them began field work in 2020, one third of them in March (32.7%), 78.2% during the lockdown (March to April 2020) and 90.9% during the first state of emergency (March to June 2020). In addition, 80% of surveys collected information on one occasion or through one measurement. The YouGov bi-weekly information study (49) was found to have collected data on COVID-19 on 29 occasions.

As regards the study population of the 55 surveys selected for the analysis, 74.5% of them addressed the general adult population as their study population, while 9.1% considered the healthcare professionals (22, 24, 57, 68, 69). The same percentage of studies (3.6%, two surveys) considered as the study population the pediatric population (23, 35), women (29, 73) or people aged above 50 years old (38, 44). We also found one survey on chronic patients (75), on people aged over 50 or 65 years old, on the university community and on armed forces professionals.

The main topics among the selected surveys were mental health (60.0%), lifestyle habits (10.9%), wellbeing (7.3%), and quality of life, life satisfaction, perceived risk of infection, resilience and working conditions (3.6%). Information regarding the objectives, information blocks and scales or composite variables was also gathered and is available in Supplementary Tables 1, 2.

As regards sampling design, four of the fifty-five surveys selected (7.3%) had a probability design (28, 44, 46, 71) and seven (12.7%) were longitudinal surveys (Figure 2) (24, 38, 43, 44, 49, 63, 78), one on healthcare professionals (24) and the rest on the general population. Furthermore, three of these seven longitudinal surveys were cohort studies predating the pandemic (38, 44, 49). 92.7% of the surveys selected for the analysis gathered their data through online surveys, e.g., Qualtrics, Google forms, Lucid, SurveyGizmo or Surveymonkey, and 7.3% by telephone.

In respect of sampling size, 35 surveys had between 2,000 and 5,000 participants (effective sample), two being found with over 50,000 participants (33, 62), both of which were online cross-sectional surveys. Additionally, 92.7% of the surveys included did not report the response rate.

As regards the statistical analysis conducted, thirty-six surveys developed a multivariate model, the most frequent being binary logistic (16), linear (eight surveys) and mixed (six surveys). Other multivariate models used were multi-level (73), cluster (44), principal components (32), random forest (28) and structural equations (6).

The distribution of groups of observations in the health surveys usually differs from the distribution in the survey population due to several reasons (coverage of the sampling frame, sample design, or patterns of unit non-response). Weighting is one of the best ways to reduce variances and to correct for frame deficiencies. In that sense, 30% implemented some type of sampling adjustment (Figure 2). The most frequent correction was of sample representativeness in view of sociodemographic variables using records or reference surveys (ten surveys). Post-stratification and calibration were applied only in four and two surveys, respectively. These methods are usually considered in official governmental surveys to minimize errors associated with incomplete sampling frames and with sampling non-response (79–81). Of note is the Health and Social Survey (71) which, in addition to calibration to reduce potential coverage or representativeness biases, implemented other methods based on Propensity Score Matching and Machine Learning to reduce biases due to lack of response in longitudinal samples. No voluntary or non-probability surveys were identified that used correction to reduce the selection bias concerned.

Lastly, most of the surveys included (67.2%) did not report on the availability of microdata.

Discussion

As far as we are aware, this is the first scoping review on health surveys relating to COVID-19 and their main methodological characteristics; actually, we found only one similar study dating from 2013 (82), albeit based on population health surveys

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TABLE 2 Methodological characteristics of the selected surveys.

Reference	Geographic scope (number of countries)	Study population	Study design	Effective sampling size	Sampling adjustments	Field work (start date)	Analysis performed
Ahrendt et al. (21)	Countries (22)	General population (≥18)	Cross-sectional**	2,000–5,000	Correction factor	April 2020	Descriptive
Ajanovic et al. (23)	Spain	General population (≤16)	Cross-sectional	2,000–5,000	N/A	July 2020	Bivariate
Alonso et al. (24)	Region (6)	Healthcare professionals	Longitudinal	5,000–10,000	Calibration	May 2020	Logistic models
Arpino et al. (25)	Countries (3)	General population (≥18)	Cross-sectional	2,000–5,000	Post-stratification	April 2020	Descriptive
Carpintero-Rubio et al. (26)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	May 2020	Bivariate
Cervera-Martínez et al. (27)	Spain	General population (≥18)	Cross-sectional*	5,000–10,000	N/A	April 2020	Linear models
Codagnone et al. (28)	Countries (3)	General population (≥18)	Cross-sectional***	2,000–5,000	Post-stratification	April 2020	Random forest models
Coronado et al. (29)	Spain	Women 40–70	Cross-sectional	2,000–5,000	N/A	April 2020	Linear models
de Pedraza and Vicente (30)	Spain	General population	Cross-sectional	2,000–5,000	Correction factor	March 2020	Logistic models
Centre d'Estudis d'Opinió (CEO) (31)	Region	General population (≥16)	Cross-sectional	10,000–50,000	Correction factor	April 2020	Descriptive
Faris et al. (32)	Spain	General population	Cross-sectional	2,000–5,000	Post-stratification	May 2020	Tobit models
Farres et al. (33)	Region	General population (≥16)	Cross-sectional	>50,000	N/A	April 2020	Bivariate
Fernández-Prados et al. (34)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	June 2020	Logistic models
Garcia-Adasme et al. (35)	Region	General population (≤16)	Cross-sectional	2,000–5,000	N/A	April 2020	Bivariate
García-Álvarez et al. (36)	Spain	General population (≥18)	Cross-sectional	10,000–50,000	N/A	March 2020	Logistic models
García-Dantas et al. (37)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Bivariate
Garcia-Esquinas et al. (38)	Spain	General population (≥65)	Longitudinal**	2,000–5,000	N/A	April 2020	Mixed models
Garrido-Cumbrera et al. (39)	Spain	General population (≥16)	Cross-sectional	2,000–5,000	N/A	April 2020	Logistic models
Gómez-Salgado et al. (40)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Logistic models
Gonzalez et al. (41)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Bivariate

(Continued)

TABLE 2 (Continued)

Reference	Geographic scope (number of countries)	Study population	Study design	Effective sampling size	Sampling adjustments	Field work (start date)	Analysis performed
Gonzalez-Bernal et al. (42)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Linear models
Gonzalez-Sanguino et al. (43)	Spain	General population (≥18)	Longitudinal**	5,000–10,000	N/A	March 2020	Linear models
Grané et al. (44)	Countries (45)	General population (≥50)	Longitudinal*,***	10,000–50,000	Calibration	June 2020	Cluster
Hidalgo et al. (46)	Spain	General population (≥18)	Cross-sectional***	5,000–10,000	N/A	April 2020	Bivariate
Jacques-Aviñó et al. (47)	Spain	General population	Cross-sectional	5,000–10,000	N/A	April 2020	Logistic models
Jané-Llopis et al. (48)	Region	General population (≥16)	Cross-sectional	10,000–50,000	N/A	April 2020	Linear models
Jones (49)	Countries (50)	General population	Longitudinal**	10,000–50,000	Correction factor	March 2020	Descriptive
Justo-Alonso et al. (51)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Bivariate
Kim and Ryu (52)	Countries (25)	General population	Cross-sectional	2,000–5,000	N/A	March 2020	Mixed models
Lázaro-Pérez et al. (53)	Spain	Armed forces professionals	Cross-sectional	2,000–5,000	N/A	August 2020	Logistic models
López-Bueno et al. (54)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Logistic models
Maestro-Gonzalez et al. (55)	Spain	General population	Cross-sectional	5,000–10,000	N/A	March 2020	Multivariate analysis (N/A)
Mansilla Domínguez et al. (56)	Spain	General population (≥18)	Cross-sectional	10,000–50,000	Post-stratification	March 2020	Logistic models
Martin et al. (57)	Spain	Healthcare professionals	Cross-sectional	2,000–5,000	N/A	April 20	Linear models
Martinez-Bravo and Sanz (58)	Spain	General population (≥18)	Cross-sectional*	2,000–5,000	Correction factor	May 2020	Descriptive
Méndez-Giménez et al. (59)	Spain	General population (≥16; <92)	Cross-sectional	2,000–5,000	N/A	March 2020	Logistic models
Miranda-Mendizabal et al. (60)	Spain	General population	Cross-sectional*	2,000–5,000	Correction factor	October 2020	Logistic models
Morales-Vives et al. (61)	Spain	General population (≥18)	Cross-sectional	2,000–5,000	N/A	March 2020	Bivariate
Oliver et al. (62)	Spain	General population	Cross-sectional	>50,000	Correction factor	March 2020	Logistic models
Viejo et al. (45)	Spain	General population	Cross-sectional	2,000–5,000	N/A	October 2020	Mixed models

(Continued)

TABLE 2 (Continued)

Reference	Geographic scope (number of countries)	Study population	Study design	Effective sampling size	Sampling adjustments	Field work (start date)	Analysis performed
Pérez-Raya et al. (22)	Spain	Healthcare professionals	Cross-sectional	10,000–50,000	Correction factor	April 20	Descriptive
Pinedo et al. (6)	Spain	General population	Cross-sectional	2,000–5,000	N/A	March 2020	Structural Equation models
Planchuelo-Gómez et al. (63)	Spain	General population	Longitudinal*	2,000–5,000	N/A	April 2020	Mixed models
Pouso et al. (64)	Countries (9)	General population	Longitudinal	5,000–10,000	N/A	April 2020	Mixed models
Rodríguez-Barranco et al. (65)	Spain	General population	Cross-sectional	2,000–5,000	N/A	April 2020	Logistic models
Rodríguez-Larrad et al. (66)	Spain	University students	Cross-sectional	10,000–50,000	N/A	April 2020	Bivariate
Rodríguez-Pérez et al. (67)	Spain	General population	Cross-sectional	5,000–10,000	N/A	March 2020	Multivariate analysis (N/A)
Rodriguez-Ruiz et al. (68)	Spain	Healthcare professionals	Cross-sectional*	2,000–5,000	N/A	October 2020	Bivariate
Romero et al. (69)	Spain	Healthcare professionals	Cross-sectional	2,000–5,000	N/A	April 2020	Bivariate
Salas-Nicás et al. (70)	Spain	General population	Cross-sectional	10,000–50,000	Correction factor	April 2020	Bivariate
Sánchez-Cantalejo et al. (71)	Region	General population (≥16)	Longitudinal**,***	10,000–50,000	Calibration, Propensity Score Matching, Machine Learning	April 2020	Mixed models
Valiente et al. (72)	Spain	General population	Cross-sectional	2,000–5,000	N/A	April 2020	Logistic models
Vall-Roqué et al. (73)	Spain	Women (14–35)	Cross-sectional	2,000–5,000	N/A	May 2020	Hierarchical models
Villanueva et al. (74)	Spain	General population (≥18;<65)	Cross-sectional	2,000–5,000	Correction factor	April 2020	Bivariate
Yélamos Agua et al. (75)	Spain	Chronic patients	Cross-sectional	2,000–5,000	N/A	April 2020	Logistic models

*Survey with 2 measurements; **survey with 3 or more measurements (Jones, SP collects 29 measurements with COVID data); ***probabilistic sample; N/A, not available in the manuscript.

conducted at Autonomous Community level in Spain and, most relevantly, without the extraordinary context provided by the pandemic, in which there was an urgent need to gather data to support timely evidence-based decisions. Moreover, searching in so many bibliographic resources is a strength of this scoping review.

Our main purpose with this review was to describe the methodological characteristics of surveys conducted early on in the pandemic, hence the search was focused on 2020 and 2021, noting that all surveys started during the first year of COVID-19. In fact, four out of every five surveys (78.2%) were conducted during the 2 months of the first lockdown period (March and April 2020). This demonstrates the rapid response by and considerable effort that the scientific community invested in attempting to provide information about the impact of COVID-19 on the population's health, with particular emphasis on mental health evidenced by the fact that more than half of the surveys (60%) focused on this as their main topic. This response was possible thanks to the internet: nine out of every ten surveys (92.7%) used social media, media sampling to recruit participants, or online subscription panels via this channel. The use of these types of survey expanded to such an extent during COVID-19 lockdowns that, along with more social considerations such as increasingly widespread internet access and use, they took over from traditional survey methods. In this regard, our study found that only four of the fifty-five surveys reviewed were conducted over the phone (7.3%) and, as was to be expected, no face-to-face surveys were identified.

However, despite the efforts made by official statistical institutions, for example the European Statistical System through its Quality Assurance Framework (83), the scientific community faced the difficulty of obtaining quality population frameworks from which quickly to extract probability samples representative of the study populations concerned. As our review shows, 92.7%

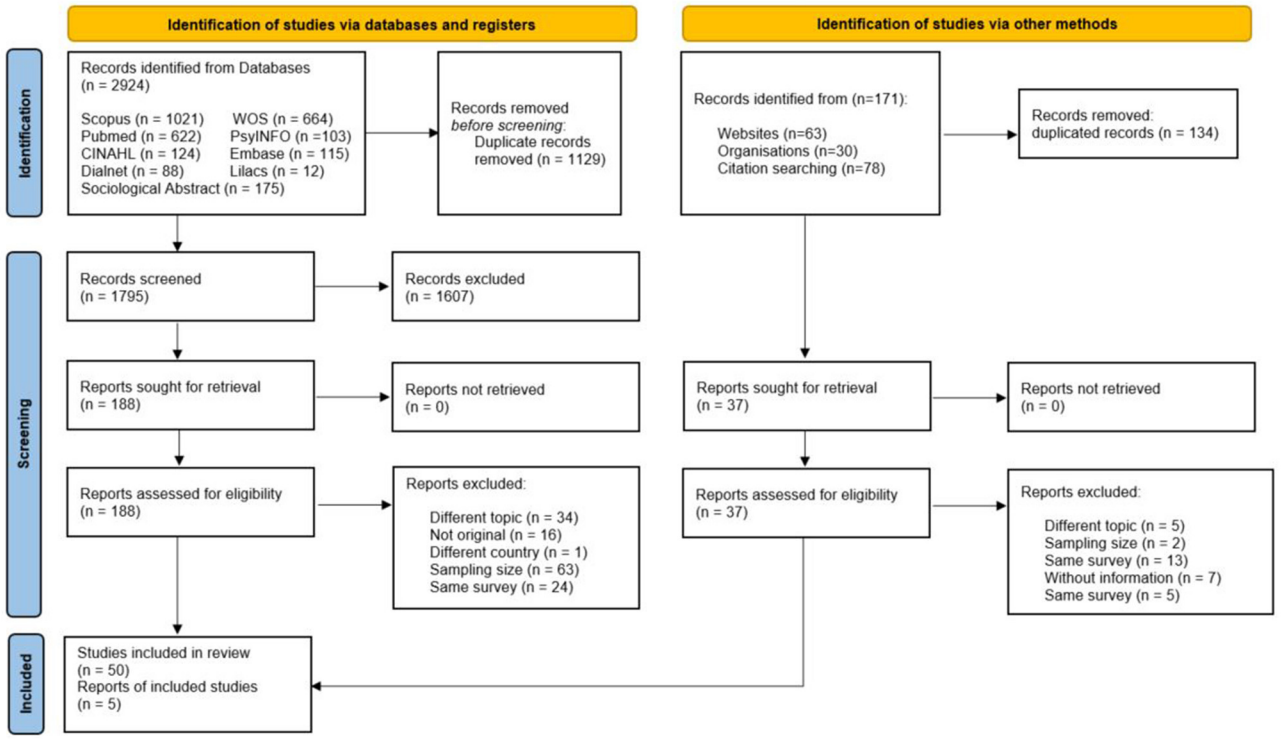

FIGURE 1
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources (77). For more information, visit: http://www.prisma-statement.org/.

of the surveys were based on non-probability sampling, which confirms their extensive use in the extraordinary setting created by COVID-19. Given the rapid inclusion of these types of study, we could ask ourselves the following question in relation to official health statistics: are probability surveys destined to disappear? In Beaumont's opinion (84), this moment has not yet arrived because the alternatives are not reliable and general enough to eradicate the use of probability surveys without having a deleterious effect on the quality of estimates.

Non-probability surveys present two advantages: they can collect large samples and they can do this in a short period of time. This is evidenced in our review, which shows that one out of every five surveys (21.8%) had a sample size of over 10,000 people, bearing in mind that one of the inclusion criteria was having an effective sample size of over 2,000. By contrast, the main drawback of non-probability surveys is that they present significant issues in terms of selection and coverage biases, thus compromising the generalization of results to the study population (85). Our review found that 30.9% of the surveys conducted implemented some type of sampling adjustment by means of correction factors, post-stratification sampling weighting, or calibration with sociodemographic variables such as sex, age or geographical area based on records or reference surveys. However, these adjustments do not correct volunteer bias (86), shown by the fact that we did not find any surveys that included non-probability selection of the people surveyed in their estimates. In this respect, different reweighting techniques have been developed in recent years using Propensity Score Adjustment, Statistical Matching, Kernel Weighting and combinations of these techniques (13, 79, 87–89) that have shown themselves to be highly effective for eliminating biases and increasing representativeness in non-probability surveys.

Despite these limitations, non-probability sampling can complement probability sampling if it is designed as a means to offset known biases in probability sampling by focusing on survey participant profiles that tend to be under-represented in such surveys (90). This notwithstanding, we did not find it being used in our review. Furthermore, non-probability surveys can be useful in some cases for providing relevant information that would not otherwise be available, for example in studies on small sub-populations where probabilistic sampling will encounter problems in fulfilling sample size requirements, good access to the study population or a suitable population framework for sample selection (91). However, here again we did not find it being used in our review, because the majority of surveys in Spain on the health impact of COVID-19 were conducted on the general adult population (74.5%). Nor did we identify any studies on more potentially vulnerable populations such as ethnic minorities, residents in care homes for the older adult or in deprived areas, other than the Health and Social Survey which, in addition to conducting surveys on the general population, also collects data on populations living in deprived areas (71). This percentage of general population surveys could be even larger, given that we eliminated forty-two studies stemming from the same survey. It must be noted

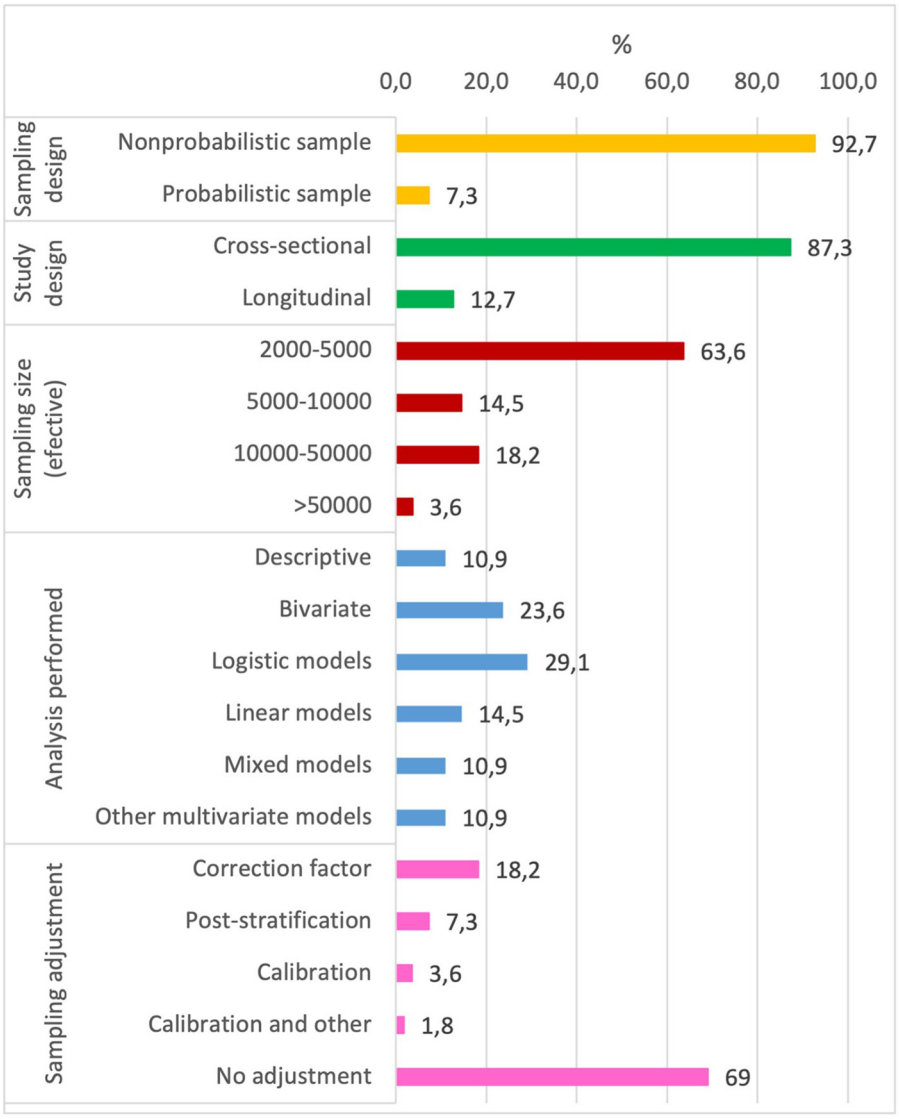

FIGURE 2
Sample design and statistical analysis of the selected surveys.

that this probability survey was able to be conducted through the construction of a population framework during COVID-19 based on linking population records (92) and social records (93). In addition, the interviews in it were conducted not via the internet but rather by telephone, a more suitable channel for reaching these types of population given the continuing digital gap. So population frameworks such as this one provide opportunities for conducting other probability surveys (by telephone or in person) on these types of population.

Another outcome of our review worth noting is the low proportion of longitudinal surveys identified (12.7%). Surveys repeated over time are more difficult to conduct and analyze, but they do permit evaluation of changes in study variables in the same population, a key area for being able to obtain an overview of the pandemic and not just of its characteristics at a given moment in time (94). A sampling design that has proved useful in social research is rotating panel surveys where there is partial renewal of units (to mitigate panelist fatigue), the main advantage of which is that both cross-sectional and longitudinal estimates can be made (71), overcoming the potential limitation of many longitudinal studies in terms of needing to have rapidly available information on the state of the population. However, none of the surveys identified in our review used this design, other than the Health and Social Survey set up at the beginning of the COVID-19 state of emergency (71). This means that many of the surveys identified do not permit the changing effect of the pandemic on health in a single population to be known. Moreover, they were conducted at a very specific moment in time in highly exceptional circumstances, which must also be taken into account when extrapolating their results.

Lastly, this review is in line with other studies that show the high volume of scientific output related to COVID-19 (95). In our case, we identified more than 3,000 studies performed in Spain

over 2 years, of which we selected 1.8% (55 surveys) for our review. Additionally, although our review centers on Spain, the studies it includes have a large international component given that 12.7% of them looked at other countries (some more than 27) (21, 25, 52, 64, 96) and 58.2% of them were published in journals situated in the first quartile (Journal Citation Reports).

As regards the search and the record created, they enable other analyses to be performed in subsequent years on specific topics such as mental health, and studies without a given exclusion criterion to be easily retrieved (thus enabling the analysis performed in this review to be repeated in other studies). For example, we considered as the last exclusion criteria surveys with a sample size of <2,000 individuals. Our objective was to select large health surveys in terms of guaranteeing that sampling errors in overall estimates were below three percentage points assuming $p = q = 0.5$, 95% confidence level (power level did not apply because we considered observational studies), 0% sample loss because we refer to effective sample (not the theoretical one), and design effect two. If a lower sample size were required, it would be very easy to retrieve those studies through Rayyan and repeat the analysis. However, although our record facilitates identifying these studies through Rayyan, it is worth pointing out that barely one third of the surveys reviewed make their data openly available, and this hinders performing these studies or other analyses such as, for example, reweighting techniques which would provide more reliable estimates. This clearly reflects the ongoing lack of research based on Open Science (97), despite the major opportunity provided by COVID-19 to reverse this situation (98).

Author contributions

Conceptualization and funding acquisition: AC-L, MR, and CS-C. Methodology: AC-L, CS-C, AO-d-L-L, EM-R, and CH-C. Data curation and analysis: AC-L, CS-C, DY, AO-d-L-L, and EM-R. Writing—original draft preparation: AC-L, CS-C, and DY. Writing—review and editing: MR, AC-L, CS-C, AO-d-L-L, EM-R, and CH-C. Project administration: AC-L. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1217519/full#supplementary-material

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Pulmonary nocardiosis following *COVID-19* in a patient with idiopathic pulmonary fibrosis and lung transplantation: a case report

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Background: Nocardiosis is an opportunistic infection that primarily affects immunocompromised patients. Pulmonary nocardiosis is the most prevalent form, but can also spread to other organs. Potential causes contributing to opportunistic infection may include immunosuppression and disruption of tight junctions, both of which can result from *COVID-19*.

Case presentation: We reported a case of a 68-year-old male patient who presented with a 10-day history of fever, cough, and productive sputum. Upon physical examination, velcro rales were detected in the right lung, while breath sounds in the left lung were clear. The patient had previously undergone left lung transplantation due to idiopathic pulmonary fibrosis four years ago. He was initially hospitalized and treated for *COVID-19* but was readmitted due to worsening symptoms. Subsequently, pulmonary nocardiosis was diagnosed utilizing metagenomic next-generation sequencing of bronchoalveolar lavage fluid. The above-mentioned condition was improved following treatment with cancidas and linezolid. Now, he is under regular follow-up.

Conclusion: This case highlights the complexity of *COVID-19* and the occurrence of secondary opportunistic infections, which require further investigation.

KEYWORDS

pulmonary nocardiosis, *COVID-19*, idiopathic pulmonary fibrosis, lung transplantation, immunosuppression

Introduction

The incidence of Nocardia infections has gradually increased due to the growing number of immunocompromised patients, including those with tumors, organ transplantation, and on chronic steroid therapy (1, 2). This paper presents a pneumonia case of *Nocardia farcinica* infection involving multiple risk factors, including lung transplantation, post-*COVID-19* status, and steroid use.

Case presentation

On December 29th, 2022, a 68-year-old male was admitted to the hospital with a complaint of fever, cough, and productive sputum persisting for 10 days. The patient developed a fever 10 days ago, with a maximum body temperature of 39.5°C. Additionally, the patient experienced

TABLE 1 Laboratory values on the first day of two hospitalizations.

Parameter	First hospitalization	Second hospitalization	Reference value
WBC(10^9/L)	4.49	12.63	3.5–9.5
Neutrophil(10^9/L)	2.85	9.95	1.8–6.3
lymphocyte (10^9/L)	1.39	1.96	1.1–3.2
CD3 + CD4 + (10^6/L)	599	1,040	537–1,282
CD3 + CD8 + (10^6/L)	171	221	258–1,042
CD19(10^6/L)	96	205	173–447
CRP(mg/L)	73.4	133.8	≤10
Procalcitonin (ng/ml)	0.07	0.14	≤0.25
ESR(mm/h)	26	51	<43

WBC, white blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

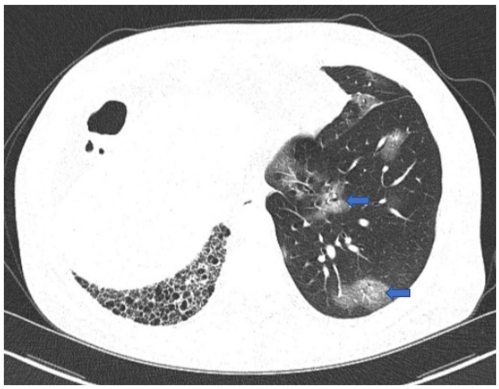

FIGURE 1
First chest CT image. The image showed *COVID-19* pneumonia with scattered ground-glass opacities in the left lung (blue arrow), and fibrosis and honeycomb changes in the right lung.

coughing and sputum production but without hemoptysis, dyspnea, chest pain, or chest tightness. Despite receiving antipyretic treatments, the patient experienced recurring fever. Consequently, he sought medical attention at the pulmonary specialist clinic and was hospitalized. Four years ago, he received left lung transplantation due to idiopathic pulmonary fibrosis (IPF) and has since been prescribed tacrolimus, mycophenolate mofetil, and prednisone. During the physical examination, velcro rales were detected in the right lung, while the breath sounds in the left lung were found to be clear. In our department, the patient tested positive for *COVID-19* nucleic acid, with a 73.4 mg/L increase in C-reactive protein (CRP), while white blood cell (WBC) and neutrophil counts were within the normal range. Meanwhile, the analysis of lymphocyte subsets revealed a decrease in $CD8^+$T cells and B cells, while $CD4^+$T cells remained within the normal range. Other laboratory values were displayed in Table 1. Scattered ground-glass opacities were observed in the left lung on first chest CT imaging, along with fibrosis and honeycomb changes in the right lung (Figure 1). Based on the epidemiology of *COVID-19* in China, along with the patient's medical history and positive examinations, a diagnosis of *COVID-19* pneumonia was made. The treatment involved the administration of Paxlovid and methylprednisolone intravenously and subsequently orally for 21 days, with a total dosage of approximately 400 mg. Simultaneously, tacrolimus was discontinued while the dosage of mycophenolate mofetil was reduced. Throughout his hospitalization, he did not require supplemental oxygen or mechanical ventilation. After the symptoms improved, he was discharged.

Two weeks later, the patient was readmitted to the hospital due to an exacerbation of cough and expectoration. The patient tested positive for *COVID-19* nucleic acid once more, with a significant increase in WBC, neutrophils, and CRP levels (Table 1). The second pulmonary CT scan showed consolidation superimposed to pre-existing fibrotic changes on the lower lobe of the right lung, which was absent in the first chest CT scan. Additionally, the *COVID-19*-related ground-glass opacities on the left lung disappeared on the second CT, with residual tiny scars (Figure 2). Given the possibility of bacterial or fungal co-infection, we used piperacillin sodium-tazobactam sodium intravenously (4.5g q8h) for a week and caspofungin (70 mg loading dose on day 1, followed by 50 mg daily) for 2 weeks.

On the second day of hospitalization, we conducted a bronchoscopy. During bronchoscopy, narrowing of the lumen in the dorsal branch of the right lower lung with visible secretions was observed; no abnormalities were detected in other lobes (Figure 3). Metagenomic next-generation sequencing (mNGS) of alveolar lavage fluid identified the presence of *Nocardia farcinica*, an opportunistic pathogen commonly associated with infections in immunocompromised patients. Following a definitive diagnosis, linezolid (0.6 g q12h) was given intravenously for 2 weeks, while molnupiravir (0.8 g bid) for five days was prescribed specifically for the *COVID-19* coronavirus. Both tacrolimus and mycophenolate mofetil were administered as per standard protocol. Finally, the inflammatory index progressively decreased, leading to an improvement in the condition. After discharge, the patient switched to oral treatment of trimethoprim-sulfamethoxazole.

Upon 14 days and 85 days after the diagnosis, the patient underwent chest CT examination, which displayed nocardiosis lesions in the right lung were gradually resolved (Figure 4). The patient is currently undergoing regular follow-up at the clinic. The medical timeline is listed in Figure 5.

Abbreviations: IPF, idiopathic pulmonary fibrosis; mNGS, metagenomic next-generation sequencing; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

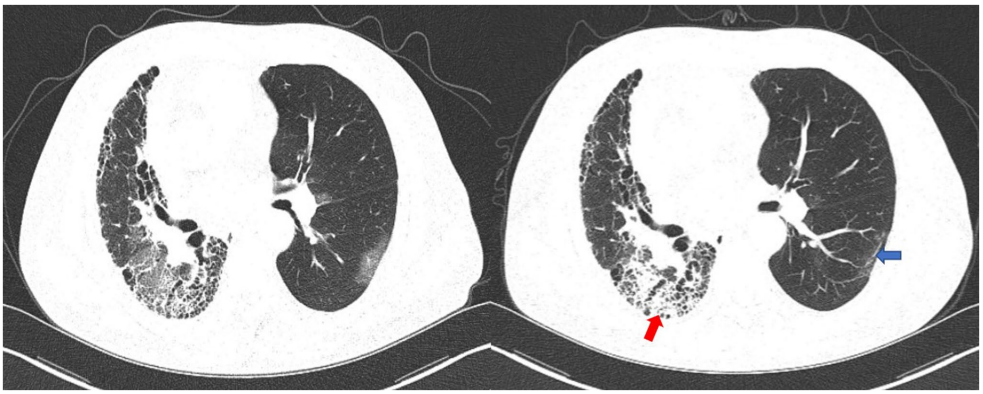

FIGURE 2
The first chest CT scan (left) and the second chest CT scan (right). The second chest CT image showed consolidation superimposed to pre-existing fibrotic changes on the lower lobe of the right lung (red arrow). The *COVID-19*-related ground-glass opacities on the left lung disappeared on the second CT, with residual tiny scars (blue arrow).

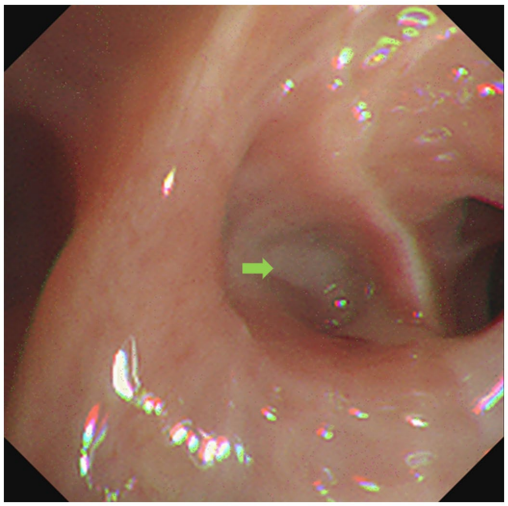

FIGURE 3
Bronchoscope showed respiratory secretion in the dorsal branch of the right lower lung (green arrow).

Discussion

Nocardia is a Gram-positive bacterium that is ubiquitous in nature, primarily found in soil and humid environments. It frequently causes infections in immunocompromised patients, including those undergoing solid organ transplantation, suffering from chronic lung disease, diabetes, malignancy, or using long-term steroid therapy (3–6). Pulmonary nocardiosis is the most common type, presenting with nonspecific symptoms such as fever, cough, and chest pain, as well as CT imaging findings of lung consolidation, nodules/masses, ground-glass opacity, and centrilobular nodules. Delayed diagnosis contributes to its high mortality rate (5, 7, 8).

This patient had numerous risk factors, including immunosuppression caused by daily antirejection therapy due to lung transplantation, *COVID-19* infection, and corticosteroid therapy. Previous studies have identified Nocardia as a prevalent pathogen in chronic pulmonary infections among patients with IPF, yet it has not been widely recognized as a contributing risk factor (9, 10). Lung transplant recipients, classified as a specific subgroup of immunocompromised patients, are particularly susceptible to Nocardia as a significant pathogen that primarily affects the native lung in cases of unilateral lung transplantation (11). Previous study on pulmonary nocardiosis following lung transplantation has largely reported that a majority cases were attributed to *N. farcinica, N. nova*, and *N. asteroids* (6).

Given the patient's stable condition following lung transplantation, we hypothesized that the disease may be attributed to *COVID-19* infection and corticosteroid therapy used for its treatment. Corticosteroids can result in secondary infections, such as fungal, viral, mycobacterial, and Nocardia (12, 13). A retrospective study has conclusively established a correlation between glucocorticoid therapy and Nocardia infection (14).

However, *COVID-19* can also induce an immunocompromised state, as observed in a case of encephalic nocardiosis occurring after *COVID-19*, even in the absence of steroid use. Nocardiosis has been reported in cases where the primary immune response is predominantly mediated by $CD8^+$T cells, while B lymphocytes and humoral immunity may play a lesser role (15). While in *COVID-19* patients, lymphopenia accompanied by a severe decline in $CD4^+$ and $CD8^+$T cells, B cells, and innate immune cells is a common feature, and this patient specifically exhibited decreased $CD8^+$T cells (16). A subsequent study has shown that lymphopenia may be associated with reduced levels of protein tyrosine phosphatase receptor type C, leptin, and tartrate-resistant acid phosphatase type 5 (17). However, the duration of this immune disorder after *COVID-19* is unclear (18). Furthermore, impairment of the tight junction complex can occur, creating conditions for bacterial attachment (17). These changes may impact the response of *COVID-19* patients to opportunistic bacterial infection caused by Nocardia.

Conclusion

This case highlights the *COVID-19*-induced immunologic derangement, along with the role of glucocorticoids, which requires further investigation to elucidate the specific immune status. It is also vital to remain mindful of the potential for Nocardia opportunistic infection following *COVID-19*.

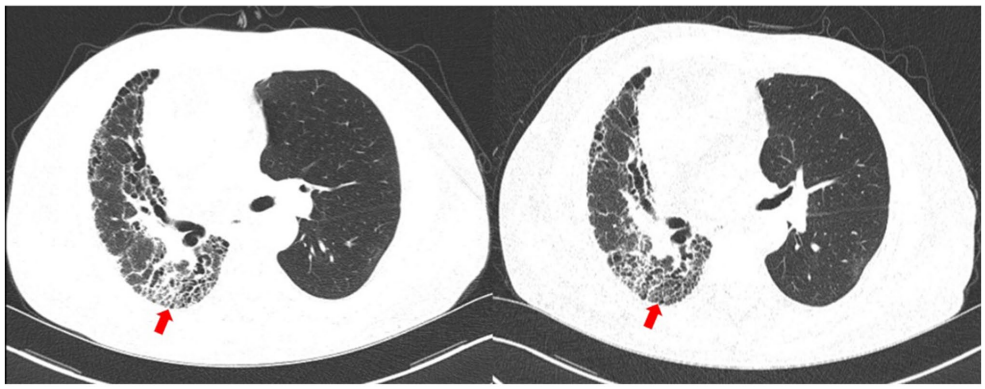

FIGURE 4
Chest CT upon 14 days (left) and 85 days (right) after the diagnosis. The nocardiosis lesions in the right lung were gradually absorbed (red arrow).

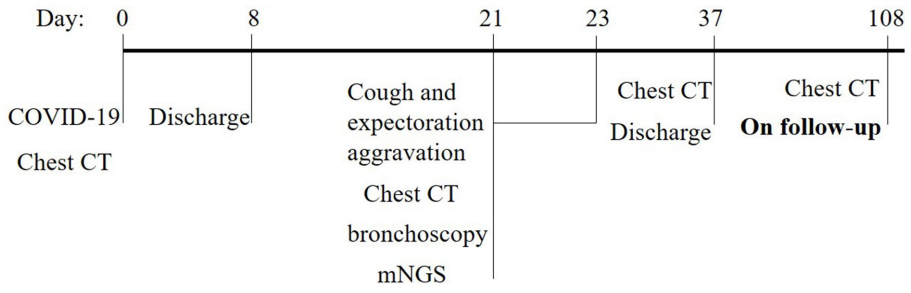

FIGURE 5
Timeline of medical history.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Zhejiang Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LC: writing – original draft, writing – review and editing. YS: writing – review and editing. FC: writing – review and editing, writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Moving the needle for COVID-19 vaccinations in Nigeria through leadership, accountability, and transparency

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Background: The first set of vaccines arrived in Nigeria in March 2021. The National Primary Health Care Development Agency (NPHCDA) set out to vaccinate at least 70% percent of Nigeria's eligible population, i.e., 111,776,503 people, by December 2022. As of June 2021, only 3% had received at least one dose of the vaccine. This presented a threat to the achievement of NPHCDA's goal. Nigeria Solidarity Support Fund (NSSF) went into a partnership with NPHCDA to accelerate the uptake of COVID-19 vaccinations across Nigeria over 3months.

Methods: Across Nigeria's 6 geopolitical zones, 6 states were selected, namely: Adamawa, Edo, Imo, Katsina, Nasarawa, and Ogun states based on performance, political will, and absence of external resources. A two-pronged approach was implemented: unrestricted funding to the sub-national level and providing technical support at the national level.

Results: 5 out of 6 states received unrestricted funding to ramp up vaccination coverage. They also received adequate vaccine supplies. A total of 12,000 healthcare workers were trained on safe immunization practices and multiple communities were engaged across the 133 local government areas (LGAs) through religious and community leaders. After 6 months, there was an average of 35% increase in the uptake of COVID-19 vaccines in the 5 states. An indicator tracker was developed for weekly reviews at the national level and the total population vaccinated in Nigeria increased from 6,186,647 to 11,985,336 at the end of the partnership.

Conclusion: Unrestricted funding, though not without its risks, can yield a significant impact on health. The intervention was co-designed with stakeholders and had leadership buy-in, accountability mechanisms, with unrestricted funding. These techniques produced an increase in the vaccination rates in the 5 states and across the country. These elements should be explored for application to other program designs such as routine immunization.

KEYWORDS

COVID-19 vaccination, leadership and accountability, parallel funding, vaccine acceptance, vaccine uptake

Introduction

The COVID-19 pandemic presented a serious threat to global public health. The impact of the pandemic was overwhelming, even for developed nations whose already strong health systems were expected to withstand the impact. Predictably, the situation elicited collective social and scientific responses from individuals and governments worldwide; this included the development of a vaccine to protect against the virus (1).

In Nigeria, the COVID-19 pandemic has had a significant impact, both in the number of confirmed cases and the economic and social effects. As of January 2023, Nigeria had reported over 266,463 confirmed cases of COVID-19 and 3,155 deaths (2). At the height of the global outbreak in 2020, the Nigerian government implemented measures such as lockdowns and travel restrictions to slow the spread of the virus. As with many other countries, these measures harmed the economy, with many businesses shutting down and unemployment rising. The Nigerian government was criticized for its handling of the pandemic, with allegations of mismanagement and lack of transparency.

The COVID-19 vaccination campaign is an ongoing effort to vaccinate eligible populations against COVID-19 worldwide, with the aim of achieving herd immunity from the virus. However, due to the changing nature of the virus, this goal was adjusted to vaccinate enough people against COVID-19, rather than to achieve herd immunity, as has been attained with many other diseases (3). Vaccination is expected to ensure protection from the disease, control the rate of infection, and reduce severe outcomes if infection occurs at all. Nigeria received the first set of COVID-19 vaccines in March 2021, through COVAX, the vaccine arm of the Access to COVID-19 Tools (ACT) (4). Through this facility, vaccines were secured from multiple manufacturers and distributed to participating countries based on their needs (5). These vaccines were handed over to the National Primary Healthcare Development Agency (NPHCDA) to coordinate the immunization program across the country. NPHCDA is the arm of the government charged with improving the effectiveness and efficiency of primary healthcare delivery in Nigeria (6), which involves vaccinations. Upon receipt of the COVID-19 vaccines, the NPHCDA set out to vaccinate at least 70 percent of the total 111,776,503 people who were eligible to receive the vaccine by December 2022 (7). The NPHCDA intended to follow a plan of vaccinating 40 percent of the population by December 2021 and the other 30 percent in 2022 (8). Vaccinations kicked off fully in March 2021, with a campaign to raise awareness about the vaccine and keep people informed about where they could get vaccinated. Notwithstanding these collective efforts, the uptake of vaccines remained marginally low and at that rate, there was a real threat against the achievement of NPHCDA's target for the year 2021 (9). As of July 2021, only 3,441,146 doses of the vaccine had been administered, which was barely 3% of the target population.

While there was a lot of optimism about the COVID-19 vaccination campaign globally, it was anticipated that implementation would not be without challenges. In Nigeria, the low uptake was attributed to funding gaps, which hindered last-mile delivery of vaccines, and challenges with accountability and transparency. After a series of consultative meetings, Nigeria Solidarity Support Fund (NSSF) and the National Primary Health Care Development Agency (NPHCDA) entered a partnership to augment the COVID-19 vaccination campaign across the country. This partnership kicked off in September 2021 (10, 11).

Objective

This report outlines the strategies employed to scale up COVID-19 vaccination in 5 low performing states in Nigeria.

Methods

Consultative meetings between NSSF and the NPHCDA revealed that the issues encountered with the COVID-19 vaccine coverage were on two broad fronts; limited funding for program activities at the subnational (state) level and some coordination issues at the national level. Hence, it was imperative that NSSF provided support at both levels to make the desired impact. Therefore, a two-pronged approach was applied through the provision of unrestricted funding at the subnational level and technical support for coordination and monitoring at the national level.

Across the six (6) geo-political zones in Nigeria, six (6) states were selected, namely Edo, Ogun, Nasarawa, Adamawa, Katsina, and Imo state. They were selected based on their status of being the lowest performing states at the time, in each of the geo-political zones. This came to a total of 133 local government areas (LGAs) and 513 implementing wards across the states. One of the six selected states, however, did not successfully implement the project.

The partnership kicked off in October 2021 and ran for a period of 3 months; which ended in January 2022.

Advocacy for last mile delivery of vaccines and demand creation

The COVAX facility helped to ensure the continued supply of vaccines to Nigeria. However, at the initial stage, the supply of vaccines was sub-optimal, making the quantity of vaccines available insufficient to meet the demand. Hence, only a few facilities in each of the states had received vaccines as of September 2021, when the partnership kicked off. NSSF worked with the NPHCDA to advocate for an increase in the supply of vaccines and to ensure that the vaccines were sufficiently distributed to the local level. This was done over a 4-week period, between October and November, 2021, to establish a reliable chain of supply and ensure continuity.

Alongside advocacy for vaccine supply, health education efforts were doubled in the participating states. This component was essential for increasing awareness about the vaccines and where people could get them, to drive demand. The primary healthcare development teams in each state worked with their media partners to develop additional information, education, and communication (IEC) materials, including jingles. The jingles were aired on radio and television. IEC materials were developed and deployed as an ongoing activity from October to December 2021.

In addition to the jingles, call-in programs were aired on the radio, which allowed people to ask questions about COVID-19, the vaccine, and its effects.

Road shows and rallies were conducted in all 5 states, to reach communities and settlements where other methods of communication may not have reached. These took place within the first two weeks of October 2021, following the flag-off events.

Training of healthcare workers

Important to any immunization exercise or campaign is the constant availability of the vaccines, as well as the mechanisms for last-mile delivery, reverse logistics, and waste disposal. Doctors, nurses, midwives, laboratory technicians, pharmacists, community health officers (CHO), and community health extension workers (CHEW) participated in a three-day intensive training, which was conducted from October 3rd–5th, 2021 in each of the LGAs and their respective communities. In addition, the NPHCDA deployed Community Health Influencers, Promoters, and Supporters (CHIPS) to drive uptake of the vaccines.

All healthcare workers and community leaders were trained to follow these steps:

T: Traditional method of vaccinating target populations using desk review of available data sources, identifying the vaccination sites, and rolling out.
E: Electronic self-registration for health workers and the public; a link that provides an online form was provided.
A: Assisted electronic registration.
C: Concomitant e-registration during walk-ins to fixed sites/ health facilities.
H: House-to-House registration using volunteers for additional push to rapidly increase the e-registration.

This is the TEACH strategy. In addition, the Electronic Management of Immunization Data (EMID) application was launched by the Federal Ministry of Health, to capture and store information on COVID-19 vaccination activities. The healthcare workers were also trained to use the application and ensure that data was captured to reflect the actual situation.

Information gaps among the healthcare workers were addressed, to increase their confidence in the efficacy of the vaccine. Ensuring that the healthcare workers were confident in the vaccine was essential for promoting the acceptance of the vaccine by beneficiaries in the various communities.

Data management and transparency

At the national level, indicators were developed to ensure accountability and uniform reporting across board. Under the direction of the State Primary Healthcare Development Agency (SPHCDA) in each state, monitoring and evaluation (M&E) teams were set up at the local government and state levels. The M&E teams and their associated M&E focal persons were trained in the use of the TEACH strategy and the Electronic Management of Immunization Data (EMID) application.

Data management was a key part of the campaign from its initiation in September 2021; this continued through the period of the partnership and afterwards, until October 2022. Immunization data, which was validated by *ad-hoc* staff, was reported manually and *via* the EMID. The records were revalidated each week to identify and reconcile discrepancies between data called-in and EMID records. These assessments were corroborated by spot checks with the LGA focal persons. Disaggregated data was reviewed to identify bottlenecks in team performance, which also informed remuneration.

Campaign coordination and technical support

Under the guidance of the NPHCDA, the states conducted weekly data review meetings between October 2021 and January 2022. These meetings provided an avenue to go over the data reported for the LGAs in each state. During the meetings, the strategies being implemented were also evaluated and ineffective strategies were revised.

At the national level, review meetings were conducted monthly, and the states were ranked based on their performance. Based on the results of the rankings, low-performing states were provided additional support centered on state-specific needs (Figure 1).

Results

At the time that the partnership began, 1,226,311 eligible people in Adamawa had received the COVID-19 vaccine. This figure increased by 175,336 by December 2021 and an additional 93,478 at the end of January 2022. The support from NSSF contributed to a 17.98% (268,814) increase in the vaccination uptake, resulting in the vaccination of 1,495,125 people in Adamawa at the end of the campaign.

Similarly, in Imo state, 2,940,851 people were targeted for the COVID-19 vaccination. During the implementation period, a total of 90,501 people received the first dose of the vaccine, while 53,190 people received the second dose.

Katsina state, which is the largest of the six states, had 5,345,789 people targeted for vaccinations. When the campaign in the state ended, 2,034,094 people had received at least one dose of the COVID-19 vaccination. This was achieved, despite the insecurity challenges that made 17 LGAs inaccessible to the vaccination team.

Before receiving support from NSSF, 1,306,185 people in Nasarawa had received at least one dose of the COVID-19 vaccine. During the period of NSSF's partnership with the NPHCDA, there was a 73.17% (955,768) increase in the vaccination uptake in Nasarawa, resulting in the vaccination of 2,261,953 people at the end of the campaign.

In Ogun state, 112,167 people were vaccinated during the period. This contributed to the total of 414,221 people who had received at least one dose of the COVID-19 vaccine in Ogun state, which is 20.71% of the target population of 2,000,000 people.

In Edo state, the grant was not implemented due to some bureaucratic issues at the state level. The issues were resolved eventually, but the implementation period had elapsed, therefore, results from the state were not included in the data reported.

At the end of the implementation period in the five states, COVID-19 vaccination coverage increased across board. At least 12,000,000 people were reached through the vaccine advocacy campaigns and 12,000 healthcare workers benefited from the training programs on safe immunization practices. Within 3 months, the population vaccinated in the 5 states was 3,514,534 people and there was a steady increase in the uptake of the vaccines across the states. As of March 2022, 5,235,493 people had been vaccinated in the five states, which is almost half of the 11,985,336 people who had been vaccinated in Nigeria at the time.

In addition, owing to the support provided by NSSF, Nasarawa state and Ogun state were reported to be the first and ninth positions, respectively, in the national COVID-19 vaccination coverage report as of July 20th, 2022 (Table 1; Figure 2).

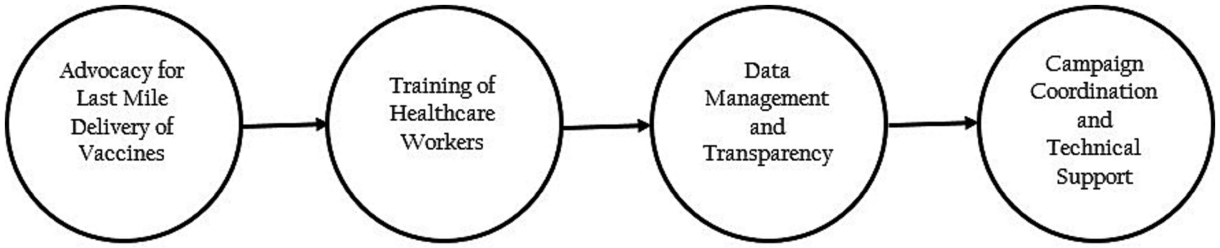

FIGURE 1
The framework used to increase COVID-19 vaccine uptake across Nigeria (Nigeria, 2022).

TABLE 1 Progression of COVID Vaccinations in the 5 states between October 2021 and March 2022.

State	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22
Adamawa	147,096	170,692	245,529	356,056	465,616	627,107
Imo	119,803	134,163	160,020	188,100	205,514	250,989
Katsina	205,165	222,031	384,310	497,399	596,504	729,147
Nasarawa	174,838	237,998	522,094	1,128,628	1,756,642	2,116,571
Ogun	456,294	619.652	921,309	1,139,049	1,441,437	1,511,679

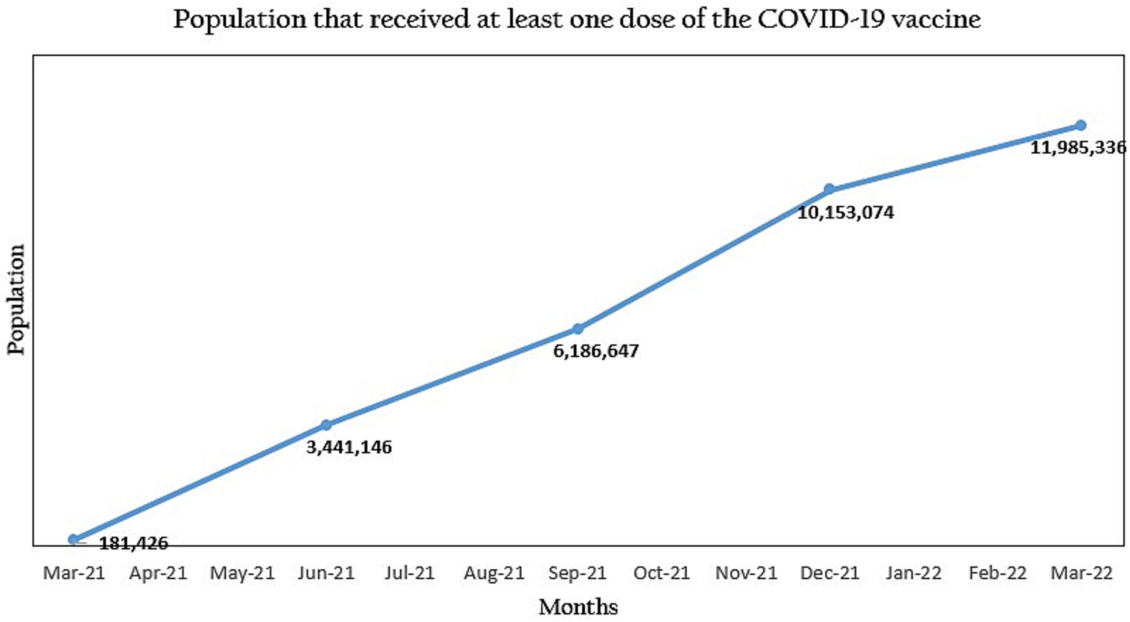

FIGURE 2
Progression of the COVID-19 vaccine uptake in Nigeria during the National Primary Healthcare Development Agency (NPHCDA) and Nigeria Solidarity Support Fund (NSSF) partnership.

Discussion

In Nigeria, lessons were taken from the experience that has been gained through the years in other immunization campaigns like the polio eradication campaign. Nasarawa state, which eventually got applauded for the increased coverage in the state, reported that they piggybacked on the Reach Every Ward (REW) strategy and were supported by the CHIPS. The importance of community ownership was also underscored, through the leaders who were educated about the vaccine and subsequently vaccinated, as well as the CHIPS agents, who were representatives of their communities and could be trusted to give relatable advice.

Advocacy plays a very important role in determining the uptake of vaccines in any region. While advocacy can often be seen as a one-way train, it is most effective when communication is bidirectional therefore, it is important to understand the source of misinformation or mistrust when fashioning advocacy messages. Nigerians are generally religious people; hence they tend to get and trust information from their religious and traditional leaders, over healthcare workers and ministries. Therefore,

educating these leaders was very important and beneficial for driving vaccination uptake in many areas. Some countries, like Zimbabwe, even went as far as allowing only vaccinated worshipers to attend gatherings physically and this further encouraged people to get vaccinated (12). In addition, a lot of work was done to correct misinformation and disinformation by employing champions within all communities, like the CHIPS agents, to strengthen communication. This was further supported by rallies and road shows, which were held every week. During advocacy visits, people were encouraged to get information about COVID-19 and the vaccine from confirmed sources, like the NCDC and NPHCDA websites, which aligns with what was done in Uganda and Tanzania (13).

Alongside healthcare workers, social mobilizers who were non-healthcare workers that lived within communities and were willing to be educated, played a very important role in creating demand for COVID-19 by educating other community members on the vaccine and its efficacy (10). It was upon this strategy that the CHIPS thrived and made an impact, creating and sustaining demand for vaccines in Nasarawa and Adamawa.

Data management was a very important part of the campaign and constituted a large part of the training conducted for healthcare workers. Electronic management of data was initially frowned upon by many countries in sub-Saharan Africa especially, as it was considered 'elitist' and not suited to the rural areas and people who live there. However, this was resolved in Nigeria using mobile vaccination teams that were tasked with going into those communities and registering the beneficiaries, then administering vaccines to them. A similar process of data management was employed in Rwanda, where the DHIS2 was used for registration of COVID-19 vaccine beneficiaries and automation of reminders (11). This process ensured a quick transmission of COVID-19 vaccination data to the national level; insights from which were used to make decisions about the strategies to be employed for increased demand creation.

While this partnership followed some methods that are common in vaccination campaigns, the success recorded may not have been achieved without the principle of additionality. NSSF was intent on working with the NPHCDA to contribute to the global goal of reducing COVID-19 infection rates through vaccinations. The grant was not implemented as a parallel project by NSSF or another private institution but the organization consulted with the NPHCDA, got information about the gaps that needed to be addressed, and worked with them to mitigate the challenges. This process allowed the NPHCDA and NSSF to geometrically increase their reach and impact.

The participating states were granted unrestricted funding for their activities. Funding granted was not tied to grant lines and this allowed flexibility in implementation and implementation research on the go. The federal and state teams owned the project and set population-based targets for each state. Hence the state teams were driven to work hard at achieving their targets. The state teams were able to take context-specific approaches to address their challenges and improve the processes as they saw fit.

Conclusion

This intervention, which was designed for 6 of the 36 states in Nigeria, but implemented in only five states was implemented through the partnership between a private sector entity, NSSF, and the government (NPHCDA). While the implementation was largely the responsibility of the NPHCDA, it was evident that immunization targets can be achieved and surpassed when stakeholders, including beneficiaries of the immunization programs, work together.

Also, the intervention showed that despite the risks that come with unrestricted funding, grants provided through this approach can yield a significant impact on health. Although Nigeria still has some work to do to achieve herd immunity, leadership buy-in, accountability mechanisms, and unrestricted funding are important factors that can significantly promote vaccination campaigns and move the needle. This was evident in the 5 states that moved from being among the lowest performing states in the country to the best in terms of the COVID-19 vaccination campaign. Their performance motivated other states to source additional funding for last-mile delivery.

While success was recorded with the COVID-19 vaccination campaign in the 5 states, a lot of work remained undone due to limited funding. This further proves that financial and technical support from donor organizations and the private sector is still necessary to catalyze the government's efforts and achievements in vaccine coverage and other health interventions.

Recommendation

The grant was not implemented as a parallel project, rather it was implemented in the principle of additionality. This allowed the states to scale impact while taking ownership of the projects and applying context-specific methods to vaccinate the populations in each state. Applying this to other grants will allow flexibility of the program and produce the expected impact.

Limitation

This paper was developed based on a grant that was awarded to five states in Nigeria for a three-month period. NSSF did not provide support for longer than 3 months due to competing program needs. However, the lessons learned from this intervention can be replicated with grants to be awarded in Nigeria and other LMICs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Telemedicine in non-communicable chronic diseases care during the COVID-19 pandemic: exploring patients' perspectives

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Purpose: This study aimed to explore challenges facing patients using Telemedicine consultations in non-communicable chronic disease clinics in primary care settings and to evaluate their satisfaction and willingness to use this service in the future.

Methods: This is an analytical cross-sectional study enrolling participants who were randomly selected from representative primary care centers in Bahrain and providing Telemedicine consultations. A semi-structured questionnaire permitted data collection using telephone interviews.

Results: A total of 251 individuals participated in the study of whom the majority were Bahraini (90.04%), and the mean age was 54.48 ± 10.78 years. Most of the participants 231 (92.03%) were satisfied with the Telemedicine consultation while only 142 (56.80%) were willing to use this service in the future. The main perceived challenges related to Teleconsultations were the lack of physical examination, inadequate time of TM consultation, fear of medical errors, and lack of privacy. The willingness to use TM consultation in the future was mainly determined by the degree of comfort to tell private information ($p < 0.01$) and to less extent the ease of the communication tool ($p = 0.005$) on multivariate analysis.

Conclusion: TM consultations could be a good complement to conventional consultation formats in the future. The sustainability of this innovative healthcare delivery tool requires addressing acceptability by users, ease of use, patient-centeredness, and technological advances to ensure privacy.

KEYWORDS

telemedicine, non-communicable chronic diseases, COVID-19, patients' perspectives, satisfaction, willingness

Introduction

Telemedicine (TM) is defined as "the use of electronic information and telecommunications technologies to support and promote long-distance clinical health care, patient and professional health-related education, public health, and health administration" (1). TM involves remote patient monitoring, mobile health applications, and more

traditional modes of communication such as text, email, voice, and video calls (2).TM services benefit patients and medical providers by reducing disease exposure, increasing healthcare accessibility, and allowing for more efficient use of hospital resources (3).

The burden of non-communicable chronic diseases (NCDs) remains a global public health challenge, resulting in high morbidity, mortality, and cost (4, 5). In 2019, NCDs were responsible for 74% of global deaths, with most Gulf Cooperation Council countries exceeding this global average (6). Over the past several years, Bahrain has made significant strides in preventing and controlling NCDs (6, 7). Nonetheless, their prevalence is increasing and NCDs such as cardiovascular disease, diabetes, cancer, and chronic lung disease currently account for nearly 75% of all deaths in Bahrain and ∼one in five adults dies from NCDs-related problems before the age of 70 (6). Furthermore, poor patient adherence increases NCD-related mortality and morbidity, which creates a burden on healthcare utilization and costs (7). Poor adherence to drugs and follow-up visits was exacerbated during the COVID-19 pandemic due to restrictions in accessibility to health settings for patients with NCDs at the global level (8). Indeed, NCDs-related mortality and morbidity could be reduced provided an optimal follow-up and implementation of preventive measures as well as limiting exposure to SARS-COV2 in the hospital settings (9). Integrating NCDs care into primary care is a cost-effective, affordable, and equitable paradigm of care that has the potential to reduce morbidity and mortality from NCDs (10).

The COVID-19 pandemic prompted the medical community to integrate TM to avoid disruption of patient care throughout the pandemic including NCDS preventive and curative services (11).

While there are many barriers to using TM, evaluating patients' satisfaction and their experience is clearly important to ensure compliance and sustainable implementation (12). Studies conducted in various contexts worldwide revealed an overall high level of satisfaction with TM services among patients and healthcare providers during the COVID-19 pandemic and reported willingness to continue its use after the pandemic (12–21).

Overall satisfaction with TM as a tool of health care delivery is likely to be influenced by the technology's perceived usefulness and the technical competence of the provider and patient (1), as well as patient's related factors such as age, gender, and level of education (12, 22). Measures of success include the provider's communication skills during the patient-doctor interaction as well as the degree of success in addressing the patient's concerns, and emotional needs during the TM consultation (23). Common reported benefits of TM were time savings from less traveling and waiting time, and improved accessibility, convenience, and cost efficiency (13). However, TM has been reported as being less suitable when a physical examination is needed, and the diagnosis was unknown (20).

A TM consultation was introduced as a pilot program in few primary care general clinics in the Kingdom of Bahrain in 2018. TM consultations for NCD care through phone format were launched in primary health care centers in the Kingdom of Bahrain during the COVID-19 period in March 2020, to ensure continuity of care and minimize the risk related to high mixing during face to face consultations. The NCD TM consultations were solely conducted by trained family physicians and NCD nurses were involved in calling patients the day before their appointments to remind them and to be prepared for the TM consultation the following day. Only follow-up patients in the NCD clinics received TM consultations, whereas new NCD patients had face-to-face consultations for their first appointment. Each NCD TM consultation was assigned 15 min, but the time can be extended according to the patient's condition and level of understanding. All physicians were providing a standardized content of TM consultations like the face-to-face following the NCD electronic medical record format, except the physical exam. Physicians were expected to document the consultation findings in NCD electronic medical record.

Despite its early implementation in the health care system, the long-term sustainability of TM needs to consider the patients' experience, expectations, and perspectives. To the best of our knowledge, this is the first study in the Kingdom of Bahrain to assess patients' satisfaction and challenges with TM consultations for NCD patients in primary care settings. It was conducted in the context of a quality improvement project to support the sustainable integration of TM as an additional mode of health care delivery to improve outreach, infection control, and reduce cost, particularly for older adults patients with NCDs in primary health care. The findings will pave the way to implement corrective action plans based on scientific evidence and the perspectives of end-users.

Materials and methods

Study design and variables

This is an analytical cross-sectional study. Outcome variables include overall satisfaction with TM consultation services for NCDs and the willingness to use it in the future. Independent variables comprise socio-demographic factors, co-morbidities, and patients' reported challenges and experiences with the service.

Target population and sample size

The target population was patients with NCDs who had TM consultations during the period of June 2020 to December 2020 in the primary healthcare centers in the Kingdom of Bahrain. The study sample is calculated using the formula for the simple random sampling approach, where Z = 1.96, $P = 0.5$, E = margin of error = 0.05. The total estimated sample size was 285. Any patient who received the service during the allocated period, Bahraini and Non-Bahraini, 18 years or older were eligible to participate in the study. Patients who cannot speak Arabic or English or suffer from mental health problems or did not provide informed consent were excluded from the study. Participants were referred as having mental health problem if recorded in their electronic medical records having diagnosis of any mental health problem according to ICD-11.

Abbreviations: TM, Telemedicine; NCDs, non-communicable chronic diseases.

Sampling method and study tool

Primary care centers in Bahrain are grouped into five health regions, and one health center was selected randomly from each health region. A computer-generated random numbers list permitted the identification of potential volunteers from the database of NCD patients registered in the centers who were served by TM during the study period.

Potential volunteers were approached by telephone interviews conducted by five trained interviewers (research members) using a semi-structured questionnaire to seek their informed consent which was documented in the consent form and collect the required information. The questionnaire and related code book were tested, piloted, and validated by senior investigators before launching the phone survey. The interviews were not recorded for ethical reasons.

Study variables

We defined two outcome variables, overall satisfaction with the TM consultation services for NCDs as well as the willingness to use it in the future. These two variables are expected to provide more valid patients' perspectives regarding this new healthcare delivery approach.

Explanatory factors included information collected in five sections regarding sociodemographic, comorbidities, participants' experience during the TM consultation, satisfaction regarding its different components, challenges faced while using the service, and recommendations for further improvement. The perceived challenges and recommendations were asked as an open question and provided answers are documented in a preconceived list from the literature (yes/no) if perceived as such. Non listed choices are documented under (other) option. Overall satisfaction with the TM consultation was evaluated from the responses to the question "How would you classify your satisfaction through your experience while using the service?" as "bad, neutral, good, very good, excellent" and from that we generated 3 categories "Not-satisfied, Neutral and Satisfied."

TABLE 1 Sociodemographic characteristics and morbidity profile of the study sample (Total number of participants = 251).

Characteristic	*n* (%)
Age group	Mean ± SD = 54.48 ± 10.78
20–40 Years	27 (10.89)
41–60 Years	149 (60.08)
> 60 Years Missing	72 (29.03) 3 (1.20)
Gender	
Male	119 (47.40)
Female	131(52.20)
Missing	1 (0.40)
Nationality	
Bahraini	226 (90.04)
Non-Bahraini	25 (9.96)
Educational level	
Non-educated	35 (13.94)
Elementary school education	29 (11.55)
Intermediate education	45 (17.93)
Secondary school education	83 (33.07)
University/Higher education	59 (23.51)
Type of comorbidities	
Hypertension	160 (63.75)
Diabetes	188 (74.90)
Dyslipidaemia	168 (66.93)
Thyroid Disease	37 (14.92)
Asthma	15 (6.10)
Number of comorbidities	
Patients with One disease	54 (21.51)
Patients with more than one disease	192 (76.49)
Missing	5 (1.99)

Statistical analysis

Categorical variables were presented as frequencies and percentages, and continuous variables were presented as means and standard deviations. From the responses frequency and percentages were calculated. Chi-square tests permitted to test the association between categorical variables. Crude Odds Ratios (COR) and the 95% confidence intervals (95% CI) allowed us to test the strength of pairwise association between the two outcome variables i.e., satisfaction and willingness to use Teleconsultations with other independent categorical variables. The logistic regression model was used to estimate the Adjusted odds ratios and their 95% CI to account for potential confounders. A p-value < 0.05 was considered statistically significant. The data was entered into Excel and then exported to Statistical Package for the Social Sciences (SPSS) software version 28 for analysis.

Ethical considerations

The study was conducted following the Declaration of Helsinki and the protocol was approved by the Research and Ethics Committee of the College of Medicine and Medical Sciences at Arabian Gulf University (approval number: E17-PI-11–21) and the primary healthcare research and ethics committee. Participants were provided information about the study and informed that participation was entirely voluntary and that refusing to participate would not affect future services. Prior to enrolling, all respondents provided informed consent by phone, which was documented by the interviewer in the consent form. Furthermore, all data collected was kept confidential and anonymous and was not used for any other purpose. Reports summarizing the findings are shared with the primary health care director to improve the service and patients

TABLE 2 Determinants of the willingness to use telemedicine services.

Factor	C.OR* (95% CI)	*P*-value	A.OR** (95% CI)	P-value
Comfortable sharing private information				
Do not agree	Ref.		Ref.	
Neutral	5.696 (2.068–15.688)	<0.001	3.740 (1.298–10.781)	0.015
Agree	12.521 (4.916–31.895)	<0.001	7.608 (2.814–20.573)	<0.001
Communication tool was easy to use				
Do not agree	Ref.		Ref.	
Neutral	5.000 (0.964–25.930)	0.055	4.869 (0.854–27.770)	0.075
Agree	17.643 (3.993–77.948)	<0.001	9.336 (1.961–44.442)	0.005

*C.OR, Crude odds ratio (Unadjusted odds ratio). **A.OR, Adjusted odds ratio

received the contact number of the investigators in case they need feedback or to address any query.

Results

Sample characteristics

A total of 251 individuals participated in the study. Slightly more than half of the study participants were female (52.40%). The mean age was 54.48 ± 10.78 years, and the majority of the participants were 41 years or older (89.11%). Most participants were Bahraini (90.04%), and 56.58% reported having a secondary school degree or more. The majority of the participants suffered from more than one NCD (76.49%) and the most reported comorbidities were diabetes (74.90%), hyperlipidemia (66.93%), and hypertension (63.75%). The sociodemographic and medical characteristics of the study participants are presented in Table 1.

Satisfaction with telemedicine consultation

Regarding the overall satisfaction with the TM consultations for NCD care, 231(92.03%) of the participants reported being satisfied, 13(5.18%) provided a neutral response, and only 7 (2.79%) reported being dissatisfied. More than a three-quarter of the participants 197 (78.49%) reported that the doctor introduced him/herself adequately and the history taking covered all the information related to their medical problem for 194 (77.29%) patients. Most of the participants agreed that the doctors gave a comprehensive explanation of their health condition ($n = 227$, 90.43%) and all their questions were properly addressed for 224 (89.24%) participants. Most of the study sample reported a good understanding of their problem after the TM consultation ($n = 207$, 82.50%), the treatment plan was shared and explained fully to them ($n = 224$, 89.24%) and the physician was able to answer all questions related to their medical condition ($n = 224$, 89.24%). Most of the participants reported that the consultation time was adequate ($n = 201$, 80.48%) and the communication tools were user-friendly ($n = 200$, 79.68%). In contrast, only 154 (61.35%) participants reported that they were comfortable sharing private information with the doctor through TM consultation.

Willingness to use TM consultations in the future

In contrast with the overall satisfaction that was reported by most of the interviewed patients, only 142 (56.80%) participants stated that they are willing to use TM consultation services in the future. On the contrary, 74 participants (29.60%) reported that they are not willing to use the service in the future while 34 (13.60%) of the participants had a neutral opinion regarding its future use.

Participants reported challenges and recommendations for the future use of telemedicine consultations

The most reported challenges by the participants were the lack of physical examination (41.20%), inadequate time for the TM consultation (14.50%), fear of medical errors (11.55%), and lack of privacy during the TM consultation (9.16%).

The main recommendations to improve the TM consultations were, to improve the physician-patient communication (28.40%), to use video calls (30.30%), and to increase the TM consultation time (21.10%).

Determinants of willingness to use TM consultations in the future

Willingness to use TM consultations in the future provides the assessment of satisfaction from a different angle. It was significantly associated with, the level of comfort to tell private information A.O.R. = 7.608, 95% CI = [2.814–20.573] and to less extent the perceived ease of the communication tool A.O.R. = 9.336, 95% CI = [1.961–44.442] (Table 2).

Discussion

During the COVID-19 pandemic, the front lines healthcare services including primary care clinics, were severely interrupted at the global level. Despite the initial unexpectedness many health systems responded timely using digital technologies during this crisis to ensure reasonable continuity of health care services. TM services have proven to be an essential component of the worldwide public health response, with the potential to serve as a "safety net" for patients when appropriately integrated (24–26).

In this study, we have evaluated patients' experience regarding TM consultations for NCD care which is a new technology in our

context introduced during the pandemic. Data collected through phone interviews included patients' level of satisfaction with the service, as well as their willingness to use the service in the future. We realized that while 92.03% of interviewed volunteers reported their overall satisfaction, where only 56.80% were positive about its future use. We have also explored challenges faced by the patients as service receivers and factors that predict the willingness of its future use. This discrepancy could reflect some biases that led to an overestimation of satisfaction and justifies triangulating this measurement through the willingness to use this service in the future. Unsurprisingly, factors associated with the willingness to use the service were the extent to which the patient is comfortable disclosing private information, and the ease of telecommunication tools. The degree of comfort in sharing private information appeared to be the most important factor associated with the future use of TM consultations. These factors are in agreement with some reported challenges of TM consultations (19, 20). Indeed, the most reported challenges perceived by the study participants related to TM consultations were the lack of physical examination, inadequate time of TM consultation, fear of medical errors, and lack of privacy during TM consultations. In this study, there was no significant association between participants' sociodemographic data and comorbidities with the future willingness of using TM consultations. Although some studies revealed similar findings (13, 27), others have reported that younger age and higher educational level were associated with more willingness to use the service in the future, this finding could be explained by higher technology literacy among a relatively younger and better-educated study sample (19, 22, 28, 29).

The level of satisfaction and willingness to use TM consultations in the future reported by patients in this study is consistent with the findings in studies conducted in different contexts globally (2, 12, 13, 21, 22, 26, 28–32). Recent studies revealed high satisfaction with virtual consultations across a range of diseases and expressed a strong preference to continue to use virtual consultations as a complement to regular healthcare services even in the post-pandemic period (13, 20). Studies in Gulf Cooperation Council countries revealed similar positive attitudes and a general acceptance of TM consultations including those conducted for NCD patients (22, 26, 30–33). The high level of satisfaction and utilization of TM consultations during the COVID-19 period could be due to their effectiveness in maintaining the continuity of health care and overcoming the risks and challenges of in-person consultations (34, 35). TM is a new modality of healthcare delivery in our context and could be a good complement to the conventional consultation formats in the future if safety, effectiveness, patient-centeredness, efficiency, equity, and acceptability to users are warranted (12, 36). The long-term sustainability of TM should be considered and scaled up even beyond the COVID-19 period, particularly when we consider the dynamics of health applications in the digital vortex (13).

In addition to the reported challenges, participants recommended adding the video format to the telephone consultation for improving patient-doctor communication and connection, as well as increasing TM consultation time. Patients in various contexts worldwide have agreed that video consultations provided the same satisfaction as in-person visits and allowed them to explain properly their health problems (37–39). New advances in "augmented and virtual reality" are nowadays focused on research, development, and health care. They will be promising in creating a breakthrough in the acceptance of TM consultations by patients with the development of cheaper online communication devices (40). However, developers are still facing challenges meeting the needs of end users (41), which raises the importance of encouraging them as developers as well as promoting implementation research in the real context. Integrating novel Telecommunication tools and formats considering adequate time and better patient-doctor communication could ensure patient-centered care and improve the acceptability and future utilization of Teleconsultations.

As part of a quality improvement project in collaboration with the primary healthcare in the Kingdom of Bahrain, the present study will provide part of the scientific evidence needed for the new improvement plan of this consultation approach in the future.

Despite the originality of this study and the importance of its findings, it suffers from some limitations. First, the results might be influenced by the sociodemographic characteristics of the included participants. Second, the reported level of satisfaction and willingness to use TM consultations might be over-reported due to the lockdown imposed by the COVID-19 pandemic during the study. Despite enrolling participants from different regions in the Kingdom of Bahrain, a selection bias could exist as certain subgroups of participants were not able to use TM consultations due to different reasons that could be related to age, disability, economic status, technology literacy, and other factors were not represented in our study sample. A recall bias could exist since phone interviews were not conducted immediately after TM consultations. In addition, a social desirability bias could have increased the level of satisfaction given that interviewers are medical doctors, though not the treating ones. Previous exposure of participants to TM consultations, not taken into account in this study, could have an influence on the overall experience, level of satisfaction and willingness of future use of TM consultation. All these limitations justify a future study, at a different period (post-COVID-19 pandemic) with a more representative sample, using a face-to-face data collection approach. Triangulating information from the perspectives of service providers and users, using mixed methods studies, would provide a comprehensive identification of the gaps to be addressed for the efficient and sustainable integration of this emerging mode of health care delivery.

Conclusion

TM consultations are an emerging pertinent complement to support the conventional consultation formats in the future. To ensure its sustainability technology must be augmented to provide a greater level of security that guarantees privacy for users and offer an experience comparable to face-face consultations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Research and Ethics Committee of the College of Medicine and Medical Sciences at Arabian Gulf University (approval number: E17-PI-11–21) and the primary healthcare research and ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because data was collected through phone interviews and participants were provided information about the study and informed that participation was entirely voluntary and that refusing to participate would not affect future services. Prior to enrolling, all respondents provided informed consent by phone, which was documented by the interviewer in the consent form.

Author contributions

FHab: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review and editing. AR: Investigation, Writing—original draft. ZH: Investigation, Writing—original draft. HAl: Investigation, Writing—original draft. JA: Investigation, Writing—original draft. FHay: Investigation, Writing—original draft. AA: Data curation, Formal analysis, Writing—original draft. HAb: Investigation, Writing—original draft. AB: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing—review and editing, Writing—original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Teleducation: medical education in the pandemic and beyond

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Medical education in the pandemic has been challenging owing to various physical and technological constraints in the current education landscape. This has resulted in reduced patient contact and opportunities for clinical exposure. In utilizing various platforms to supplement teaching, we adopted the use of Telegram, a cloud-based messaging application as an education aid for 3 cohorts of medical students in 1 medical school in Singapore. Herein, we share our experience with Telegram as a novel platform to augment medical education and to supplement clinical training amidst the various constraints. We believe that the circumstances have allowed us to find a method that may serve as an effective adjunct in education. Qualitative feedback has been positive and generally in line with our goals. We believe that further work could involve utilizing other features of the application, or by developing specialized applications to serve the same purpose. More needs to be done to consider applicability in different cultural and socioeconomic contexts.

KEYWORDS

telegram, medical education, pandemic, teaching, education technologies

1. Introduction

The COVID-19 pandemic greatly affected clinical based medical education. Student-patient and student-doctor interactions which are an integral component of medical education have been limited due to restrictions put in place to curb the spread of COVID-19. This, undoubtedly, served as a source of concern for many medical students, citing the impact of markedly reduced clinical exposure (1). As a result, digital adaptation of technology using applications such as Zoom and/or Microsoft Teams have been used to instruct medical students while physical tutorials and lessons were minimized.

Instead of physical tutorials, Zoom-based tutorials have become the new-normal over the past year. However, attending multiple Zoom based lectures over the day have brought forth the issue of "Zoom fatigue." This is attributed to non-verbal overload, namely: reduced mobility, mirror effect of looking at oneself on the screen, increased cognitive load of sending and reading non-verbal signals, and prolonged eye gaze at close distances (2).

Instead of delivering medical education *via* a constant stream of lectures, we decided to compartmentalize teaching into bite-sized content. We chose to utilize Telegram, a cloud-based messaging application which can create channels, polls, host unlimited file sharing content and to foster discussion. (3) Beyond the above capabilities, Telegram has access to various official and user-created bots which add further functionality to the platform, ranging from daily

reminders for important events of the day to even checking the time for the next available bus at a given station.

In this article, we define our experience with the platform as a teaching tool and provide examples as to the methods of utilization of some functions within the application. Through piloting medical education *via* the Telegram application, we aimed to show that the platform was suitable to enhance student-tutor interaction, supplement learning for medical students, foster interactions among students and be a sustainable mode of education. We hypothesize that the adoption of teaching *via* the Telegram application has the potential to augment medical education *via* the above factors, with possible applications beyond the pandemic.

2. Pedagogical principles

Cognitivism (4) has served as a guiding pillar for much of medical education's history, with the focus on lectures, tutorials and use of medical textbooks forming the backbone of acquiring medical knowledge. This method has its disadvantages, such as the lack of consideration for socio-cultural effects on cognitive development and the utility of interactive learning (5).

In our current era, medical education has progressed to involve problem-based learning, encompassing connectivist (6), constructivist (7), and humanist (8) approaches to optimize learning. (9, 10) It is neither fully apprenticeship-based nor classroom based. Discussions and problem-based learning help bridge the gap between theory and applied knowledge in clinical medicine.

Telegram was selected as a platform as it was the most used messaging application among students at our institution. Also, it has advanced features over other mobile chat messaging applications. Telegram's features include comments for each broadcast message, allowing for organized forum-like discussions; quizzes for single-best answer questions; polls that allow feedback to be gathered. In our study, we mainly used the ability to create a forum styled Telegram group to facilitate questions by topic, file sharing for important information and summaries of various teachings, as well as polls to get feedback on the deficiencies that may need further coverage by the tutors. This allows for us to apply the principles of connectivism and constructivism to facilitate problem-based learning for our students, and in so doing, bridge the gap between theory and applied clinical medicine.

We attempted to achieve this by creating 3 forum-styled Telegram groups. This was to aid with segmenting each group for its specific purposes – for information and material sharing, for clarification of doubts, and for application of their knowledge with various clinical pictures and vignettes as cases. Polls were used on a 2-weekly basis for assessment of topics that the students felt that they were weaker in to clarify doubts. Cases and vignettes were given as threads within the Telegram to allow for various students to answer and discuss the various points given within the case.

3. Learning objectives, environment, and pedagogical formats

We started to engage medical students in Singapore *via* the Telegram application from March 2020. We targeted undergraduate medical students on their General Surgery clinical rotations, from years 3 to 5. Each cohort has roughly 300 students. We utilized Telegram channels, a function which allows for "broadcasting" messages - or, in our case, clinical cases and questions (Figure 1). The forum-style channels allowed for students to leave comments on the main question, fostering discussion and allowing for medical educators to clarify doubts should they arise and progress the question in a sequential fashion as necessary. This was used as a tool to supplement the teaching of medical students. Using channels, students were exposed to common clinical scenarios and were challenged to formulate an appropriate clinical approach.

The platform served to encourage greater application in clinical scenarios *via* the use of Objective Structured Slide Examination (OSSE) style questions to allow students to apply their knowledge to a clinical scenario (Figure 2). The platform allows for effective student-tutor interaction where immediate clarification of any misconception can be corrected in a targeted and timely fashion (Figure 3). Also, as multiple students can engage in the channel-based discussion, this allows for mutual learning.

The benefit of using the channels function also allowed for nomination of multiple administrators (i.e., teaching assistants) to assist the owner (i.e., consultant medical educator) in chairing the discussion sessions. This provided the opportunity for a larger pool of faculty to reach out to the same audience set, allowing for a greater diversity of discussion.

4. Assessment of interventions

We believe that we have largely met the goals we sought to achieve with this project.

We believe that the quality and quantity of discussions show that Telegram channels can serve as a suitable **platform for student-tutor interaction** (Figure 1). Organization of cases into separate threads, file sharing capabilities, reply functions, and polls to gather feedback provide the necessary functions required for effective interaction.

Additionally, the goal of **supplementing learning** was met. With 24/7 access, Telegram allows tutors and students to respond and prepare at their convenience. While clinical teaching should ideally take place during office hours, we note that most discussions took place after hours. Heavy clinical loads often force tutors to hold tutorials after-hours or be wrought with delays and cancelations. This platform eliminates logistical issues such as gathering and scheduling constraints and creates opportunities for students and tutors to interact at each other's convenience. It offers an additional benefit of working across time zones. This adds another layer of potential in education-based international collaboration.

We hoped to have achieved more **inter-participant discussion**. Perhaps the lack of anonymity, and the inability to hide previous responses that may serve as "spoilers," have resulted in largely one or two participants attempting each case. The authors believe that discussions between participants could allow them to learn from one another and rely less on tutor input.

The authors feel that Teleducation has also allowed more **efficient outreach** than conventional tutorials, since a single tutor could work with multiple students at once. We also believe that this is a sustainable method of education with potential - the platform allows for training of new tutors and educators that can train subsequent batches of participants. The hope is for participants to improve, and eventually lead discussions with fellow participants and juniors.

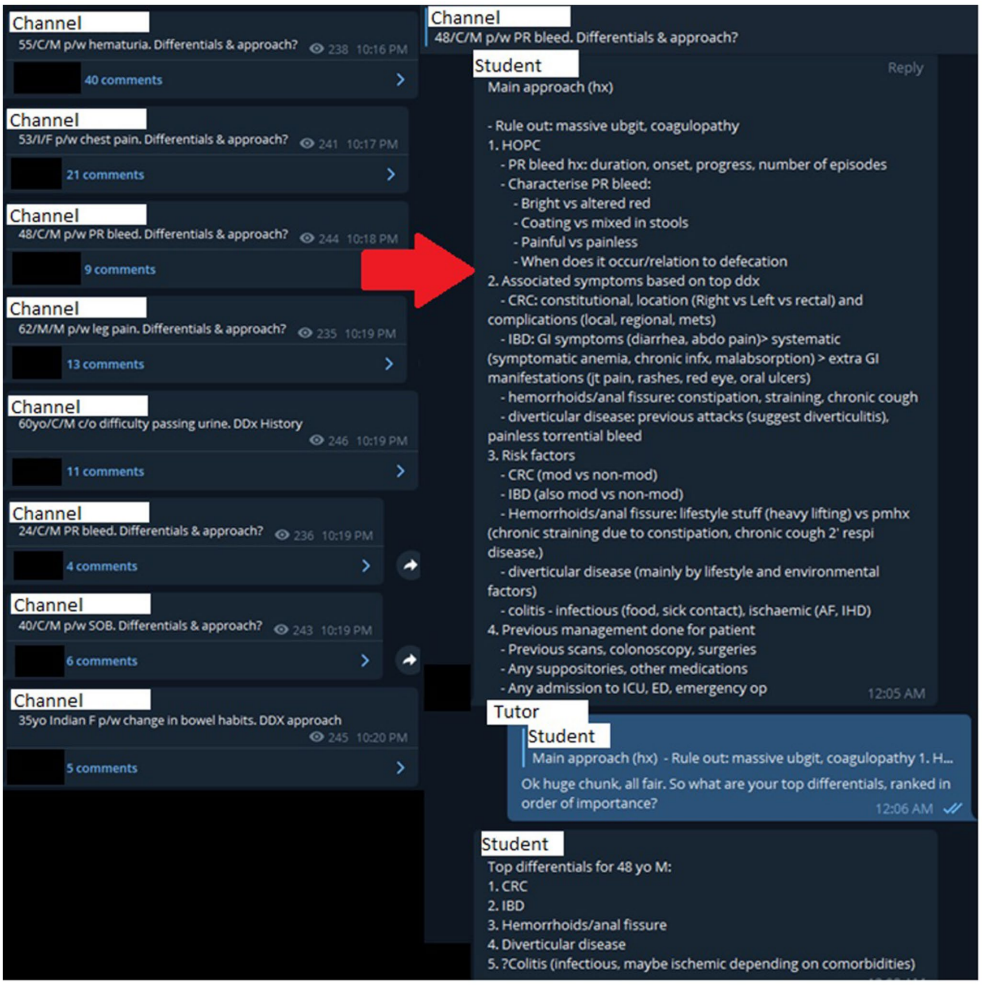

FIGURE 1
Case discussion on a 48 year-old Chinese male presenting with per-rectal bleeding. PR: Per-rectal; Hx: History; HOPC: History of presenting complaint; CRC: Colorectal cancer; IBD: Inflammatory bowel disease; GI: Gastrointestinal; AF: Atrial fibrillation; IHD: Ischaemic heart disease; ICU: Intensive care unit; ED: Emergency department.

In terms of metrics of the platform, participation was about 82.0–90.3% for the students from Years 3–5 of the first batch, excluding the tutors. The average number of responses per thread ranged from 2–47, with a median response of 21 responses. Response times by tutors were prompt, as the threads were created often during hours when the tutors were available and during waking hours (up to about 11:00 PM), and when posts are scheduled, responses would be within the hour as there is a small team of tutors assisting for this endeavor.

For objective evaluation, we plan to administer pre- & post-application surveys to qualitatively define the effectiveness of the platform. The authors felt a head on comparison was unfair, since it would mean purposefully denying an outlet of education for those not in the intervention arm in these trying times. Additionally, these surveys were not previously administered for several reasons. The channel was originally born out of necessity, to help teach in a time where COVID-19 made clinical teaching and face-to-face discussions largely non-feasible. Much of it was rudimentary in nature and started as a small group as a trial. Only later did the idea fully evolve to its current state, with the channel starting in Mar 2020. Moreover, it was logistically difficult as it did not coincide with the academic year, causing it to be difficult to accurately gage the effectiveness of said interventions. Further evaluation will be performed in the coming academic year. Sample surveys are provided in the Supplementary Materials (Supplementary Material I & II). This will likely be implemented as part of the end of Surgery posting evaluation to assist in capturing all students who have been involved in the group to get their feedback and to serve as a touch point for any glaring issues that can be rectified as we continue to use the platform.

5. Discussions, constraints, and lessons learned

Using Telegram as an education platform is novel and has been rapidly adopted owing to limitations put forth by the pandemic (11). Its flexibility and functionality provide a robust springboard for educators. Also, it can help better equip our students with the thought processes and knowledge required to function as a doctor.

An added benefit is that the application allows for closer, guided interaction between tutors and students. Medical education *via* telegram forum style allows for assessment of answers and prompt clarification of any doubts or mistakes. Additionally, if there are any questions about the topic, students can leave a comment to further discuss the point, allowing everyone to benefit from their doubts

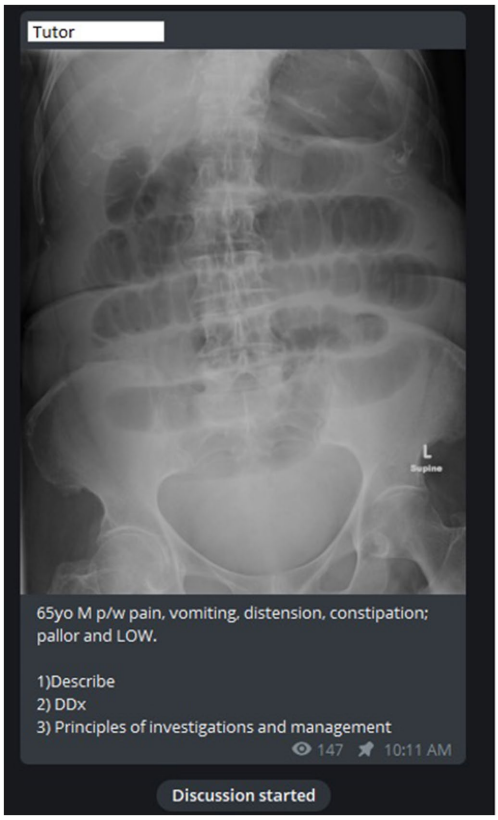

FIGURE 2
Case discussion with an abdominal radiograph of a 65 year old male. P/W: Presenting with; DDx: Differential diagnoses.

immediately. This fosters interactive learning and is a useful adjunct to the traditional didactic style of education which most people are used to.

Having a discussion on a forum-style app allows for retrospective review of discussions by active and passive participants alike. This contrasts with face-to-face tutorials, where there is by default no documentation of a discussion.

Nonetheless, we concede that there exist various challenges. Telegram's main purpose as a messaging platform can serve as a distraction, as raised by various other authors. "Some students found the application a source of disturbance and distraction while studying," with feedback indicating that the constant notifications from groups and channels can be distracting (3). However, in our experience, this has been mitigated by the "always on" nature since students are free to answer at their leisure. Also, its scalability can also be viewed as a weakness. While there is the possibility of greater outreach with an economy of effort, this might skew the teacher-to-student ratio, which can reduce the effectiveness of using telegram as a tool to augment medical education. Building on this, the number of participants as well as its public nature might serve as deterrence toward active participation. While passive learning has its benefits such as better test scores, active learning yielded better understanding of the target concept.4 This delicate balance between active and passive learning and its benefits is an important issue to deliberate and achieve.

While we feel that Telegram has potential, we concede that much of what we have achieved is but a basic utilization of the platform, and that its use as a teaching aid is still in its infancy. Drawing from other sources, future directions can include bite-sized information messages like Journal Feed (12), which features updates in Emergency Medicine in short and succinct summaries. Additionally, new platforms with additional features could further facilitate learning and participation. Features could include summarization of new landmark studies or guidelines, allowing for discussion of such topics, and quiz/game styled based cases to allow gamification which may enhance learning. Also, anonymized replies can help to improve participation, and it is useful for students who are less confident in answering on a public domain. Prompts and guiding questions can also be supplied on demand for challenging questions. Similarly, an upvote tool could prove useful in incentivizing high-quality contributions to the discussions. These can also be helpful to passive reviewers by directing their attention to more helpful or popular answers.

To improve scalability, artificial intelligence may prove useful as automated answering bots. Ideally, these could prompt the participant for missing elements in their answers to encourage further critical thinking. In a more primitive form, automated bots could privately reveal suggested answers to participants after a response. This reduces the time needed to respond to individual answers.

The possibilities are endless, and these barely scrape the surface of what is possible. We hope that this could play a role in optimizing education resources and improving the quality of medical education, but also note that applicability can be limited by different cultural and socioeconomic practices. Nonetheless, we hope that this proof of concept might inspire the use of locally relevant resources to supplement education.

6. Conclusion

Teleducation is a useful tool that medical education institutions can consider adding to their arsenal of teaching pedagogies. It not only augments but provides a useful constant presence in an "always on" fashion to engage and push students to explore topics in more detail as well as further their interests in areas of medical science. However, much more can be done to improve content delivery and assess quantitatively and qualitatively the effect of this new novel teaching pedagogy in undergraduate medical education.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors contributed to the conceptualization, manuscript preparation, editing and proofreading. All authors contributed to the article and approved the submitted version.

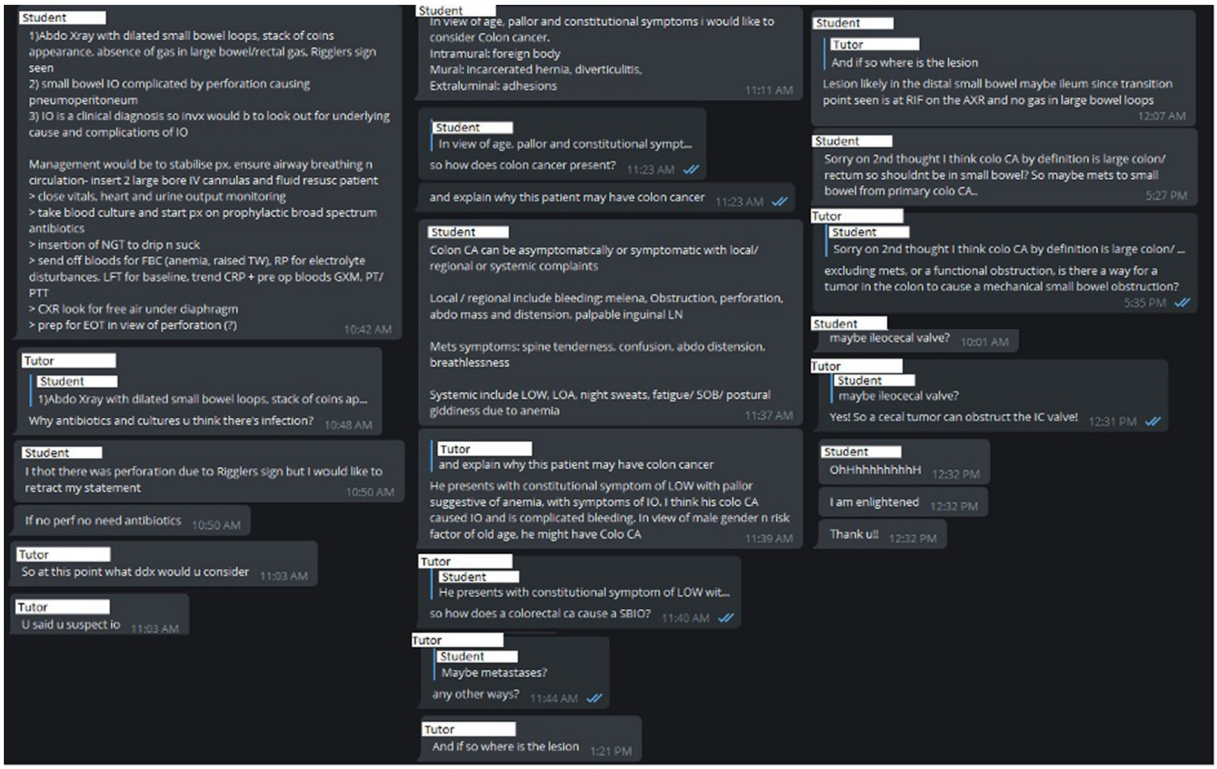

FIGURE 3
Discussion regarding case in Figure 2. IO: Intestinal obstruction; IV: Intravenous; NGT: Nasogastric tube; FBC: Full blood count; TW: Total white count; RP: Renal panel; LFT: Liver function tests; CRP: C Reactive Protein; GXM: Group and cross match; PT/PTT: Coagulation panel; CA: Cancer; LOW: Loss of weight; LOA: Loss of appetite; LN: Lymph nodes; SOB: Shortness of breath; SBIO: Small bowel intestinal obstruction; RIF: Right iliac fossa; AXR: Abdominal X-Ray; IC: Ileocecal.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1251732/full#supplementary-material

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A comparative analysis of the COVID-19 Infodemic in English and Chinese: insights from social media textual data

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The COVID-19 infodemic, characterized by the rapid spread of misinformation and unverified claims related to the pandemic, presents a significant challenge. This paper presents a comparative analysis of the COVID-19 infodemic in the English and Chinese languages, utilizing textual data extracted from social media platforms. To ensure a balanced representation, two infodemic datasets were created by augmenting previously collected social media textual data. Through word frequency analysis, the 30 most frequently occurring infodemic words are identified, shedding light on prevalent discussions surrounding the infodemic. Moreover, topic clustering analysis uncovers thematic structures and provides a deeper understanding of primary topics within each language context. Additionally, sentiment analysis enables comprehension of the emotional tone associated with COVID-19 information on social media platforms in English and Chinese. This research contributes to a better understanding of the COVID-19 infodemic phenomenon and can guide the development of strategies to combat misinformation during public health crises across different languages.

KEYWORDS

COVID-19, infodemic data, word frequency analysis, topic clustering analysis, sentiment analysis

1 Introduction

During the beginning of the COVID-19 pandemic, there was a surge in misinformation, false information, and rumors spreading rapidly across various media platforms. This phenomenon came to be known as the infodemic. The infodemic refers to the overwhelming abundance and rapid spread of misinformation, conspiracy theories, and unverified claims related to the pandemic (1). It accompanied the spread of the virus itself and was fueled by uncertainties, fear, and confusion during the early stages of the outbreak (2). Numerous falsehoods and conspiracy theories circulated globally, making it challenging for individuals to discern accurate information. Some examples include claims that the virus was intentionally created or released, that certain medications or alternative remedies could cure or prevent the virus, or that 5G networks were somehow linked to the spread of the disease. The infodemic had significant implications on public health, as it hindered effective pandemic response efforts. False information about prevention measures, symptoms, and treatments could potentially mislead the public and endanger lives. It also led to widespread panic, social unrest, and stigmatization of certain groups. Although the World Health Organization (WHO) declared an end to

COVID-19 as a global health emergency, it is important to note that combating the infodemic remains an ongoing challenge.

COVID-19 is a global pandemic, and misinformation knows no boundaries. Conducting a comparative analysis across different languages allows us to gain a comprehensive, global perspective on the infodemic. On one side, each language has its unique linguistic characteristics, cultural norms, and online behaviors. Analyzing social media data in different languages can uncover language-specific nuances that shape misinformation patterns and responses. On the other side, analyzing data from multiple languages uncovers common themes, misinformation tactics, and influential narratives. Understanding these cross-cultural trends allows for exchanging knowledge and implementing effective global strategies. According to Statista (3), English and Chinese are the top-2 most common languages used on the Internet. Therefore, this paper aims to conduct a comparative analysis of the COVID-19 infodemic in both English and Chinese languages by utilizing textual data extracted from social media platforms. The main contributions of our work are summarized as follows:

1. Two balanced infodemic datasets are introduced by adjusting previously collected social media textual data with annotations from healthcare workers where all records are classified into three distinct groups: true, false, and uncertain.
2. Word frequency analysis is conducted to identify the 35 most frequently occurring infodemic words to acquire knowledge on the prevalent patterns and trends of word usage in two languages.
3. Topic clustering analysis is executed to uncover thematic structures to gain insights into the similarities and differences between different topics or subject areas across two languages.
4. Sentiment analysis is performed to determine the percentage of positive, neutral, or negative sentiments within infodemic records to understand the emotional tone and attitudes expressed in two languages.
5. A discussion is held to grasp the language-specific nuances and cross-cultural trends of both the overall records and the records classified into three groups. The latter offers perspectives at a more refined level by incorporating the professional knowledge of healthcare workers.

The subsequent sections of this paper are organized as follows. Section 2 introduces related works. Section 3 displays the two balanced infodemic datasets. Section 4 provides the results of word frequency analysis, topic clustering analysis, and sentiment analysis, respectively. Afterward, a discussion is illustrated in Section 5. Finally, section 6 presents conclusions.

2 Related works

The majority of scholarly research about infodemic centers on addressing misinformation while trained models incorporating word embeddings stand out as the most commonly utilized methods (4). Glazkova et al. (5) proposed an approach using the transformer-based ensemble of COVID-Twitter-BERT models to detect COVID-19 fake news in English. Chen et al. (6) studied a novel transformer-based language model fine-tuning approach for English fake news detection during COVID-19. Paka et al. (7) set up a cross-stitch semi-supervised neural attention model for COVID-19 fake news detection which leverages the large amount of unlabelled data from Twitter in English. Chen et al. (8) used fuzzy theory to extract features and designed multiple deep-learning model frameworks to identify Chinese and English COVID-19 misinformation. Liu et al. (9) developed a deep learning based model and fine-tuned it to adapt to the specific domain context of COVID-19 news classification in English, Chinese, Arabic, and German. While these models have undoubtedly improved the efficacy in combatting misinformation during the COVID-19 pandemic, they often overlook the critical aspect of elucidating the underlying characteristics of the infodemic. Without being transformed into human-understandable knowledge, their outputs would have limited efficacy in aiding human efforts to combat the infodemic and develop targeted countermeasures and mitigation strategies.

Certain academic studies pay their attention to comprehending the patterns exhibited within the COVID infodemic through an in-depth analysis of its content. Gupta et al. (10) identified topics and key themes present in English COVID-19 fake and real news, compared the emotions associated with these records and gained an understanding of the network-oriented characteristics embedded within them. Wan et al. (11) described the prominent lexical and grammatical features of English COVID-19 misinformation, interpreted the underlying (psycho-)linguistic triggers, and studied the feature indexing for anti-infodemic modeling. Zhao et al. (12) used 1,296 COVID-19 rumors collected from an online platform in China, and found measurable differences in the content characteristics between true and false rumors. Zhou et al. (13) investigated both thematic and emotional characteristics of COVID-19 fake news at different levels and compared them in English and Chinese. All of the aforementioned works prioritize conducting analysis using a binary truth classification system, precisely distinguishing between true and false categories, to minimize discrepancies arising from truth labeling. However, it is incumbent upon us to acknowledge the inherent challenges faced when adjudicating the authenticity or veracity of certain statements during the labeling process.

The majority of collected records utilized in the analysis and detection of the infodemic phenomenon are typically categorized and labeled as either true or false (14). Nonetheless, a limited number of studies have undertaken an alternative approach by classifying these records into 3–5 categories to have a more comprehensive understanding of the infodemic and its impact at a finer level of granularity. Cheng et al. (15) built up an English COVID-19 rumor dataset by gathering news and tweets and manually labeling them as true, false, or unverified. Haouari et al. (16) proposed an Arabic COVID-19 Twitter dataset where each tweet was marked as true, false, or others. Luo et al. (17) collected widely spread Chinese infodemic during the COVID-19 outbreak from Weibo and WeChat while each record was indicated as true, false, or questionable after a four-time adjustment. Kim et al. (18) produced a dataset encompassing English claims and corresponding tweets, which were organized into four groups: COVID true, COVID fake, non-COVID true, and non-COVID fake. Dharawat et al. (19) released a dataset for health risk assessment of COVID-19-related social media posts. There are English tweets and tokens and all of them were classified into five categories: real news/claims, not severe, possibly severe misinformation, highly severe misinformation, or refutes/rebuts

misinformation. Given the profound interconnectedness between the infodemic and health records and its notable implications for public health, the active involvement of healthcare workers could help advance the comprehension of the infodemic. However, only (17) have considered this aspect while categorizing the collected records.

Considering the above-mentioned analysis, most studies have predominantly focused on English records. Therefore, it is valuable to conduct a comparative study of the COVID-19 Infodemic in multiple languages. The previously collected social media textual data offer an initial starting point while the integration of healthcare workers' professional knowledge serves to enhance insights at a more refined level. Additionally, conducting an analysis incorporating lexical, topical, and sentiment features would contribute to a comprehensive understanding of the underlying characteristics.

3 Data collection

English and Chinese records are chosen for this study because of their status as the two most prevalent languages used on the Internet (3). A summary of the encompassed data is presented in Table 1.

The English data is sourced from Patwa et al. (20). It collects 5,100 fake news from public fact-verification websites and social media. On the other side, there are 5,600 real news and they are tweets crawled from official and verified Twitter handles of the relevant sources using Twitter API. The dataset is split into train (60%), validation (20%), test (20%) and the training set has been selected for this study. The training set was published on October 1, 2020 (21) and consists of 3,360 real news and 3,060 fake news. We have invited three healthcare workers to manually classify these 6,420 records into three distinct groups: true, false, and uncertain. Their assessments rely exclusively on their judgments without any reference to external sources, and the assigned label for each record is determined by employing a majority agreement methodology. To address the limited number of instances in the real group (830 records), we randomly selected 830 records from both instances labeled as true and uncertain. Finally, a total of 2,490 records were kept, with an equal distribution for each group to mitigate any potential bias and to ensure fairness in representing various categories.

The Chinese data is derived from Luo et al. (17). This dataset gathers a total of 797 original records, which include manually verified Weibo posts from the Sina Community Management Center between January 21 and April 10, 2020, and specifically checked news from the WeChat mini-program "Jiaozhen" until March 31, 2020. All instances are classified into two types based on their content: strongly related health records and weakly related health records. The weakly related health records are further subdivided into specific categories, which include local measures, national measures, patient information, and others. Subsequently, four rounds of adjustments are conducted: (1) adjusting labels for instances classified as weakly related health records, (2) adjusting labels for records initially marked as partially true or conditionally true, (3) removing dummy records in the sub-group of local measures, (4) adding strongly related health records from authoritative sources to the true group. In the end, the dataset consists of 1,055 records overall, with 409 labeled as questionable, 276 as false, and 335 as true, ensuring that each group contains roughly an equal number of records. Since there is high intercoder reliability between the final labels and labels annotated by healthcare workers, we keep the classification results from Luo et al. (17) while simply replacing the label questionable with uncertain.

TABLE 1 A summary of the encompassed data.

Languages	Sources	Labels		
		True	False	Uncertain
English	Patwa et al. (20)	830	830	830
Chinese	Luo et al. (17)	335	276	409

4 Methods and results

4.1 Word frequency analysis

Weiciyun (22) is utilized in this section to conduct word frequency analysis for both English and Chinese records. It serves as a practical and user-friendly online tool for generating word clouds and visualizing text data. Before analysis, the built-in language-specific tokenization and stopword removal techniques provided by Weiciyun are leveraged to yield clean and meaningful text data. Afterward, content filtration based on part-of-speech is applied to retain only nouns, gerunds, and proper nouns. In terms of English text, only content with a word length of at least 3 and a frequency of at least 2 is selected. Similarly, for Chinese text, content with a character length of at least 2 is chosen. Finally, the 35 most frequent words are presented and they are illustrated with font size scaled to their frequencies while the detailed word frequencies of these words can be found in Table 2. To ensure translation consistency and reduce subjectivity, the word clouds maintain the original Chinese characters while providing a reference translation in Appendix 1 as needed.

The word clouds of all records in English and Chinese are presented in Figure 1. Firstly, it is noteworthy that the most frequently mentioned terms in both languages are the same, including "virus" (病毒), "pandemic" (疫情), "patient" (患者), and so on. Secondly, the term "mask" (口罩) is mentioned in both languages but holds greater prominence in the Chinese word cloud. Thirdly, the name "Wuhan" (武汉), which corresponds to the initial epicenter of the COVID-19 outbreak in China, appears in larger font size in the Chinese word cloud, while no specific city-related word is present in the English cloud. Fourthly, the term "death" appears with greater frequency in the English data than in the Chinese records where it is noticeably absent. Finally, the individual most frequently mentioned in English is President Donald Trump, whereas, in Chinese, it is Zhong Nanshan (钟南山), an esteemed academician in the field of healthcare.

The word clouds presented in Figure 2 categorize records into three groups in both English and Chinese. The true or false labeled groups primarily consist of common terms, which are predominantly derived from the expertise of healthcare professionals. These terms revolve around virus transmission methods, prevention measures, and treatment approaches. On the other hand, the uncertain group encompasses a diverse range of terms. Within this group, both English and Chinese records demonstrate an awareness of regional considerations. Notably, the Chinese word cloud places a greater emphasis on specific locations such as "Wuhan" (武汉), "Beijing" (北京), "Shanghai" (上海), "Canton" (广州), and "Chengdu" (成都). In

TABLE 2 Word frequency of the 35 most frequent words displayed in Figures 1, 2.

All records				Records labeled as true				Records labeled as false				Records labeled uncertain			
English	W.F.	Chinese	W.F.	English	W.F.	Chinese	W.F.	English	W.F.	Chinese	W.F.	English	W.F.	Chinese	W.F.
Covid	833	病毒	185	Covid	476	病毒	71	Coronavirus	353	病毒	71	Cases	336	肺炎	84
Coronavirus	617	肺炎	179	People	141	口罩	60	People	91	肺炎	59	Covid	274	武汉	48
Cases	430	口罩	110	Spread	126	肺炎	36	Covid	83	口罩	32	Coronavirus	162	病毒	43
People	319	疫情	56	Coronavirus	102	患者	28	Virus	79	疫情	13	Tests	123	疫情	39
Health	177	武汉	55	Health	97	消毒剂	22	Trump	62	患者	11	Deaths	103	医院	20
Tests	159	患者	54	Risk	87	症状	17	Pademic	51	美国	10	Number	101	美国	20
Spread	147	美国	30	Cases	76	医用	16	Cure	51	酒精	10	People	87	中国	19
Deaths	145	钟南山	26	Face	73	飞沫	14	President	49	钟南山	9	States	85	口罩	18
Virus	138	消毒剂	26	Others	67	建议	11	Vaccine	47	疫苗	8	India	78	钟南山	16
Testing	137	酒精	25	Testing	63	风险	10	Video	42	武汉	7	Today	71	患者	15
Pademic	125	疫苗	24	Symptoms	62	酒精	10	Government	38	大蒜	6	Testing	64	北京	15
Vaccine	119	医院	22	Patinets	52	疾病	10	Corona	37	大量	6	State	62	上海	14
Number	119	中国	22	Virus	50	证据	10	China	37	病人	5	Indiafightscorona	59	意大利	14
States	116	病人	20	Pandemic	47	感染者	9	News	33	日本	5	Health	47	病人	11
India	111	症状	20	Masks	46	人群	9	Health	33	抗体	4	Report	44	疫苗	10
Patients	109	医用	18	Mask	46	儿童	8	Claims	32	院士	4	Vaccine	43	病例	9
Risk	107	风险	17	Care	44	居家	8	Chinese	31	医生	4	Rate	42	湖北	9
Face	87	北京	17	Hands	43	通风	8	Masks	31	病毒感染	4	Case	41	人员	9
Test	87	人员	17	Use	42	人员	8	Bill	28	空气	4	Nigeria	39	成都	9
Trump	84	病例	16	Contact	42	物品	7	World	28	白酒	3	Data	38	院士	8
State	83	意大利	16	Distancing	40	效果	7	Gates	27	防病毒	3	Lakh	38	入境	7
Masks	83	建议	15	Home	39	传染性	7	Flu	26	小时	3	Lockdown	37	医生	7
Days	82	上海	14	CDC	39	人类	7	Novel	25	病情	3	Day	35	视频	7
Today	81	飞沫	14	Measures	37	距离	7	Donald	25	中国	3	Patients	35	全国	7
Symptoms	81	抗体	13	Cloth	35	核酸检测	6	Being	24	流鼻涕	3	Days	32	全部	6
Indiafightscorona	75	院士	13	Disease	34	疫苗	6	India	24	纸尿裤	3	Test	32	阳性	6
Others	73	感染者	13	Test	34	动物	6	Claim	23	气溶胶	3	Yesterday	31	员工	6
Home	72	阳性	12	Treatment	30	食品	6	Outbreak	22	二氧化氯	3	Week	31	印度	6
CDC	71	核酸检测	12	Days	29	情况	6	Home	22	消毒剂	3	First	30	国家	5
Government	71	医生	11	Vaccine	29	传播者	6	Lockdown	22	牛羊肉	3	Million	30	物资	5
Data	70	疾病	11	Data	29	重症	6	Patients	22	喉咙	3	Recoveries	29	酒精	5
Lockdown	70	湖北	11	Infection	29	手部	6	Disease	21	肥皂	3	Coronavirusupdates	28	特朗普	5
Care	69	空气	11	Countries	29	手套	6	Test	21	食品	3	Pandemic	27	风险	5
Video	68	证据	11	Deaths	27	传染病	6	Days	21	食用	3	Isolation	27	广州	5
Case	67	人类	10	Person	27	紫外线	5	Message	20	瘟疫	2	Numbers	27	医疗	5

W.F., Word Frequency.

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FIGURE 1
Word clouds for all records.

contrast, the English word cloud labeled as uncertain indicates a temporal focus by frequently including terms like "Today," "Yesterday," "Days," and "Week." It is worth mentioning that these time-related terms are not explicitly included in the Chinese word cloud.

4.2 Topic clustering analysis

In this section, the Latent Dirichlet Allocation (LDA) topic model is implemented to uncover hidden topics and thematic structures from both English and Chinese records. LDA is a widely adopted technique in the field of natural language processing, wherein documents are represented as stochastic mixtures across latent topics, and each topic is characterized by a distribution over words (23). For enhanced comprehension of the clustered topics, we employ the LDAvis package (24) to visualize the results using multidimensional scale analysis. We set the initial range of topic numbers to [1, 15], and the final determination of the optimal number of topics relies on the highest coherence score. The step size is retained as 1, while α and β are maintained at their default values. Furthermore, language-specific tokenization and stopword removal techniques are employed to mitigate the influence of text analysis when applying LDA to analyze different languages. For English text, whitespace-based tokenization is employed, and the widely recognized Chinese word segmentation tool Jieba is utilized for Chinese tokenization. The built-in function from the Natural Language Toolkit (NLTK) library in Python is leveraged to access a collection of stopwords specifically for English, whereas the widely used cn_stopwords.txt file is applied to remove stopwords from Chinese text. Finally, in line with sub-section 4.1, the original Chinese characters are preserved in the visualization graphs, supplemented with a reference translation provided in Appendix 2.

The visualization graphs of all records in English and Chinese are presented in Figure 3. Firstly, the number of clustered topics in the English records is significantly fewer compared to the Chinese records. Specifically, there are only 4 topics identified in the English records, whereas the Chinese records encompass 13 topics. Secondly, the English topics are mutually exclusive with no overlap. The proximity between Topic 1 and Topic 2 is high, while the remaining topics exhibit considerable dissimilarity. Conversely, in the visualization graph of the Chinese records, the topics demonstrate interconnectedness. Notably, Topic 2 overlaps with Topic 9, as does Topic 8 with Topic 11. Thirdly, Topic 1 stands out in the English records as it covers a significant portion of the tokens, specifically 35.2% in the top 30 most relevant terms. On the other hand, Topic 1 has a comparatively smaller presence in the Chinese records, accounting for only 11% of the tokens in the top 30 most relevant terms. Its size is not as noticeable when compared to Topic 2 and Topic 3, where the difference is not considered significant. Finally, there are shared terms that appear in the top 30 most relevant terms of Topic 1 in both languages, indicating a mutual focus from both sides.

The visualization graphs in Figure 4 categorize records into three groups in both English and Chinese. The annotation of each visualization graph remains the same as shown in Figure 3. Due to space limitations, they are not included in Figure 4. Firstly, the pattern of topic numbers remains consistent across the groups labeled as true and uncertain. However, in the group labeled as false, the English records show a significantly larger number compared to the Chinese records. Secondly, within the groups labeled as true, the percentage of tokens in the top 30 most relevant terms of Topic 1 is similar in both languages while there exists a difference of more than 10% in the other two groups. Finally, the groups labeled as true or false primarily consist of common terms in the top 30 most relevant terms in both languages. Nevertheless, the uncertain group encompasses a diverse range of terms. This observation further supports the conclusion mentioned in sub-section 4.1.

4.3 Sentiment analysis

Monkeylearn (25) is utilized in this section to conduct sentiment analysis on English records. The platform offers a user-friendly graphical interface that enables users to create personalized text classification and extraction analyzes by training machine learning models. In the analysis of Chinese records, ROST_CM6 (26), a widely used Chinese social computing platform, is employed to generate the results. ROST_CM6 enables various text analyzes, including microblog, chat, and web-wide analyzes. It is important to note that Monkeylearn generated multiple emotions for 145 instances due to the length or complexity of certain English records. To maintain consistency, these instances were manually annotated by three annotators, and the emotional tone was determined based on the majority agreement. Finally, each record was broken down into positive, negative, or neutral categories.

FIGURE 2
Word clouds for records classified into three groups.

The pie charts and bar charts in Figure 5 present the sentiment proportion of all records in English and Chinese. It indicates that over 50% of the information, in both English and Chinese, is characterized as negative. Specifically, English records have a negative proportion of 59.96%, while Chinese records have a negative proportion of 50.71%. This implies that regardless of the language system, over half or more of the infodemic being disseminated to the public carries a negative tone. In addition, the distribution of positive and neutral information differs between the two language systems. Within the Chinese records, there is a balance between positive (25.69%) and neutral (23.60%) information. On the other hand, in the English records, the proportion of positive information exceeds that of neutral information significantly, with 31.12% being positive and only 8.92% being neutral. These findings suggest that individuals within the English language system tend to adopt a more positive attitude when confronted with the infodemic during the COVID-19 pandemic. Conversely, individuals in the Chinese language system lean toward a more neutral and conservative stance.

The pie charts and bar charts in Figure 6 categorize records into three groups in both English and Chinese. In the true group, the sentiment proportions for Chinese records have remained relatively stable compared to the results displayed in Figure 5. However, for English records, there has been an increase in the proportions of positive and neutral information. In the false group, it is observed that the proportions of negative information have increased in both languages and remain relatively consistent. Additionally, false

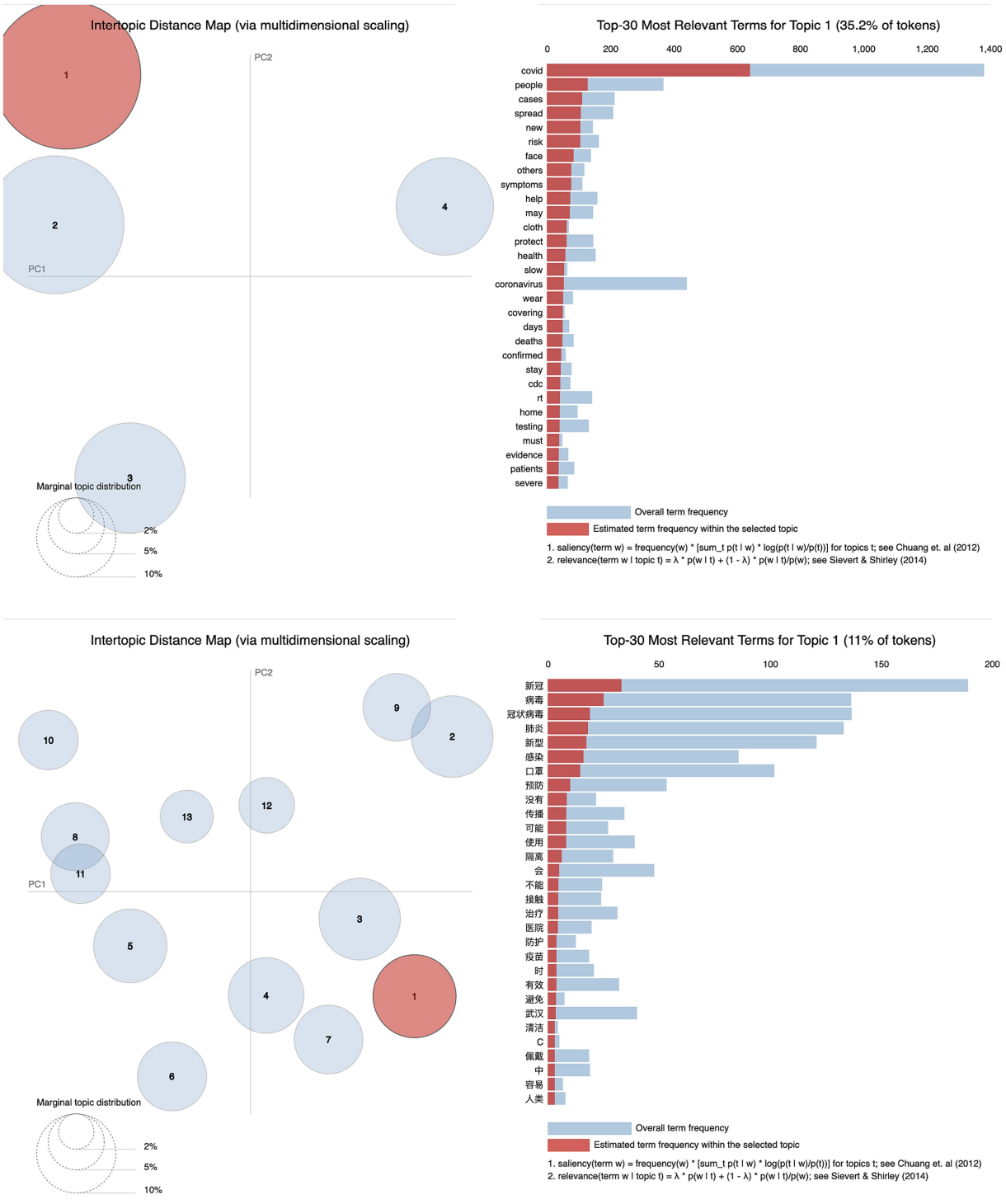

FIGURE 3
Visualization graph of LDA topic modeling for all records.

records exhibit the highest proportion of negative sentiment among the three groups. Moving on to the uncertain group, the sentiment proportions for English records have not shown significant changes compared to the false group. However, for Chinese records in the uncertain group, the proportion of negative sentiment has decreased, resulting in a relatively balanced distribution of the three sentiment categories.

5 Discussion

Regarding word frequency analysis, the distinctions between the English and Chinese word clouds reflect some unique perspectives. Firstly, the term "mask" holds particular significance in the Chinese context, reflecting the country's proactive approach to mask-wearing as a preventive measure against the virus. This cultural aspect is not as

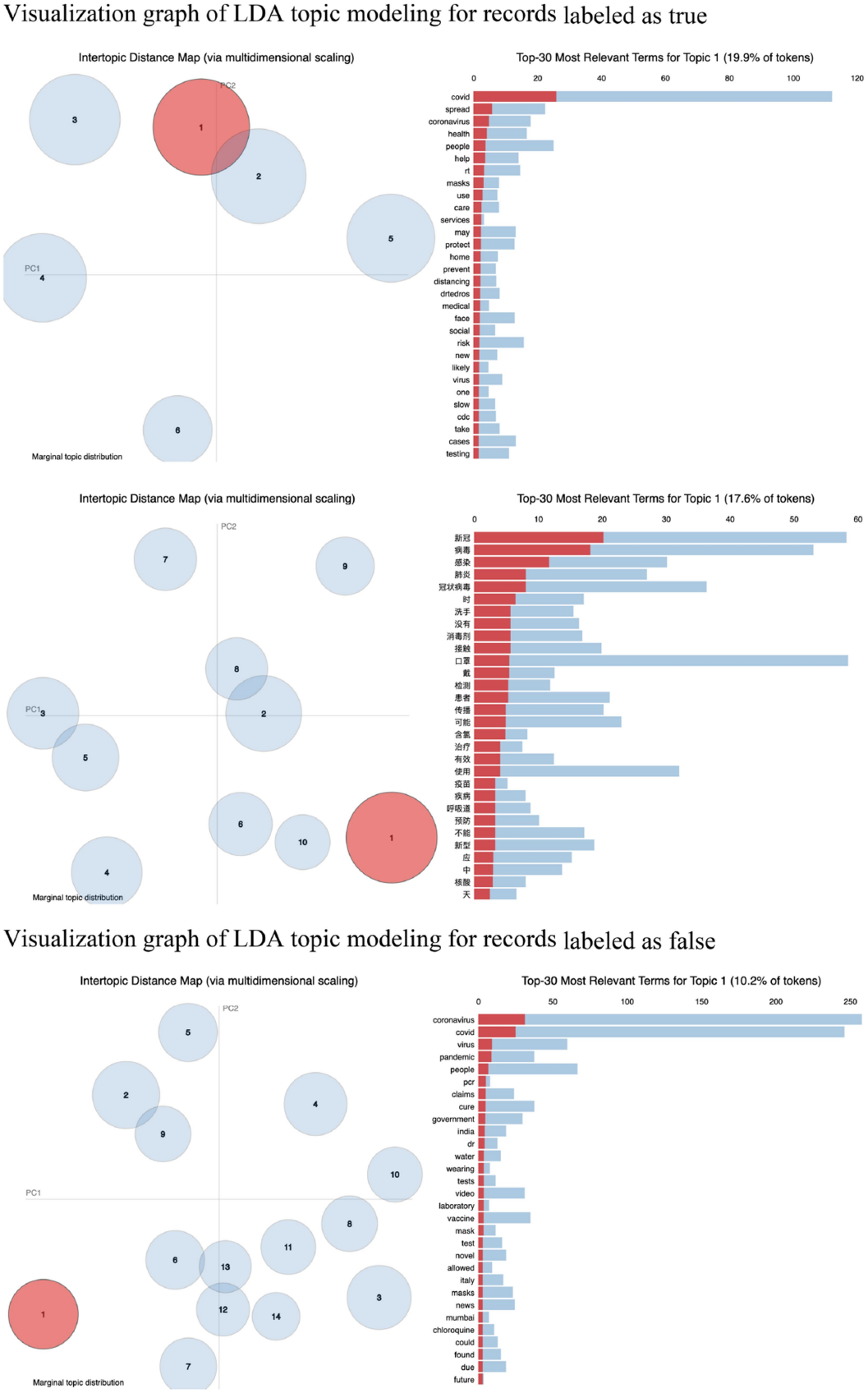

FIGURE 4 (Continued)

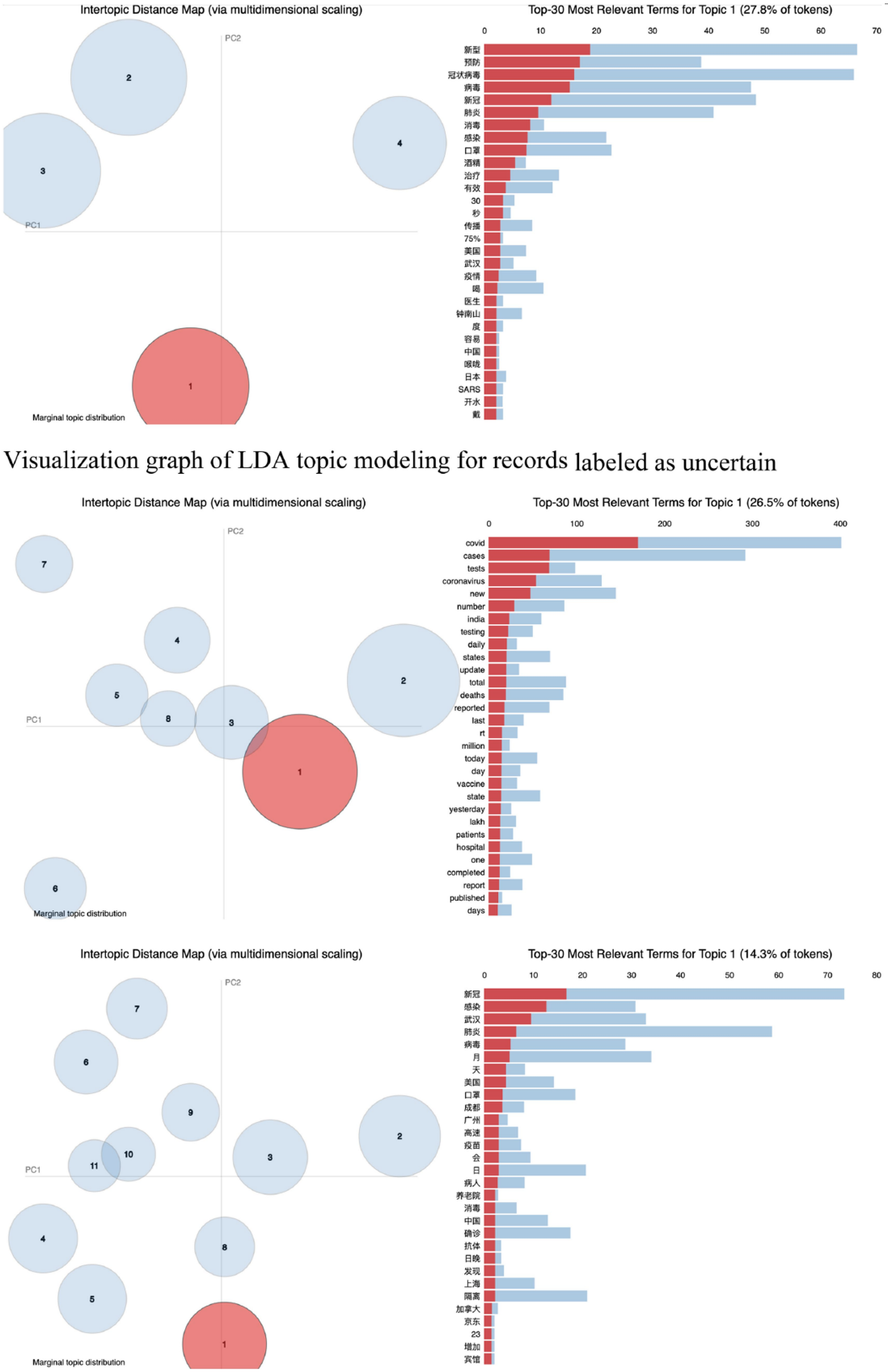

FIGURE 4
Visualization graph of LDA topic modeling for records classified into three groups.

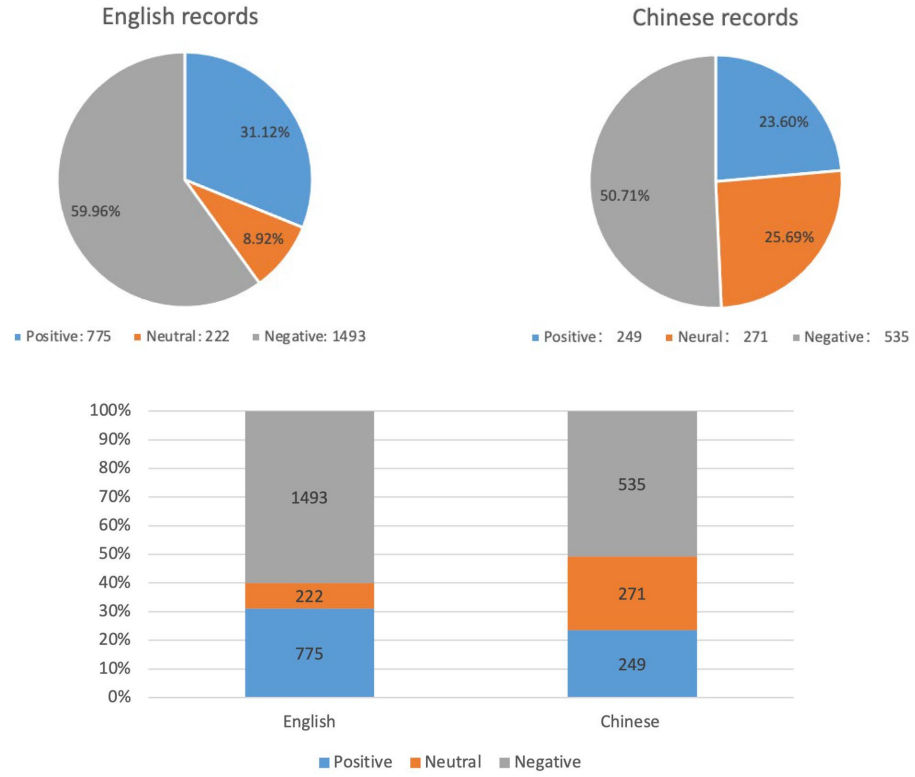

FIGURE 5
Sentiment analysis results for all records.

prominent in the English word cloud, indicating potential differences in the adoption and perception of this protective measure. Secondly, the variation in the frequency of the term "death" between the English and Chinese word clouds sheds light on the different tones and focuses within each language. The higher occurrence in the English cloud may indicate a greater emphasis on the global loss of life and the severity of the situation, whereas its absence in the Chinese cloud might suggest a more limited or sensitive discussion surrounding this aspect. Thirdly, the individuals most frequently mentioned, President Donald Trump in English and Zhong Nanshan, an esteemed healthcare academician in Chinese, further exemplify the contrasting perspectives. It highlights the significance of political figures in English discussions and the recognition of medical experts and authoritative voices in the Chinese discourse. Finally, the region-specific emphasis in the Chinese cloud and the temporal focus in the English cloud showcase the nuances and contextual factors shaping the discussions in each language. These city names suggest a focus on regional impact and potential localized concerns within China while these time-related terms reflect the need to stay updated with real-time information within English conversations.

The topic clustering analysis highlights the distinct characteristics and priorities within the English and Chinese discussions on COVID-19. Firstly, the English records have a lower number of clustered topics compared to the Chinese records in most cases. This discrepancy suggests that the English discussions on COVID-19 may exhibit a more focused and limited scope while the Chinese records suggest a wider range of perspectives and a more nuanced understanding of various aspects. Secondly, the group labeled as false stands out as an exception to this pattern, with the English records displaying a significantly larger number of clustered topics compared to the Chinese records. This stark difference may indicate a higher prevalence of diverse false narratives and misinformation spread across various sources within the English language. Thirdly, the presence of shared terms in the top 30 relevant terms of Topic 1 signifies a shared focus between both languages, particularly within the group labeled as true and false. This common attention highlights the significance of specific themes or concerns in the global discourse surrounding COVID-19, transcending linguistic and cultural boundaries. Finally, there are noticeable differences in the top 30 relevant terms of Topic 1 within the uncertain group between the Chinese and English languages. These variations emphasize disparities in how uncertain records are conceptualized and discussed within the Chinese and English language communities, which can likely be attributed to variances in cultural, linguistic, and contextual factors.

When it comes to sentiment analysis, the comparative results in English and Chinese records offer valuable insights into emotional trends. Firstly, it is evident that in most cases, over 50% of the information in both languages skews toward negativity, indicating a prevalent negative sentiment in the collected infodemic data. This is likely influenced by the nature of the discussed topics, the tone employed, and the general sentiment of those generating the records. Secondly, English records typically demonstrate a notably higher proportion of positive sentiment with a substantial margin compared to their Chinese counterparts. This disparity can be attributed to various factors, such as cultural contexts, linguistic nuances, or even the diverse user demographics associated with each language. Thirdly,

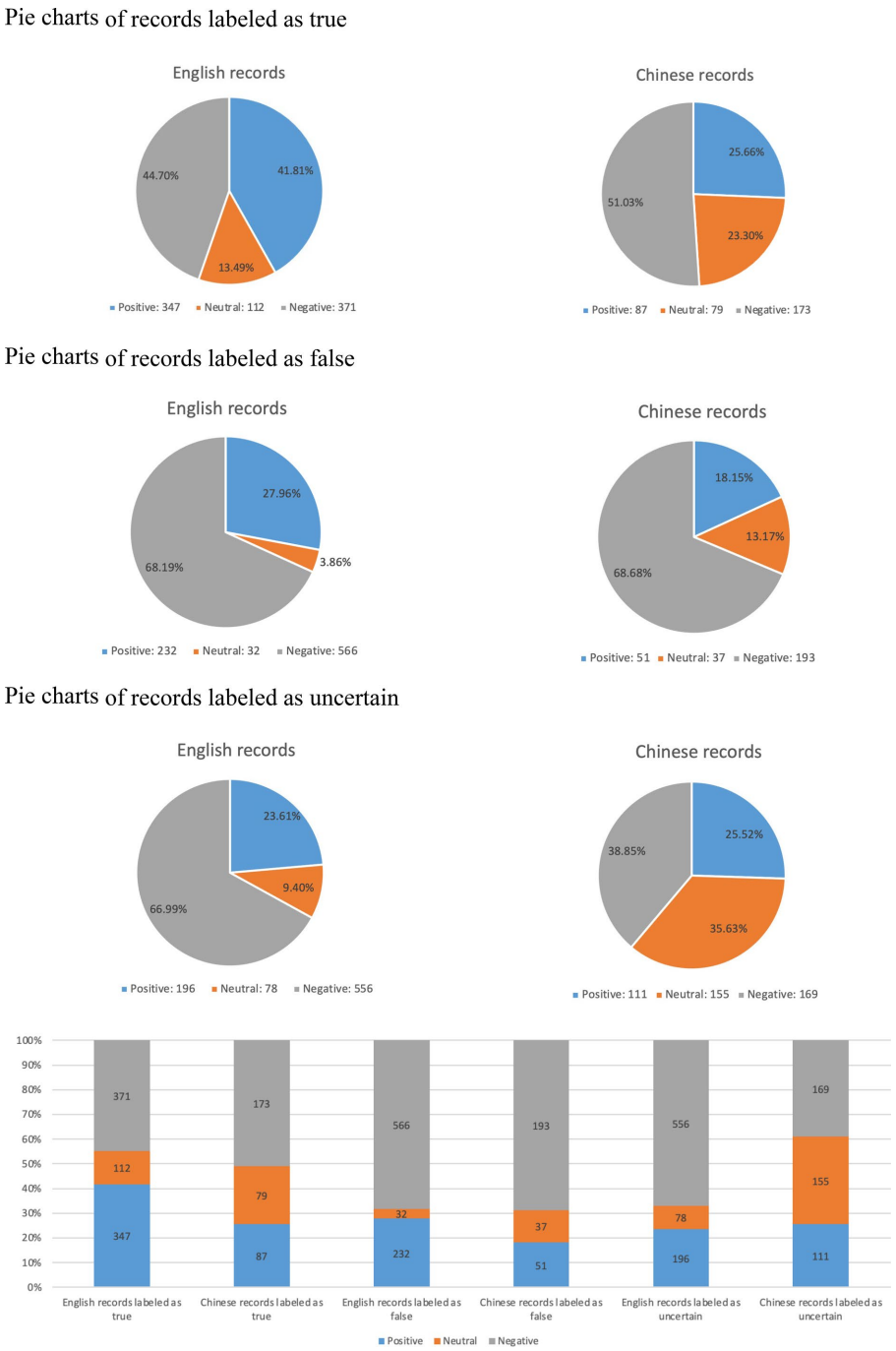

FIGURE 6
Sentiment analysis results for records classified into three groups.

false records consistently manifest the highest proportion of negative sentiment among the three groups in both languages. This observation implies a strong association between misinformation and the generation of negative sentiment among readers. As a result, there is a critical need to actively combat the spread of false records since misleading content not only deceives individuals but also significantly impacts their emotional well-being. Finally, English records in the uncertain group display a nearly identical proportion of negative sentiment, while Chinese records show a decline in negative sentiment. This divergence implies a potential shift toward increased clarity or certainty in the Chinese records classified as uncertain, suggesting that Chinese sources may provide more conclusive or reliable content in this group compared to their English counterparts.

There are several limitations to this study. Firstly, most data collected from the two datasets were obtained from authoritative and representative channels that specifically focus on gathering and presenting valuable information related to popular online topics. However, relying on these sources can introduce biases as the selection of sources and editorial decisions may influence the representation of different perspectives and prioritize certain

viewpoints. Secondly, the English records' labels are determined by invited healthcare workers' judgments using a majority agreement methodology. This approach can lead to variations in labeling due to individual differences in interpretation, knowledge, and biases. The absence of clear guidance or standardized criteria for healthcare workers further contributes to potential inconsistencies in labeling decisions. Thirdly, the retention rate for English data sourced from (20) is low. After manual classification, only 830 records were included in the real group, which is the smallest group out of the three. Ultimately, a total of 2,490 records were retained for equal distribution among each group. Considering the initial count of 6,420 records, the overall retention rate is only 38.78%.

6 Conclusion and future works

This paper presents a comparative analysis of the COVID-19 infodemic in English and Chinese languages, utilizing textual data extracted from social media platforms. Firstly, to ensure a balanced representation and a fair assessment, two infodemic datasets were introduced through the augmentation of previously collected social media textual data with annotations provided by healthcare workers. Secondly, word frequency analysis was conducted, revealing the 35 most frequently occurring infodemic words in both English and Chinese. This comparison offers valuable insights into the prevalent discussions surrounding the COVID-19 infodemic. Thirdly, topic clustering analysis was performed to identify thematic structures present in both languages. This exploration provides a deeper understanding of the primary topics related to the COVID-19 infodemic within each language context. Finally, sentiment analysis was carried out to evaluate the distribution of positive, neutral, and negative sentiments. This investigation helps comprehend the overall emotional tone associated with COVID-19 information shared on social media platforms in the English and Chinese languages.

In the future, we intend to conduct a study considering the contextual factors. The two proposed datasets in this paper solely consist of original posts from social media, excluding reposts and replies. Additionally, certain records were sourced from official handbooks, authoritative webpages, and fact-verification websites, which lack propagation information. Therefore, the first issue is to collect the user social engagements from the social platform based on infodemic content, including the timestamp of who engages in the records dissemination process. The second line of interest is to conduct a comprehensive understanding of how infodemic spreads within the online community by effectively analyzing users' interactions and their engagement records. Finally, an in-depth analysis will be implemented to seek valuable insights into the mechanisms and dynamics of infodemic propagation, aiming to uncover why and how infodemics occur.

Data availability statement

The original datasets can be found: https://www.dropbox.com/scl/fo/1qug1snyu49bsiuj53hty/h?rlkey=kew7715ubl83jhmtvcroxv7uj&dl=0. Further inquiries can be directed to the corresponding author.

Author contributions

JL: Conceptualization, Writing – original draft. DP: Visualization, Writing – review & editing. LS: Writing – review & editing, Methodology. DEB: Supervision, Writing – review & editing. XL: Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1281259/full#supplementary-material

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What did we learn about tocilizumab use against COVID-19? A single-center observational study from an intensive care unit in Serbia

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Background: Selection of effective and safe therapy for management of patients with coronavirus disease is challenging. Tocilizumab (TZB) has emerged as a potential treatment option for COVID-19. Several aspects regarding Tocilizumab treatment remain uncertain, such as the optimal timing for its administration and the safety profile, including the potential risk of infections. The aim of the study is to present the clinical characteristics of patients with COVID-19 following the application of Tocilizumab.

Methods: This is a retrospective analysis of 121 patients with severe forms of COVID-19 previously treated with Tocilizumab was conducted. All patients were admitted to intensive care units (ICUs).

Results: Of 121 patients, the majority were men 72 (59.5%) with a median age at presentation of 65 ± 13 years. Only 9 (7.43%) patients were without comorbidities, while the other 112 (92.55%) had two or more comorbidities. Almost all of the 120 patients (99.2%) needed oxygen therapy, such as nasal cannulas in 110 (90.9%) patients, high flow nasal catheter (HFNC) in 4 (3.3%) patients, and continuous positive airway pressure (CPAP) in 5 (4.1%) patients while 1 patient was intubated at the time of hospital admission. The average time from Tocilizumab application to admission to the ICU was 3 days. During clinical deterioration, almost half 57 (47.1%) of the patients were intubated, and 52 (82.5%) of these intubated patients ($p < 0.001$) had lethal outcomes. The most significant predictors for a lethal outcome according to multivariate analysis were diabetes mellitus ($p < 0.001$) followed by a subsequent elevation in C-reactive protein levels (CRP; $p < 0.002$) and ferritin ($p < 0.013$) after Tocilizumab application. Bloodstream infections were found in 20 (16.5%) patients, most frequently with Gram-negative pathogens like *Acinetobacter* spp. as in 12 (18.6%) patients, *Klebsiella* spp. in 6 (8%) patients, and *Pseudomonas* spp. in 2 (3.2%) patients. Urine culture isolates were found in 9 (7.43%) patients, with *Candida* spp. being most frequently isolated in 7 (5.8%) patients, followed by *Klebsiella* spp. and *Pseudomonas* spp. in 1 patient each (0.8%). Significantly lower survival was seen in patients with proven infection.

Conclusion: The benefit of tocilizumab was not found in our study. The high mortality rate among intubated patients after Tocilizumab use suggests appropriate patient selection and monitoring and emphasizes the risk of superinfections.

Diabetes mellitus, increased levels of CRP, and ferritin were identified as the most significant predictors of poor outcomes in contrast to increased levels of IL-6.

KEYWORDS

COVID-19, tocilizumab, superinfections, outcome, complications

Introduction

For more than 3 years, the whole world struggled with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the end of May 2023, at the pandemic's end, several questions were still without answers, and one of the most important was the selection of an effective and safe treatment for patients with COVID-19 (1). Approximately 15% of COVID-19 patients develop severe disease, while around 5% progress to a critical condition (2). In critically ill COVID-19 patients, cardiovascular collapse, followed by multiorgan dysfunction and shock, could be found as causes of death. Severe forms of SARS-CoV-2 infection are characterized by excessive production of pro-inflammatory cytokines, leading to a phenomenon known as a "cytokine storm" (3). There is a significant increase in the level of cytokines such as interleukin-6 (IL-6), interleukin-2 (IL-2), ferritin, fibrinogen, and lymphocytes. Tocilizumab (TZB) represents a recombinant humanized monoclonal IL-6 receptor antibody of the IgG1 subtype (4). One of the advantages of tocilizumab is its prolonged half-life and irreversible binding to IL-6 receptors, including both the soluble and the membrane-bound forms (5). Likewise, the beneficial role of TZB has been shown in some inflammatory diseases such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman disease, Crohn's disease, and cytokine release syndrome (CRS) induced by chimeric antigen T-cell (CAR-T) immunotherapy (6). Serbian national protocol is supported by the Ministry of Health and contains 13 revisions, including the use of TZB in the therapy of COVID-19 patients with moderate disease and a gradual escalation in their requirement for oxygen support, including the need for mechanical ventilation (7). The use of TZB in critically ill COVID-19 patients is still controversial because of the reported proof that TZB reduced the risk of mechanical ventilation, although it does not have a substantial impact on mortality rate (8, 9). The aim of this study is to present the clinical characteristics of patients with COVID-19 following the application of Tocilizumab.

Materials and methods

This is an observational retrospective study of 7,949 consecutive patients older than 18 years, treated in intensive care units (ICU; total six, with capacity of 120 beds) in the largest Covid hospital in Europe, Batajnica, Belgrade, from 4 December 2020 to 1 June 2021. Among 7,949 patients, 121 (1.52%) were treated with TZB and, because of clinical deterioration, transferred to ICU. All included patients received TZB previously in second-level hospitals or temporary Covid hospitals.

The inclusion criteria for TZB administration in prior hospitals are unknown.

The criteria for admission to the intensive care unit (ICU) included severe respiratory failure necessitating invasive or non-invasive mechanical ventilation (MV) followed by a deterioration in respiratory function, radiological progression, and positive reverse transcriptase-polymerase chain reaction (RT-PCR) results from nasopharyngeal swabs for SARS-CoV-2. Data regarding the patient's medical history, vital signs, oxygen saturation, blood chemistry parameters, microbiological analyses, radiological findings (including chest X-ray and computed tomography), treatment regimen, and outcome were recorded for each individual. A CT score, or Computed Tomography score, is a numerical assessment used in medical imaging to quantify and describe findings in CT scans, helping the assessment of the severity or extent of abnormalities in the scanned area. Blood chemistry variables were initially recorded upon presentation then maximum values achieved during hospitalization, as well as variables at discharge from the hospital or time to death. Non-invasive ventilation included continuous positive airway pressure (CPAP), full face masks, and Helmet. Patients who were on high-flow oxygen therapy with a flow rate of 70 L/min receiving a 100% fraction of inspired oxygen (FiO_2) and who had a partial pressure of oxygen (PO2) below 8 kPa and oxygen saturation below 90%, which is considered as severe respiratory insufficiency, were also transferred to the intensive care unit (ICU).

The treatment of all patients was conducted in accordance with a national protocol for severe forms of COVID-19 disease, including corticosteroid therapy (methylprednisolone up to 2–3 mg per kg), followed by low medium heparin weight (LMHW), gastro-protective, antibiotic, or antifungal therapy based on microbiological or laboratory findings.

Statistical analysis

The normal distribution of continuous variables was tested using the Kolmogorov–Smirnov test, and variables are presented as mean ± SD or median (interquartile range) as appropriate. Differences in continuous variables between the group of survivors and non-survivors were assessed by Student's *t* test for normal distributed variables or Mann–Whitney U test for non-normal distributed variables. Categorical variables are presented as counts and percentages and the Chi-square or Fisher's exact tests were used to analyze differences between analyzed groups. Univariate Cox proportional-hazards regression analyses were used to identify predictors for in-hospital mortality. Variables that show a significant predictive value with a *p*-value of less than 0.1 were included in a multivariate Cox model using a forward stepwise (likelihood ratio) method of entry. Kaplan–Meier survival curves were used to illustrate differences in survival between groups. Statistical significance was assessed by the Log-rank test.

TABLE 1 Patients' characteristics.

	Total $N = 121$	Survival $N = 58$	Non survival $N = 63$	p
Men n (%)	72 (59.5%)	38 (65.5%)	34 (54.0%)	0.196
Age ± SD	65 ± 13.5 (min–max 30–94)	61 ± 13.1 (min–max 30–94)	70 ± 12.5 (min–max 34–90)	<0.001
Age categories				
<69 years	73 (60.3)	42 (72.4%)	31 (49.2%)	0.003
Between 70–79 years	28 (23.1)	13 (22.4%)	15 (23.8%)	
>80 years	20 (16.5)	3 (5.2%)	17 (27.0%)	
Arterial hypertension, n (%)	70 (57.9%)	27 (46.6%)	43 (68.3%)	0.016
Diabetes mellitus, n (%)	32 (26.4%)	8 (13.8%)	24 (38.1%)	0.002
Hematological malignancies, n (%)	4 (3.3%)	0 (0%)	4 (6.3%)	0.12
HRI, n (%)	8 (6.6%)	2 (3.4%)	6 (9.5%)	0.276
COPD, n (%)	15 (12.4%)	7 (12.1%)	8 (12.7%)	0.916
Hypothyreosis, n (%)	5 (4.1%)	2 (3.4%)	3 (4.8%)	0.717
Previous thrombosis, n (%)	8 (6.6%)	3 (5.7%)	5 (7.9%)	0.72

HRI, chronic renal insufficiency; COPD, chronic obstructive pulmonary disease.

Statistical analyses were performed using the statistical package for social sciences, version 28 (SPSS, Chicago, Ill). Statistical significance was defined as $p < 0.05$.

Results

Out of a total of 7,949 hospitalized patients from December 4, 2020, to June 1, 2021, a cohort of 121 patients was included in the analysis. The median duration from the administration of tocilizumab to admission to the intensive care unit (ICU) was 3 days (IQR 2–4). Additionally, the median duration from the onset of symptoms to ICU admission was 5 days (IQR 3–5.5). The collected data were divided into two groups based on whether patients were survivors or non-survivors. Patient characteristics are shown in Table 1. The majority of patients, 72 patients (59.5%), were men. The mean age at presentation was 65 ± 13 years, with 73 (60.3%) aged fewer than 70 years, 28 (23.1%) aged between 70 and 79 years, and 20 (16.5%) aged older than 80 years. In addition, 9 patients (7.43%) presented without comorbidities, 18 (14.87%) patients had one comorbidity, and 94 (77.68%) had two or more comorbidities. Among the primary non-malignant comorbidities, the most commonly observed conditions were arterial hypertension, present in 70 (57.9%) patients, followed by diabetes mellitus in 32 patients (26.4%) and chronic obstructive pulmonary disease (COPD) in 15 patients (12.4%). Hematological malignancies were most common among malignant diseases (in 4 (3.3%) patients). Most of the patients in our study exhibited typical clinical symptoms, including loss of smell (116, 95.9%) and loss of taste (115, 95%) along with elevated body temperature. Clinical and laboratory findings at the time of hospital admission are presented in Table 2. Antivirals (Favipiravir) were applied in 10 (8.3%) patients markedly in those with a later lethal outcome ($p < 0.012$). The requirement for oxygen therapy was determined based on the oxygen saturation level measured using pulse oximetry. Almost all the patients 120 (99.2%) needed oxygen therapy. At the time of hospital admission, oxygen was delivered using nasal cannulas in 110 (90.9%) patients, high flow nasal catheter (HFNC) in 4 (3.3%) patients, and continuous positive airway pressure (CPAP) in 5 (4.1%) patients, while 1 patient was intubated. The average CT severity score was 14 ± 5.9. All patients received the best basic and supportive care and anti-COVID treatment in accordance with the national protocol, including antibiotics, antimycotics, anticoagulation, and corticosteroid therapy. The average stay in ICU was 6 days, while significant time spent on MV was seen in non-survivors ($p < 0.001$). During clinical deterioration, almost half of the patients were intubated 57 (47.1%), namely those who died later 52 (82.5%; $p < 0.001$). Overall, in cured patients, during time of deterioration, nasal cannulas, HFNC, and CPAP were most applied ($p < 0.001$). Among intubated patients, 52 (82.5%) had lethal outcomes, and only 5 (8.6%) survived. The following potential laboratory prognostic parameters were evaluated: white blood cells (WBC), C-reactive protein (CRP), IL-6, ferritin, and lactate dehydrogenase (LDH.). Regarding the analysis of chest X-ray after TZB administration, in the majority of patients 85 (70.4%)radiographic progression was noticed, improvement was achieved in 19 (15.7%), and chest X-rays without changes were noticed in 17 (13.9%). The most significant predictor for lethal outcome was age ($p < 0.001$, HR 1.045, CI 0.95% 1.022–1.069). Survival according to the age category is shown in Figure 1. Other significant parameters for survival were comorbidities like arterial hypertension ($p < 0.005$, HR 2.162, CI 0.95% 1.261–3.704) and diabetes mellitus ($p < 0.001$, HR 2.46, CI 0.95 1.466–4.083). Among laboratory parameters, CRP after TZB application ($p < 0.002$, HR 1.008, CI 0.95% 1.003–1.013) and ferritin level after TZB application ($p < 0.001$, HR 1.001, CI 0.95% 1.000–1.002) were the most significant (Table 3). Multivariable regression analysis confirmed diabetes mellitus ($p < 0.001$, HR 7.096, CI 0.95% 3.098–16.253) as the strongest predictor for lethal outcome followed by CRP ($p < 0.022$, HR 1.009, CI 0, 95% 1.001–1.016) and ferritin level ($p < 0.013$, HR 1.001, CI 0.95% 1.000–1.002; Table 4). Kaplan–Meier curve number 2 showed influence of diabetes mellitus on survival. Blood stream infections were found in 20 (16.5%). Gram negative pathogens were dominant, *Acinetobacter* spp. in 12 (18.6%), *Klebsiella* spp. in 6 (8%),

TABLE 2 Laboratory and clinical findings at the time of hospital admission.

	Total *N* = 121	Survival *N* = 58	Non survival *N* = 63	*p*
CRP (mg/L) median (IQR)	75.2 (82.03)	71.3 (75.8)	85.8 (91.9)	0.427
WBC (G/L)	8.4 ± 6.64	7.8 ± 6.15	9.1 ± 7.21	0.412
IL-6 (pg/ml)	82.0 (123.15)	82.0 (103.73)	81.45 (131.18)	0.869
Ferritin (ng/ml)	983.5 (1224.0)	1335.8 (1456.1)	767.3 (1104.15)	0.364
LDH (U/l)	447.5 (422.0)	447.5 (369.5)	447.0 (501.75)	0.71
Favipiravir, *n* (%)	10 (8.3%)	1 (1.7%)	9 (14.3%)	0.012
Oxygenotherapy *n* (%)				
Nasal cannulas	110 (90.9%)	55 (94.8%)	55 (87.3%)	0.199
HFNC	4 (3.3%)	0 (0%)	4 (6.3%)	
CPAP	5 (4.1%)	2 (3.4%)	3 (4.8%)	
MV	1 (0.8%)	0 (0.0%)	1 (1.6%)	
Ambiental air	1 (0.8%)	1 (1.7%)	0 (0%)	
Oxygenotherapy at worsening, *n* (%)				
Oxygen mask	21 (17.4%)	20 (34.5%)	1 (1.6%)	<0.001
HFNC	26 (21.5%)	21 (36.2%)	5 (7.9%)	
CPAP	13 (10.7%)	8 (13.8%)	5 (7.9%)	
MV	57 (47.1%)	5 (8.6%)	52 (82.5%)	
Ambiental air	4 (3.3%)	4 (6.9%)	0 (0%)	
Time from symptoms beginning to prior hospital admission (IQR)	5 (4)	5.5 (3)	5 (5)	0.137
Time from hospital admission to TZB application (IQR)	3 (3)	4 (2)	3 (2)	0.472
Days spent in ICU	6 (5)	8 (8)	6 (6)	0.086
Days spent on MV	1 (5)	0 (0)	3 (5)	<0.001
CT severity score	14 ± 5.9	16 (10)	13 (13)	0.855

CRP, C-reactive protein; WBC, White blood cells; IL-6, interleukin-6; LDH, lactate dehydrogenase; HFNC, high flow nasal cannulas; CPAP, continuous positive airway pressure; MV, mechanical ventilation; TZB, tocilizumab; ICU, intensive care unit; MV, mechanical ventilation, CT, computed tomography.

and *Pseudomonas* spp. in 2(3.2%). Urine culture isolates were found in 9 (7.43) patients, among them *Candida* spp. was most frequently seen in 7 patients, while *Klebsiella* spp. and *Pseudomonas* spp. were seen in 1 patient each. Positive urine culture analyses were significantly found among non-survivors ($p = 0.03$). Significantly lower survival according to positive blood and urine cultures isolates were shown on Kaplan–Meier curves 3 and 4.

Discussion

This single-center study included 121 patients with COVID-19 who were admitted to the intensive care units (ICU). The study examined the various clinical, laboratory, and microbiological parameters of these patients.

Beneficial use of TZB has been described in many studies and even through prospective open multicenter studies on patients with severe disease (10).

More than half of our patients were male. This finding is consistent with the results of certain meta-analyses that suggest a higher risk of severe COVID-19 among male patients (11). The increased risk for disease severity was higher in older age groups; however, there is no definitive age cut-off point identified. Additionally, older age has been associated with an elevated fatality rate in COVID-19 cases (12). In our study group among the oldest patients (those older than 80 years), a lethal outcome was noticed in 85%. Our data are similar to those reported by the Center for Disease Control and Prevention (CDC), where death occurred in 80%, with the highest percentage being among those older than 85 years (13).

For the follow-up of patients with hyperinflammatory syndrome, it is recommended to monitor CRP (C-reactive protein), ferritin, D-dimer, and LDH (lactate dehydrogenase) in addition to clinical symptoms and radiological findings (14). Multivariate analysis in our study has shown that increased levels of CRP and ferritin after tocilizumab applications in our patients should be considered significant predictors for poor outcomes.

Elevated levels of inflammatory markers such as D-dimer and ferritin, as well as proinflammatory cytokines like IL-6, have been linked to severe COVID-19 disease. Blocking the inflammatory pathways has been hypothesized as a potential strategy to prevent disease progression in these cases (15). Regarding the biomarkers suitable for monitoring tocilizumab (TZB) therapy, the cut-off value

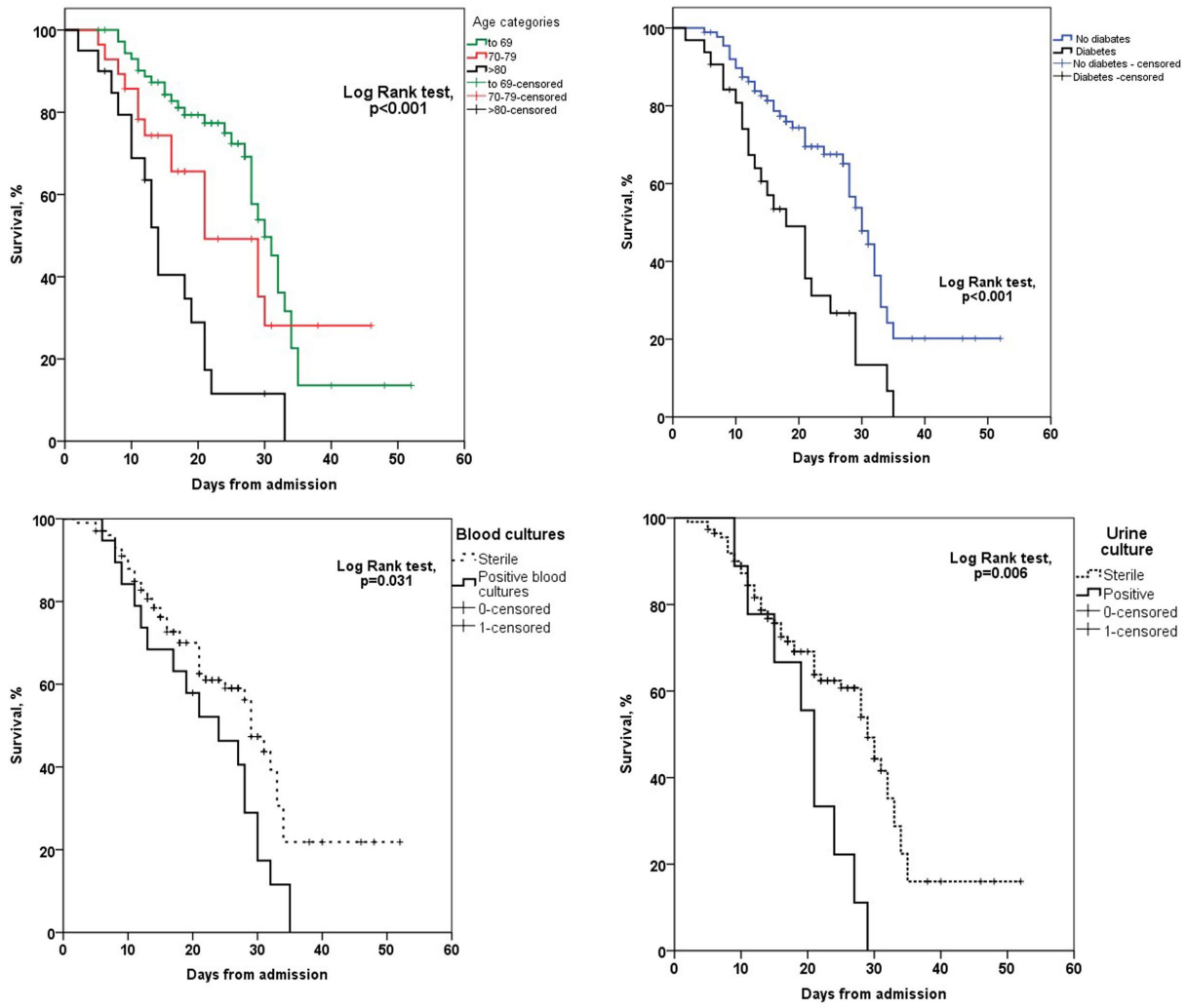

FIGURE 1
Kaplan–Meier curves survival analysis according to the age category, diabetes status, urine and blood culture.

TABLE 3 Univariate regressive model for lethal outcome predictors.

	B	P	HR	CI 0.95%
Age	0.044	<0.001	1.045	1.022–1.069
Arterial hypertension	0.771	0.005	2.162	1.261–3.704
Diabetes mellitus	0.895	0.001	2.460	1.466–4.083
CT severity score	0.049	0.557	1.050	0.893–1.235
WBC (G/L) at ICU admission	0.001	0.385	1.001	0.999–1.003
CRP (mg/L) at ICU admission	0.003	0.111	1.003	0.999–1.008
IL-6 (pg/ml) at ICU admission	0.001	0.385	1.001	0.999–1.003
Ferritin (ng/ml) at ICU admission	−0.001	0.298	0.999	0.998–1.000
LDH (U/L) at ICU admission	0.001	0.502	1.001	0.999–1.002
WBC (G/L) discharge/death	−0.016	0.600	0.984	0.928–1.044
CRP (mg/L) discharge/death	0.008	0.002	1.008	1.003–1.013
IL-6 (pg/ml) discharge/death	0.001	0.354	1.001	0.999–1.001
Ferritin (ng/ml) discharge/death	0.001	0.001	1.001	1.000–1.002
LDH (U/L) discharge/death	0.001	0.273	1.001	0.999–1.001

CT, computed tomography; ICU; intensive care unit; CRP, C-reactive protein; WBC, White blood cells; IL-6, interleukin-6; LDH, lactate dehydrogenase.

TABLE 4 Multivariate analysis for lethal outcome predictors.

	B	P	HR	CI 0.95%
Age	-	0.066	-	-
Arterial hypertension	-	0.101	-	-
Diabetes mellitus	1.960	<0.001	7.096	3.098–16.253
CRP (mg/L)	0.009	0.022	1.009	1.001–1.016
Ferritin (ng/ml)	0.001	0.013	1.001	1.000–1.002

CRP, C-reactive protein.

for C-reactive protein (CRP) effectiveness differs. Lower CRP and IL-6 values than expected were observed in the studied cohort, likely attributed to the influence of TZB. For instance, in the RECOVERY study, the inclusion criteria required a CRP level greater than 75 mg/L (16), while in the TOCIBRAS and BAC-Bay studies, a CRP level greater than 50 mg/L was used (17, 18). It was shown if CRP was >35 mg/L, TZB reduces mortality up to 35%, while TZB effectiveness in CRP < 35 mg/L was still unknown (19). Regarding CRP findings in our patient group, the significant difference in CRP values after TZB noticed between survivors and non-survivors suggested that increased CRP levels in non-survivors could be due to infections.

We noticed that TZB temporarily increased circulating IL-6 level (because competitive binding with IL-6) receptors, and for this reason, the IL-6 concentration was only recommended at treatment beginning but was not suitable for treatment monitoring (10). Our findings indicated a significant difference in IL-6 levels after tocilizumab (TZB) administration between survivors and non-survivors. This observation may suggest the long half-life of TZB following its application could potentially be attributed to the presence of concomitant superinfection. A recent study reported that critically ill COVID-19 patients exhibited imbalanced iron levels. Hyperferritinemia was also observed in our study and connected with serious lung damage, which increased the susceptibility of COVID-19 patients to superinfections. Due to the lower blood pH and increased levels of pCO2 in COVID-19, ferritin becomes unstable and has a tendency to release iron. This released iron can be readily taken up by various pathogens, potentially leading to infection. Iron deficiency 2 months after COVID-19 disease predisposes recovered patients to high risk of fungal disease (20). Regarding our results ferritin level after TZB administration among non-survivors was significantly higher and indicated that superinfections could be an important risk factor for lethal outcomes. In multivariate analysis, ferritin level was found to be an important predictor of lethal outcome.

Numerous studies have tried to show an adequate time for TZB effectiveness. In the REMAP-CAP study, TZB was effective within 2 days of referral to ICU (8). Similar results were shared by StopCovid investigators, suggesting that patients who received TZB within 2 days of admission to the ICU had a reduced risk of death compared to patients who did not receive TZB. In contrast to our study where all patients (100%) received corticosteroid treatment, a significantly lower percentage of patients (18.5%) were treated with concomitant corticosteroids and Tocilizumab (TZB) in some previous reports (21). In the CHIC study, TZB was administered after initial treatment with corticosteroids but did not show a better response (22). Recovery study demonstrated improved survival outcomes in patients treated with TZB (31 vs. 33% $p = 0.0028$) reduced the need for invasive mechanical ventilation and increased the likelihood of hospital discharge within 28 days (16). Steroids, like dexamethasone and methylprednisolone, have been widely employed to resolve hyperinflammation and inflammatory lung damage in COVID-19 patients. Following the publication of the RECOVERY trial, dexamethasone was approved by the World Health Organization (WHO) as an immunomodulatory drug for use in COVID-19 patients requiring oxygen. The benefit of dexamethasone was particularly notable in patients who required mechanical ventilation. Since the onset of the pandemic, glucocorticoids have been recommended for critically ill COVID-19 patients (23). Methylprednisolone therapy was associated with decreased rate of progression to mechanical ventilation and an increased likelihood of successful extubation in patients requiring mechanical ventilation (24). In our study cohort methylprednisolone was usually used in doses of 2–3 mg/kg and, in severe forms of COVID-19, 5–7 mg/kg.

Results from most successful studies showed that concomitant use of TZB and corticosteroids was more effective than TZB monotherapy (25). The results of our study demonstrated a high mortality rate (82.5%) among critically ill patients with COVID-19 who required mechanical ventilation. These findings correspond with previously published papers that have also reported high mortality rates in this patient population (26–28).

All of our patients required respiratory support at the time of ICU admission. Previously published papers showed that after TZB administration, invasive MV was applied in 29%, CPAP in 42%, and HFNC in 29%; our study results showed MV being applied in 57 (47.1%), CPAP in 13 (10.7%), and HFNC in 26 (21.5%) (8). A large percentage of intubated patients in our study could be explained with severe forms of COVID-19 at hospital admission and rapid clinical deterioration. The average time for worsening after TZB administration was 3 days. Apart from invasive mechanical ventilation upon deterioration, the duration of symptoms prior to hospitalization is an independent predictor of mortality in these patients. Published data from the early stages of the pandemic have indicated death rates ranging up to 62% in patients admitted to the intensive care unit (ICU), while in mechanically ventilated patients, the death rate reached up to 97% (29). The mortality rate among intubated patients with COVID-19 is higher when compared to patients with other viral pneumonia who also require mechanical ventilation (67 vs. 22%) (27, 28). Published results were still controversial; there are concerns ranging from how mechanical ventilation should be avoided in COVID-19 to those regarding the beneficial role of early intubation in COVID-19 patients (30, 31). Our results showed that only 3 days were spent on MV for non-survivals, suggesting critical forms of disease or an inappropriate patient selection for TZB applications. This question could be without answer. According to our results, among survivors, only 5(8.6%) patients were successfully extubated. Some authors showed that the higher mortality rate in critically ill COVID-19 patients is due to older age, the impact of comorbidities, higher D-dimer values, higher CRP, use of invasive mechanical ventilation, vasopressors, and renal replacement therapy. Our results concluded that the presence of comorbidities such as arterial hypertension and diabetes mellitus were as significantly associated with unfavorable outcomes, which was not in consent with findings of some authors (32). The study period coincided with the dominance of the Delta variant of the SARS-CoV-2 virus, and the majority of our

patients were infected by this variant. The Delta variant exhibited higher contagiousness with a mortality rate 133% higher than the original strain, while the hospitalization risk rose by 108%, and the probability of ICU admission increased by 235% (33). The comparative analysis of radiological changes between the survivors and non-survivors after TZB administration showed progression of dominantly interstitial lesions in 85 (70.4%) patients without significant difference between survivors and non survivors (75.9 vs. 65.1%). Our results are consistent with previously published data when it comes to non-survivors, but they are not consistent regarding survivors where TZB administration was found to be beneficial (34).

Comorbidities have been consistently linked to severe illness and mortality in patients with SARS-CoV-2 infection. In some previous reported papers, more than two underlying conditions were found as predictors for disease severity as was also shown in our paper (35). In accordance with these data, among the patients included in our study, 94 (77.7%) patients had two or more preexisting comorbidities, which are recognized as potential risk factors for disease severity and lethal outcomes. Survival analysis demonstrated the prognostic significance of arterial hypertension and diabetes mellitus when compared to other clinical and therapeutic variables as predictors for survival. Moreover, the multivariate analysis indicated that diabetes mellitus emerged as the most significant risk factor for lethal outcomes.

In addition to the effect on survival, after TZB use, some authors have noticed large number of superinfections, like pneumonia and bloodstream infections in 39% patients (36). Superinfections in COVID-19 patients requiring transfer to the ICU are recognized as an important and challenging complications. There is a lack of information about superinfections in COVID-19 patients because most of these patients were treated with broad-spectrum antibiotics and antimycotics. Indeed, the use of drug targeting therapy like antagonists of IL-1 and IL-6 receptors has been associated with an increased risk of superinfection in patients with COVID-19 (37). There are recommendations to avoid TZB in patients with immunosuppression, alanine aminotransferase levels greater than five times the upper normal limit, in patients with high risk for gastrointestinal perforation, in serious bacterial or fungal infections, in patients with an absolute neutrophil count <500 cells/μl, platelet count <50.000 cells/μl, or known hypersensitivity (38). In countries highly burdened by tuberculosis, screening for latent tuberculosis is mandatory before TZB use, much like how prophylactic treatment with ivermectin for strongyloidiasis in endemic areas (39). However, current guidelines were not focused on identification of patients with risk of fungal or bacterial infections after tocilizumab administration such as those with preexisting lung diseases. In some cases, post–treatment monitoring of patients and early detection for bacterial and fungal infection is needed (40). Increased infection risk may be compounded with concomitant use of glucocorticoids with TZB (41). Bacterial infections and superinfections after TZB use were seen in various studies. According to Menzella et al., patients who were treated with TZB had a nearly two times higher susceptibility to developing secondary bacterial infections or superinfections compared to the non-treated group (42). The most superinfections found were ventilator-associated pneumonia caused by *Staphylococcus aureus* in about 50% of cases. In the literature, there have been reports of candidemia and invasive pulmonary aspergillosis occurring in patients who were treated with TZB (43, 44). In our study cohort, bacteriemia was found in 20 (16.53%) patients, with *Acinetobacter* spp. being most frequently found, as was described in some previous papers. It is known that prolonged stays in the intensive care unit (ICU) for COVID-19 patients and the use of immunomodulatory therapies, including TZB, can potentially elevate the risk of superinfections caused by multidrug-resistant *Acinetobacter* spp., which presents one of the most dangerous threats to life (45). Bacteriemia after TZB administration in our study was a significant cause of death in comparison with patients with sterile blood cultures ($p = 0.031$) (36). In our study group, urosepsis was found to be a significant predictor for lethal outcome, in 9 (7.4%) patients, with *Candida* spp. being most frequently isolated ($p = 0.003$). The survival rate according to bacteriemia and urosepsis was significantly lower. We assume that number of isolates from blood, central venous catheters, or urine cultures should be greater because, at time of admission to ICU, our patients were treated with broad-spectrum antibiotics, namely cephalosporins of the second or third generation, fluorochinolones, and carbapemens (46). Blocking the IL-6 pathway is crucial for immune system function and may contribute to infections and superinfections due to immune system suppression. IL-6 plays role as differentiation factor for B cells to synthesize immunoglobulins. IL-6 plays a vital role in antibody synthesis, and drugs like TZB may impact immune defense against COVID-19 by affecting IL-6-mediated antibody production (47). Contrary to some reports, certain authors have observed that the administration of TZB in COVID-19 patients did not result in a decreased antibody response to SARS-CoV-2 (47, 48).

Tocilizumab's place in the treatment of COVID-19 is not clearly defined. There are many controversial dilemmas about TZB use in COVID-19, like TZB monotherapy versus combinations with corticosteroids, the timing of TZB administration, patient selection, as well as a cost–benefit analysis of TZB therapy (49).

Likewise, the results of several studies failed to prove the benefits of TZB because inclusion criteria were based on a lower degree of respiratory insufficiency with oxygen support up to 10 liters or high flow nasal cannula with small number of intubated patients (9).

Our study has few limitations. First of all, data of concomitant corticosteroids use and the inclusion criteria for TZB applications in prior hospitals were unknown. Our study group lacked a control group for comparison, precluding patients with the same condition who did not receive TZB. Thoracic computed tomography was done at the time of admission but not during treatment for the majority of our patients.

Conclusion

In our study, despite the current guidelines recommending the use of Tocilizumab in patients with severe forms of COVID-19, we did not find any evidence of its beneficial effects. The high mortality rate among intubated patients after Tocilizumab use suggests appropriate patient selection and monitoring. Clinicians should keep in mind the risk of superinfections after Tocilizumab administration. The concomitant use of corticosteroids and structural lung damage seen in COVID-19 pneumonia may potentially increase the risk of infection. Diabetes mellitus as well as increased levels of CRP and ferritin were found to be the strongest predictors for a poor outcome, and this was not the case for increased levels of IL-6 as was mentioned before. Authors of this manuscript strongly believe that Tocilizumab

effectiveness varies between different waves of SARS-CoV 2. Indeed, randomized controlled trials will be necessary for further investigations into the effectiveness of Tocilizumab in COVID-19 patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Clinical Center of Serbia. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the majority of patients were in a critical clinical condition, on mechanical ventilation, hence unable to provide written consent. Additionally, the study was observational, and the principle of patient anonymity was observed.

Author contributions

VB and TA-V contributed to conception and design of the study. AR organized the database. VB performed the statistical analysis. TA-V wrote the first draft of the manuscript. DM wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Patient safety discourse in a pandemic: a Twitter hashtag analysis study on #PatientSafety

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Background: The digitalization of medicine is becoming a transformative force in modern healthcare systems. This study aims to investigate discussions regarding patient safety, as well as summarize perceived approaches to mitigating risks of adverse events expressed through the #PatientSafety Twitter hashtag during the COVID-19 pandemic.

Methods: This research is grounded in the analysis of data extracted from Twitter under the hashtag #PatientSafety between December 1, 2019 and February 1, 2023. Symplur Signals, which represents a tool offering a method to monitor tweets containing hashtags registered with the Symplur Healthcare Hashtag Project, was used for analyzing the tweets shared in the study period. For text analytics of the relevant data, we further used the word cloud generator MonkeyLearn, and VOSviewer.

Results: The analysis encompasses 358'809 tweets that were shared by 90'079 Twitter users, generating a total of 1'183'384'757 impressions. Physicians contributed to 18.65% of all tweets, followed by other healthcare professionals (14.31%), and health-focused individuals (10.91%). Geographically, more than a third of tweets (60.90%) were published in the United States. Canada and India followed in second and third positions, respectively. Blocks of trending terms of greater interest to the global Twitter community within the hashtag #PatientSafety were determined to be: "Patient," "Practical doctors," and "Health Care Safety Management." The findings demonstrate the engagement of the Twitter community with COVID-19 and problems related to the training, experience of doctors and patients during a pandemic, communication, the vaccine safety and effectiveness, and potential use of off-label drugs. Noteworthy, in the field of pharmacovigilance, Twitter has the possibility of identifying adverse reactions associated with the use of drugs, including vaccines. The issue of medical errors has been also discussed by Twitter users using the hashtag #PatientSafety.

Conclusion: It is clear that various stakeholders, including students, medical practitioners, health organizations, pharmaceutical companies, and regulatory bodies, leverage Twitter to rapidly exchange medical information, data on the disease symptoms, and the drug effects. Consequently, there is a need to further integrate Twitter-derived data into the operational routines of healthcare organizations.

KEYWORDS

patient safety, Twitter, hashtag, COVID-19, adverse events, pharmacovigilance, vaccine, healthcare

1. Introduction

The World Health Organization (WHO) identifies patient safety as one of the top concerns for global health. Currently WHO estimates that annually, sub-standard health care practices result in the deaths of 2.6 million people worldwide, disproportionally more in low- and middle-income countries. Globally, 4 out of 10 patients in primary and outpatient care experience adverse events, of which alarming 80% are preventable. The objective of patient safety, therefore is the mitigation of harm to patients during healthcare provision (1).

Unsafe medical practices encompass a range of issues, from errors in the prescription of medicines (e.g., in relation to dosing, timing of application, or drug interactions), with particular relevance to older adults, to nosocomial infections and non-compliance with safety rules during surgical procedures, injections, and blood transfusions. Furthermore, issues such as diagnostical errors, the use of radiation techniques, sepsis, and venous thromboembolism also contribute to the problem. These insights have been supported by multiple studies (2–9).

Extant literature shows that majority of adverse events associated with the provision of medical care are reported within the inpatient settings. More than half of these events in the hospital happen in the operating room and a third in the patient wards. Outside the hospital, general practitioners offices and patient's homes are the most commonly implicated places of patient harm (10, 11).

Today, the digitalization of healthcare has great potential to improve the quality of medical care, taking patient safety into account. The professional utilization of social networks, including the healthcare field, is an area of constant growth. Twitter has emerged as instrumental in global public sphere research, as it allows rapid dissemination of information across borders and languages. Internet discussions tagged with hashtags, and the social groups engaged in these conversations, are shaping an interdisciplinary field that intertwines public opinion study, public sphere research, social network analysis, and conference outcomes (12–14). Thus, Twitter can be an additional source of information with relevance for patient safety. In this context, the Digital Health and Patient Safety Platform (DHPSP), an open innovation hub, was developed to facilitate collaborative research and development of innovative digital products and personalized solutions focused on enhancing patient safety and human health, and Twitter communication has been instrumental tool for the development of this platform. Along this line, it has been determined that COVID-19, health care, digital health technology, and scientific communication were the top subjects that caught the attention of the #DHPSP Twitter community (15).

Within another relevant research example, Nakhasi et al. carried out an analysis of tweets related to medical errors. Out of 1.006 tweets analyzed, 839 (83%) reported different error types: procedural (26%), medication (23%), diagnostic (23%), and surgical (14%). The authors highlight the potential of Twitter for patient safety-related analysis (16). Another study by Sharma et al. highlights that patients use Twitter to share personal, often disturbing, healthcare experiences (17).

A study by Chai et al. on the effectiveness of using the medical toxicology tweetchat (#firesidetox) collected growing number of impressions, and tweets led the authors to conclude that the tweet-chat model is feasible and well-received for discussing relevant medical toxicological topics (18).

Twitter scientometric analysis is also increasingly employed to evaluate the research outcomes related to patient safety. The data obtained from this resource is a rich source of information for analysis.

Although the WHO has declared the end of COVID-19 pandemic as a global health emergency, there is a threat of new variants of the virus. Unfortunately, the number of global COVID deaths recorded by WHO has reached 7 million over the 3 years, yet the director-general of the World Health Organization estimates that the true death toll is closer to 20 million (19). One key factor for the high mortality is the lack of initial experience in patient safety in the pandemic context, another - insufficient availability of vaccines. Lack of hospital preparedness and infrastructure (especially in low- and middle-income countries) and vaccine hesitancy have also been important contributors to negative public health outcomes.

The increased number of publications studying various aspects of patient safety, especially in light of COVID-19 pandemic, as well as the significant influence of Twitter on the development of all areas of society, have determined the relevance of studying the problem of patient safety based on the Twitter platform (20).

This study's aim was to discern public discourse on patient safety and summarize perceived approaches to reducing the risks of adverse events using the hashtag #PatientSafety during the COVID-19 pandemic on Twitter.

2. Materials and methods

Tweets containing the hashtag #PatientSafety were analyzed from December 1, 2019, to February 1, 2023. The choice of such an interval is connected to the beginning of the COVID-19 pandemic in China. The study end date is related to a significant decrease in confirmed cases of COVID-19, according to WHO, in January 2023.

One of the features of Twitter is the conciseness of the tweets (messages) transmitted with it and the ability to instantly spread information along the chain. A hashtag is a type of tag marking with a starting sign #, a word or phrase used to identify digital content, such as a blog or post, corresponding to a specific category or subject (21). Users label tweets with hashtags to separate the themes of tweets and use them as means of finding or marking specific posts. The hashtag allows users to form an information wave consisting of messages on a specific topic, potentially forming a trend. The user can join the topic discussion at any stage by creating a response message.

We used the Symplur Signals tool, which allows researchers to track tweets containing hashtags registered in the Symplur Healthcare

Hashtag Project (22). Symplur combines social media analytics and healthcare data to help users understand trending healthcare topics. When using a medical hashtag, this tool allow to generate an array of data regarding co-occurring hashtags, trending terms, the geography of participants, the influence of accounts, the dynamics of tweet activity, the Healthcare Social Graph Score, etc. The empirical basis of the study was an array of data from the social network Twitter on the hashtag #PatientSafety. The Symplur algorithm is used to measure the impact of specific accounts and the importance of the content they share for selected datasets and parameters. All tweets containing the hashtag #PatientSafety have been analyzed using Symplur signals without any restrictions on language, user location, or other parameters.

During the study, the most active stakeholders on Twitter were identified. In addition, the resulting data array was analyzed regarding the geography of the participants.

For text analytics of an array of trending terms obtained using the Symplur Signals tool, at the first stage we used the MonkeyLearn word cloud generator platform (available at https://monkeylearn.com/wordcloud/). Based on the analysis of trending terms, a visualization of significant terms (a word cloud) was built according to the frequency of their use. The color of words in the cloud depends on the frequency of the word in the text. Next, we identified three main directions based on the graphical representation of significant words. For each direction, the most frequently occurring trending terms are highlighted.

To identify the main topics of discussion with relevance to the hashtag #PatientSafety, an additional bibliometric analysis was carried out in the Web of Science database for the period from 2019 to 2023. The search for articles was carried out using the fields "title," "abstract" and "key words." The keywords used were "patient safety" and "Twitter." The number of articles in this collection was 54. The array of data obtained was analyzed using the VOSviewer program version 1.6.18, which is in the public domain.

The Symplur Signals tool also generated a dataset for the hashtag #PatientSafety, containing information about co-occurring hashtags and their frequency. The paper presents the most frequently occurring related hashtags.

The Healthcare Social Graph Score was used as a quantitative assessment of the level of impact of the studied profiles. The value of this algorithm relates to the accurate identification and ranking of genuine influencers in any conversation about healthcare. Previous work by Mobarak et al. demonstrated the importance of this tool (23). It was revealed that the assessment of the social graph of health in scientific journals in the field of surgery positively correlates with their impact factor (the latter being more establish indicator of academic influence). A higher impact factor is associated with presence and activity on social media, particularly Twitter.

By monitoring more than 35,000 healthcare-related issues on Twitter in real-time, the Healthcare Social Graph Score is calculated. For each of the 35,000 topics, a top impact profile list for the previous year is prepared based on the tracking. Utilizing SymplurRank, an impact algorithm, rankings are produced. Symplur measures the caliber of the talks for each topic each week in addition to these rankings. The conversation volume and quality scores are combined to create a weighted estimate for the impact scores. The final step is to normalize each social media profile's 52 weekly rankings and quality scores into a single value, which is then scaled from 0 to 100. The Healthcare Social Graph Score is the name given to this last figure (24).

To identify risks and develop approaches to their minimization, general scientific methods were used, in particular system, content analysis, scientific synthesis, logical generalization, and comparative analysis, among others.

This study does not contain any information about specific Twitter user accounts, and all the data presented is anonymous.

3. Results

The analysis yielded 358′809 tweets, shared by 90′079 Twitter users, amassing a total of 1′183′384′757 impressions (views).

Studies of the composition of stakeholders using the hashtag #PatientSafety unveiled heterogeneous groups, with overlapping activities related to the field of healthcare. Figure 1 showcases the activity associated with the #PatientSafety hashtag use on Twitter by these specific groups.

Symplur categorizes healthcare stakeholder accounts as follows[1]: doctor: those believed to be licensed, MDs, DOs, and PhDs who bill directly for services. Also includes medical residents; HCP: those believed to be other healthcare professionals (i.e., nurses, dietitians, respiratory therapists, nurses, pharmacists, etc.); patient advocate: person who publicly self-identify in their Twitter bio as a patient advocate for a specific disease or condition; caregiver: a professional caregiver or a person who is currently or has been a caregiver of a family member or other closely associated individual; researcher/academic: person who is working in the field of health-related research and/or academia (a PhD who does not treat patients falls in this category); journalist/media: person whose profession is journalism or other news-related media. Doctors who are editors of journals do not get this label; individual other health: person working in the healthcare industry in a nonclinical role; individual non-health: person not known to be directly working in the healthcare industry; org. Provider: inpatient facilities, medical groups, labs, imaging centers, and other outpatient facilities; org. Research/academic: accredited schools of higher learning (i.e., universities, colleges, etc.) and healthcare research institutions/centers; org. Advocacy: an organization focused on a specific set of health issues or medical specialty for the purpose of support, guidance, and education; org. Media: all organizations whose primary purpose is publishing or broadcasting; org. Other healthcare: organizations fulfilling roles within the healthcare industry but not providing direct clinical care; org. Non-health: all organizations not falling into an established category.

The data indicates that doctors (18.65% of all tweets), organizations in healthcare (14.31% of all tweets), and individuals in other health-related fields (10.91% of all tweets) held the top three places of stakeholder ranking.

With WHO declaration of the coronavirus pandemic in March 2020, the life of society has moved to the online space. The tweet-posting activity of leading stakeholders in the selected study area had a pronounced positive trend in March 2020 (Figure 2). The

1 https://help.symplur.com/en/articles/103684-healthcare-stakeholder-segmentation

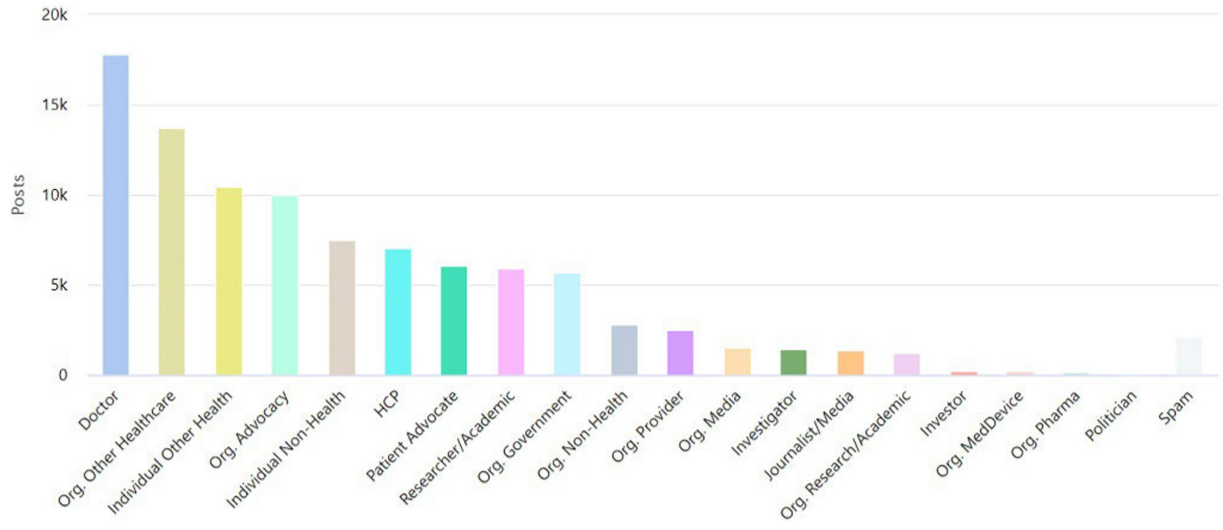

FIGURE 1
The number of tweets related to the hashtag #PatientSafety shared by major health care stakeholders.

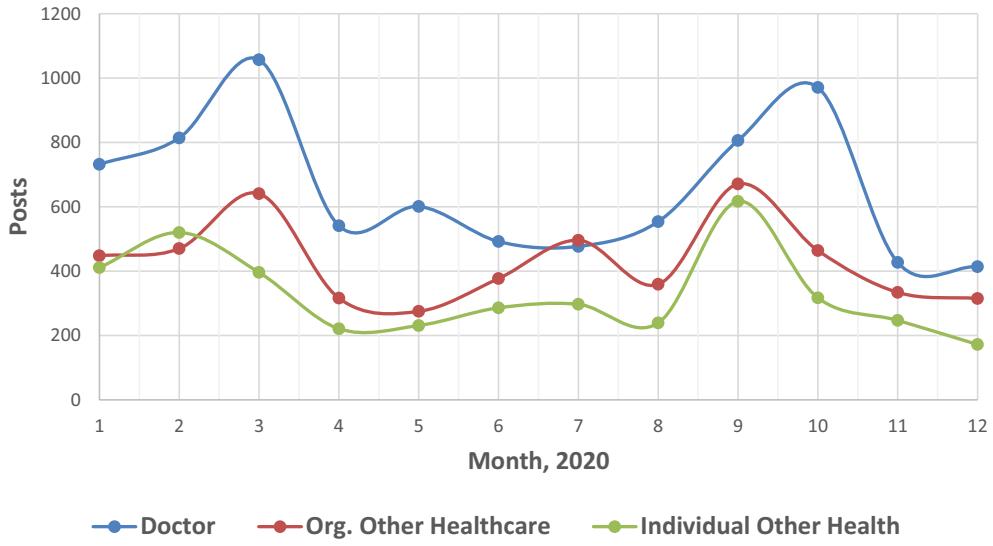

FIGURE 2
Dynamics of publication activity associated with the hashtag #PatientSafety by leading stakeholders on Twitter (2020).

second wave in the fall is associated with Pfizer's discussion of vaccine development.

Geographical analysis of tweets (Table 1), including the hashtag #PatientSafety, revealed that more than a third of tweets (60.90%) were published in the United States. Canada and India followed in the second and third positions, respectively. More than 1% of tweets were posted by each Australia, Saudi Arabia, Switzerland, and Nigeria. In total, more than 100 countries were found to have made at least one tweet post dedicated to patient safety. A map (Figure 3) has been constructed that clearly illustrates that interest in the research subject exists worldwide.

One of the interesting indicators of Twitter is the analysis of co-occurring hashtags with #PatientSafety. Users, in conjunction with the hashtag #PatientSafety, most frequently used the following hashtags: #Healthcare, #COVID19, #patientcare, etc. (Table 2).

In order to identify the most influential accounts posting tweets using #PatientSafety, an analysis was carried out following the SymplurRank algorithm. Among the top influencers, there was an equal proportion of males and females, comprising 32% of each. These accounts included those of healthcare executives, doctors, researchers, nurses, editors, etc. Organizations, institutions, and communities represented the remaining 36 percent of accounts.

The thematic focus of tweets was also studied using the content analysis of trending terms using the MonkeyLearn word cloud generator platform. All terms were excluded from common words that have no value in the framework of this work, as well as words and expressions directly calling the research subject (for example, Patient

Safety). The Figure 4 shows the visualization of significant trending terms (a cloud of words) by the frequency of their use.

Based on the word cloud, we identified three groups that are most widely discussed in the global Twitter community using the hashtag #PatientSafety, with these three groups (blocks) being "Patient," "Practical doctors," and "Health Care Safety Management" (Table 3 presents the three blocks together with the top trending terms that are most frequently mentioned in the #PatientSafety tweets).

Analysis of online communications and public sentiment regarding patient safety could be of benefit for healthcare improvement. Some of the most accessible and current data acquisition sources are social media platforms such as Twitter. Analysis of such data supplements informed decisions and conclusions in medical practice.

However, limitations regarding the generalization of the results of studies of Internet platforms related to user bias should also be noted. The limitations of medical information, which can be found on social networks and other online sources, include, in some cases, insufficient quality and reliability. In addition, medical information may be unreasonable, incomplete, or unverified (25).

An additional bibliometric analysis of the Web of Science database was performed using VOSviewer version 1.6.18 in the area of discussing patient safety on Twitter for the period 2019–2023. The result of the bibliometric analysis in the VOSviewer program is presented in Figure 5. The program identified three clusters similar to the Twitter analysis outcomes, which are indicated in the Figure 5 in green (Patients, ensuring their safety and COVID-19), blue (Doctors, social media opportunities), and red (Health safety management, including pharmacovigilance) colors. Circles conventionally indicate a keyword; the larger the diameter of the circle, the higher the frequency of references to the corresponding concept.

The identified main topics of discussion, according to the analysis of trending terms and bibliometric research in the Web of Science database, are presented below.

TABLE 1 Top 5 countries sharing #PatientSafety tweets.

	Countries	Users	Percentage (%)
1.	United States	25,985	60.90
2.	Canada	6,095	14.28
3.	India	2,543	5.96
4.	Australia	2,164	5.07
5.	Saudi Arabia	497	1.17

4. Discussion

4.1. Patients, ensuring their safety, and COVID-19

Real-time analysis of public attitudes related to patient safety during COVID-19, including vaccine safety and effectiveness, patient-doctor communication, and patient support by relatives and loved ones, will allow the clinician to effectively manage patient safety.

Our findings demonstrate the sustained interest of the Twitter community in the COVID-19 issue during the pandemic. It was revealed that together with #PatientSafety, the co-occurring hashtag #COVID-19 has been mentioned 11,213 times. Twitter has been used as a platform by WHO, health agencies, government organizations, hospitals, doctors, and medical journals from different countries to distribute timely information related to patient safety during COVID-19. Thereby, 21 #PatientSafety tweets were shared by WHO in the study period, and the WHO account was mentioned 7,285 times. Consequently, the population has been able to promptly receive the latest verified information provided by WHO, and the WHO has been highly regarded as a key organization with relevance to patient safety.

The analysis also confirmed that Twitter was also actively used by doctors treating patients with COVID-19 to inform the medical community and patients about their experience promptly.

Our data are consistent with results obtained by other scientists. Pangborn et al. analyzed the Twitter messages for 1 year (from March 13, 2020, to March 12, 2021) during the pandemic. The authors

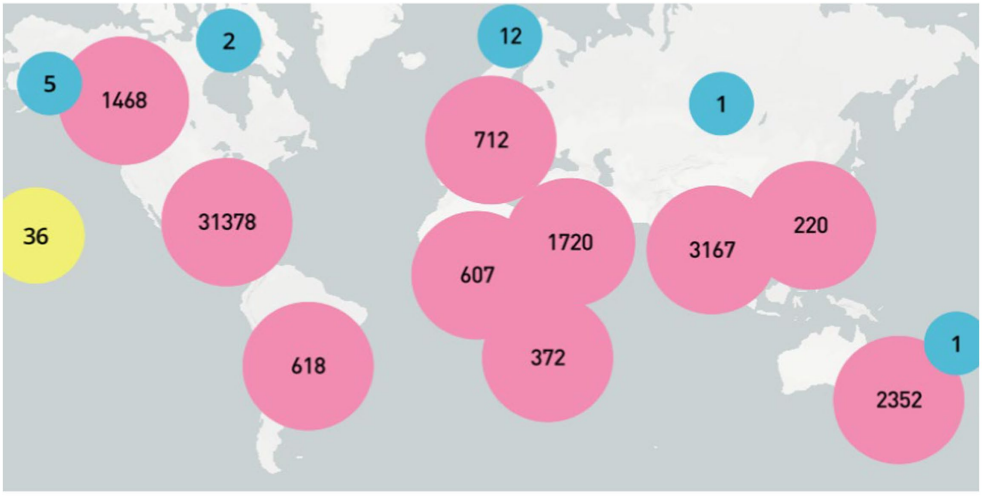

FIGURE 3
Regional distribution of the posted tweets.

TABLE 2 Co-occurring hashtags with #PatientSafety.

N	Hashtags	Count
1.	#Healthcare	23,210
2.	#COVID19	11,213
3.	#patientcare	9,501
4.	#worldpatientsafetyday	8,807
5.	#hospital	8,222
6.	#digitalhealth	7,403
7.	#doctors	6,934
8.	#MedTwitter	6,649
9.	#MedEd	6,413
10.	#health	6,112
11.	#HealthTech	6,087
12.	#Quality	5,828
13.	#AHRQ	5,171
14.	#medicine	5,099
15.	#nurse	5,052
16.	#NHS	4,646
17.	#patients	4,580
18.	#patientexperience	4,096
19.	#ptsafety	4,070
20.	#publichealth	3,717

TABLE 3 Trending terms that are most frequently tweeted with #PatientSafety.

	Trending terms	Frequency
"Patient" block		
1.	Patients	12,025
2.	Support	4,263
3.	Health	4,007
4.	Health care	1,626
5.	World patient safety day	836
"Practical doctors" block		
6.	Learn	8,204
7.	Improve	4,114
8.	Healthcare professionals	900
9.	Lean healthcare management	835
10.	PSNet featured research	821
11.	Health worker safety	388
"Health Care Safety Management" block		
12.	Risk	3,677
13.	Quality	3,657
14.	Harmed	3,424
15.	Medical errors	738
16.	Due to unsafe medicine practices	651

FIGURE 4
Visualization of significant trending terms (a word cloud) with the hashtag #PatientSafety by frequency of their use.

conclude that Twitter was used by family doctors as a platform on which they shared their experiences (26).

A block of trending patient-related terms highlights the need for active patient-doctor communication. Within the hashtag #PatientSafety, Twitter users widely discuss the issue of the safety and effectiveness of vaccination against COVID-19, and patient participation in the treatment process. Users who post tweets about the positive impact of vaccination emphasize the need to protect themselves, their families, and society; the possibility of avoiding a severe form of the disease; and doctors' recommendations. On the other hand, there was also distrust of the vaccine, which was developed and investigated in a short time, and concern regarding possible side effects of the vaccine.

In contrast to the assumed high level of ambiguity over the safety of vaccinations against COVID-19, the findings of our prior work in real-time utilizing surveys on Twitter show that there is an increasing readiness to get vaccinated among the Twitter community participants (27). Similar results were obtained by Lyu et al. Tweets related to COVID-19 vaccines were analyzed from March 11, 2020, to January 31, 2021. Sentiment estimates showed that the sentiment was increasingly positive despite the swings. The analysis of emotions also showed that trust was the most predominant emotion, followed by expectation, fear, sadness, etc. On November 9, 2020, Pfizer stated that its vaccine was 90% effective, and the feeling of trust peaked (28). The Hoffman BL study, which includes a survey on COVID-19 vaccination and an analysis of Twitter messages, showed that encouraging the exchange of personal stories about the COVID-19 vaccine on social networks, combined with measures aimed at specific reasons for hesitancy about the COVID-19 vaccine, can be an effective means of reducing uncertainty about the COVID-19 vaccine (29).

One more problem related to patient safety during the pandemic is the diminished support of loved ones. Hriberšek et al. revealed that the Twitter community supported the notion that during the patient's stay in the hospitals in the pandemic period, the patient's loved ones must be involved. Both patients and their loved ones will have a better hospital experience as a result of their moral support and communication, which increases patient safety (30).

Thus, analysis of the "patient" block of trending terms revealed the following possibilities for reducing the risks of adverse events in patients: obtaining information from doctors about the advisability of vaccination and the choice of vaccines, especially for those at risk (diabetics and older adults), the symptoms, and the course of COVID-19; using the Internet of Medical Things; and the support and care of the patient from his relatives and friends.

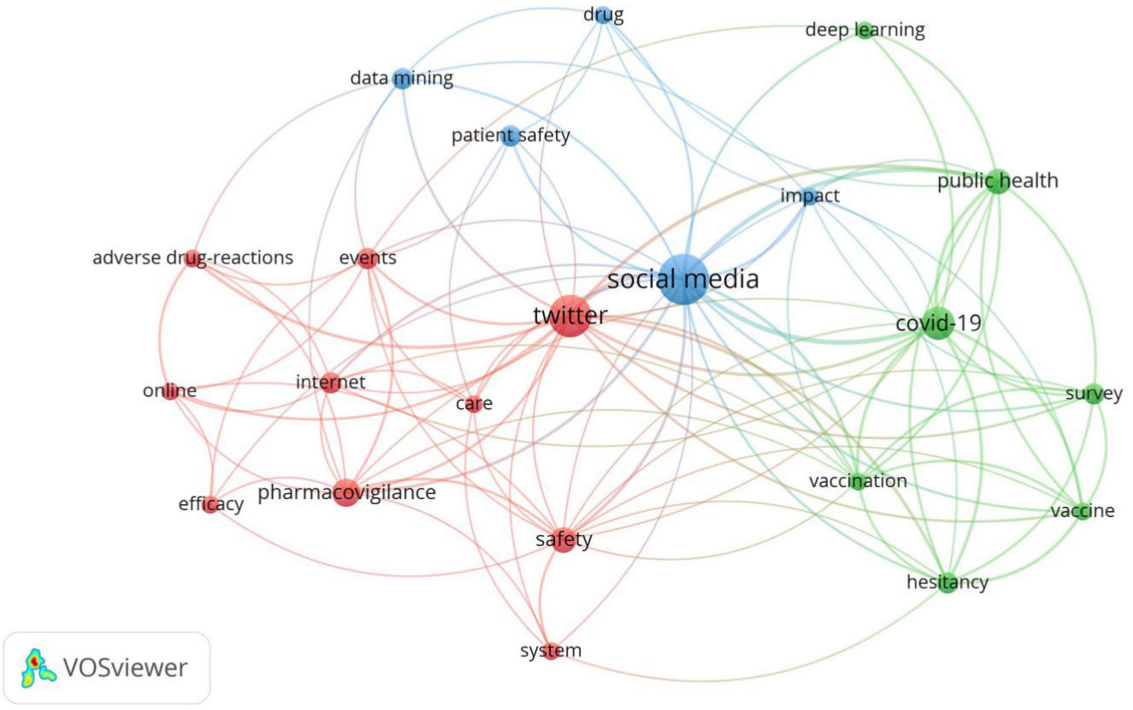

FIGURE 5
A map of the keywords of publications about patient safety discussions on Twitter in Web of Science (2000–2023).

4.2. Doctors, social media opportunities

The doctor's ability to store, analyze, and use information is significantly expanding with the additional use of computer technology. The Twitter platform is widely used by healthcare professionals for additional knowledge sharing, experience exchange, and continuous professional development.

Analysis of trending terms associated with the "Practical doctors" block suggests a significant role of the human factor in ensuring patient safety. The importance of advanced training for doctors, constant communication between doctors and patients, doctors and teams, and implementing modern information technologies into medical practice (artificial intelligence, machine learning, social media platforms such as Twitter, etc.) should be noted. Meanwhile, risk factors for the healthcare quality include occupational burnout associated with excessive load and negative organizational factors.

The pandemic period provided an opportunity to understand the importance and feasibility of introducing modern digital solutions into the healthcare system. One of the trending terms in the tweets in our study was "learn." There is no doubt that Twitter provides the opportunity for doctors to gain knowledge and information about open innovations to ensure patient safety during the COVID-19 pandemic.

In a similar context, the study of Dost et al. using the social media platforms Twitter, LinkedIn, and WhatsApp to assess the knowledge of specialist anesthesiologists and their attitude toward strategies and methods of treatment in the intensive care unit in patients with a suspected or confirmed diagnosis of COVID-19, is of interest. The latter work has revealed that the majority of doctors showed the correct attitude toward ensuring airway patency; assistant researchers with little professional experience were seen to be indecisive or inclined to make incorrect decisions (31).

In the context of education, there are also studies about the possibility of using Twitter as part of the interprofessional curriculum of the patient safety course for students and teachers (32).

There is no doubt that modern medical digital information technologies improve doctors' working conditions and the quality of health care. Thus, it is reported that it was possible to reduce the number of erroneous medications, reduce the number of adverse events, and improve compliance with clinical recommendations when moving from paper records to electronic medical records. However, patient safety also includes digital safety. Patients aware of the effectiveness of modern information systems are concerned about the increased risk of personal information insecurity in digital databases. Blockchain technology analyzes the storage architecture of medical data and ensures that it cannot be altered or tracked (33–35).

Thus, for the second block of trending terms, the following opportunities have been identified as contributors to reduce the risks for patients and improve their safety: advanced training for doctors, constant communication between doctors and teams, international sharing of best practices by doctors, and the implementation of modern information technologies into medical practice [artificial intelligence (machine learning), social media communications etc.].

4.3. Health safety management, including pharmacovigilance

The modern approach to drug and vaccine development is based on a deep understanding of the nature of diseases and use of the latest

achievements in pharmacy, and it combines the experience of classical medicine and modern technologies. Twitter might additionally help to identify public willingness for vaccination and has been utilized to detect adverse events of medicines and vaccines, thereby strengthening modern pharmacovigilance systems that rely on spontaneous reporting and health observations.

The third block of trending terms of the #PatientSafety tweets, "Health Care Safety Management," relates to tools to combat adverse events in medicine.

The pharmacovigilance system plays an important role in ensuring the safety and effectiveness of medicine and patient therapy. The use of any medicine is always associated with the risk of adverse events. Preventing adverse events with the use of medicines is more rational than taking measures to eliminate them, which determines the need for risk management. It should be noted that Twitter has the potential to serve as additional source to identify adverse events associated with the use of medicines, including vaccines.

An analysis of trending terms and co-occurring hashtags revealed that Twitter participants actively participated in conversations related to the risk of adverse events from both vaccines against COVID-19 and other medicines. These findings are in line with the results of other authors.

Thus, Lian et al. analysed tweets (from December 1, 2020, to August 1, 2021) containing personal experience with COVID-19 vaccinations, as well as information about the dose, type of vaccine (Pfizer, Moderna, and Johnson & Johnson), and symptoms. It has been established that the four most populous US states (California, Texas, Florida, and New York) had the most discussions about adverse events on Twitter. The frequency of Twitter discussions of adverse events coincided with the course of the COVID-19 vaccination. Touch tenderness, fatigue, and headaches were the three most common adverse effects of all three COVID-19 vaccines in the United States. The authors conclude that it is possible to use social media data to monitor adverse events (36).

Bennett et al. based on the analysis of adverse hematological events associated with vaccines using the Twitter platform, note the need to improve pharmacovigilance approaches (37). Despite the fact that social networks contain information noise and do not have the ability to check the accuracy of patients' messages about possible adverse events, they also have advantages due to their coverage and depth.

Thus, the accelerated approval of vaccines to combat the COVID-19 pandemic emphasized the need to quickly obtain data on their safety in the post-marketing period. A possible additional source of data is Twitter.

The interest of Twitter users using the hashtag #PatientSafety in the problem of adverse events to vaccines and other medicines has also been identified. The main flow of relevant publications is devoted to using of medicines from different pharmacotherapeutic groups. These findings fit well with the results of other authors.

Li et al. noted that the modern pharmacovigilance system for medicine safety relies on spontaneous reporting systems and data from health observations (38). However, the detection of adverse drug events may occur with delay and a lack of geographic diversity. The researchers extracted potential adverse event reports from Twitter, as they did from the US FDA (The United States Food and Drug Administration) Adverse Event Reporting System, and then integrated those signals. The authors conclude that the accuracy of signal detection using social networks can be improved by combining Twitter signals with signals from the spontaneous message system. However, further research is needed to use an integrated system that includes Twitter.

The following previous works have explored the use of Twitter as an additional element of pharmacovigilance.

Golder et al. evaluated the consistency of data on the side events of statins from Twitter social media compared to other sources. It was revealed that most adverse events showed a high level of agreement between Twitter and regulatory data. While being a complex approach, pooling of data from multiple sources can provide a broader safety profile for any drug (39). Similar results were obtained by Smith et al. in analyzing tweets mentioning adalimumab in relation to adverse events (40).

Patel et al. assessed glucocorticoid-related adverse events using Twitter and spontaneous reports of adverse events to the national drug regulatory authority. The authors conclude that pharmacovigilance using Twitter data could be a valuable additional source of information on drug safety (41).

Thus, studies demonstrate consistency between adverse event data from Twitter and regulatory bodies, emphasizing the value of multi-source data in creating a comprehensive drug safety profile and, as a consequence, patient safety.

On the other hand, social networks serve as a platform for disseminating information about the adverse events of drugs. When safety concerns involving pharmaceutical drugs that have received FDA approval arise, the FDA releases drug safety communications to patients, healthcare providers, and the general public. Social media is used to spread these safety messages and guarantee their widespread adoption. In this context, Sinha et al. evaluated the spread of two posts on social media (Twitter and Facebook) for sleeping pills zolpidem. The authors conclude that social networks have opportunities to distribute drug safety communication messages for preventing adverse events for patients (42).

Another problem that Twitter users are discussing with the hashtags #PatientSafety (and in addition often with #COVID-19) is the "off-label" use of medical products. "Off-label" use of a medical product means its use in situations where such a product is intentionally used for medical purposes but does not correspond to the information approved by regulatory authorities about it.

Among the major healthcare problems in the first waves of the pandemic was the lack of vaccines and drugs for the treatment and prevention of COVID-19. This led to the use of many off-label drugs (hydroxychloroquine, azithromycin, etc.) for treating patients with COVID-19 (43). In this regard, pharmacovigilance information shared on social networks, including Twitter, also plays an important role in identifying risks.

During the COVID-19 pandemic, four drugs received a lot of public attention: hydroxychloroquine, ivermectin, the latter both representing drug therapies with anecdotal evidence, and molnupiravir and remdesivir, both of which represents FDA-approved treatment options for eligible patients. Hua et al. looked into 609,189 tweets from the US between January 29, 2020, and November 30, 2021. The study demonstrated how social network users view and react differently to drug use that is not for a purpose for which the FDA approved them and that occurs at various COVID-19 stages (44). This suggests that in order to promote safe medication use, health systems, regulators,

and legislators should establish targeted ways to monitor and lower disinformation.

Thus, analysis of all posts, including on Twitter and other social networks, including both positive and negative research results, is necessary to present a complete picture of the safety profile of drugs as perceived by users, in the context of patient safety. Acquiring of such information may prevent adverse events in patients later on. It is worth noting that such information might benefit the joint work of drug manufacturers and regulatory authorities, to provide more complete protection for the patient from adverse reactions and prevent the development of serious adverse events.

To better comprehend the public mood and concerns surrounding adverse drug and vaccine responses, it should be mentioned that medical organizations, pharmaceutical corporations, and regulatory agencies may also use publicly available information offered by the public on social media.

According to the WHO, medication errors are among the most important healthcare problems. This matter is also actively discussed by Twitter users and scientists in scientific publications. Among the trending terms in our study, "medical errors" should also be noted. Medical errors can have serious consequences for the patient.

A retrospective study has found that the majority of medication errors were caused by dosing errors and errors in drug frequency, mostly attributed to physicians among hospitalized patients with COVID-19 in Saudi Arabia. The most frequent drug categories implicated in medication errors and adverse events, respectively, were antibiotics (32%), and antineoplastics (25%) (45).

Makary et al. reported that adverse events are the third leading cause of death in the US population (46). Although the results of this study have been criticized by scientists (47), the relevance of the problem is not in doubt. Reason et al. in their work suggest using a systematic approach in managing adverse events (48).

Additional use of Twitter data analysis might aid the establishment of a systematic approach to managing patient safety. Publicly available information on social media is useful for healthcare organizations and regulatory agencies to understand public sentiment on drug safety and monitor medication errors.

The analysis performed allowed us to formulate generalized approaches to strategies for reducing the risks of adverse events in patients, as follows.

4.4. Summarized approaches for strategies to reduce the risks of adverse events in patients

The current study reveals the discussions and attitudes of Twitter users toward patient safety during the COVID-19 pandemic. Such kind of analysis might yield real-time understanding of public sentiment about the question under investigation, thereby contributing to understanding the evolving situation. Thus, this type of research gets beyond the drawbacks of the conventional social science technique, which is based on small-scale, time-consuming, retrospective, and delayed interviews and surveys, and provides a valuable additional source of information.

Summarized approaches for strategies to reduce the risks of adverse events reflected in the #PatientSafety discussions on Twitter are shown in Figure 6.

It should be noted that along with the benefits of additional use of the Twitter platform for managing patient safety, there are a number of limitations. Health misinformation was widespread online during the COVID-19 pandemic (49). The WHO declared it an "infodemic," reflecting an overabundance of accurate and inaccurate information that makes it difficult for people to identify reliable information sources. The spread of misinformation contributes to delayed treatment, patient anxiety, and harm to health. In this context, Skafle et al. summarized the results of 19 studies of social media misinformation about COVID-19 vaccines and their implications (50). These studies show that social media misinformation has a negative impact on vaccine trust and use. The authors conclude that further research is needed for the benefit of public health. In connection with this phenomenon, WHO has developed recommendations in 2020 to address misinformation (51). It is suggested that social media companies be involved in the dissemination of credible information. It is planned that social media platforms will implement mechanisms to warn users about the presence of misinformation in the content, including based on machine learning.

The WHO policy brief (2022) (52) offers a range of policy recommendations for all stakeholders: increasing digital literacy, arguing the need to combat the infodemic, providing secure online platforms, establishing multi-stakeholder networks to combat the infodemic, improving risk communication, and implementing ongoing monitoring of harmful and deceptive content on the Internet.

Future research may help to develop superior strategies to overcome the above-mentioned infodemic obstacles and improve patient safety management.

5. Conclusion

The use of digital technologies together with the latest advances in medicine is an important approach in improving health conditions, ensuring patient safety, and extending life. The following areas of possible use of Twitter as a valuable additional source of information were identified in the present work: ensuring patient safety during COVID-19; using Twitter by physicians to share additional knowledge, experience, and continuing professional development; Twitter as an additional element of pharmacovigilance, an additional monitor of medical errors in taking drugs.

Thus, the performed Twitter analysis established that the components of the patient safety process reflected in the online discussions are: active communication between the patient, the doctor, and loved ones; the support and care of the patient from loved ones; advanced training of doctors; team communication; international sharing of best practices by doctors; implementation of modern digital technologies in medical practice; a system approach to preventing adverse events, including pharmacovigilance, in particular using feedbacks collected through the Twitter platform; and the timely analysis and prevention of the causes of medical errors. In order to prevent misinformation on social networks, including Twitter, implementation of the WHO recommendations to warn users about the presence of misinformation in the content could be a promising approach, including applications based on machine learning.

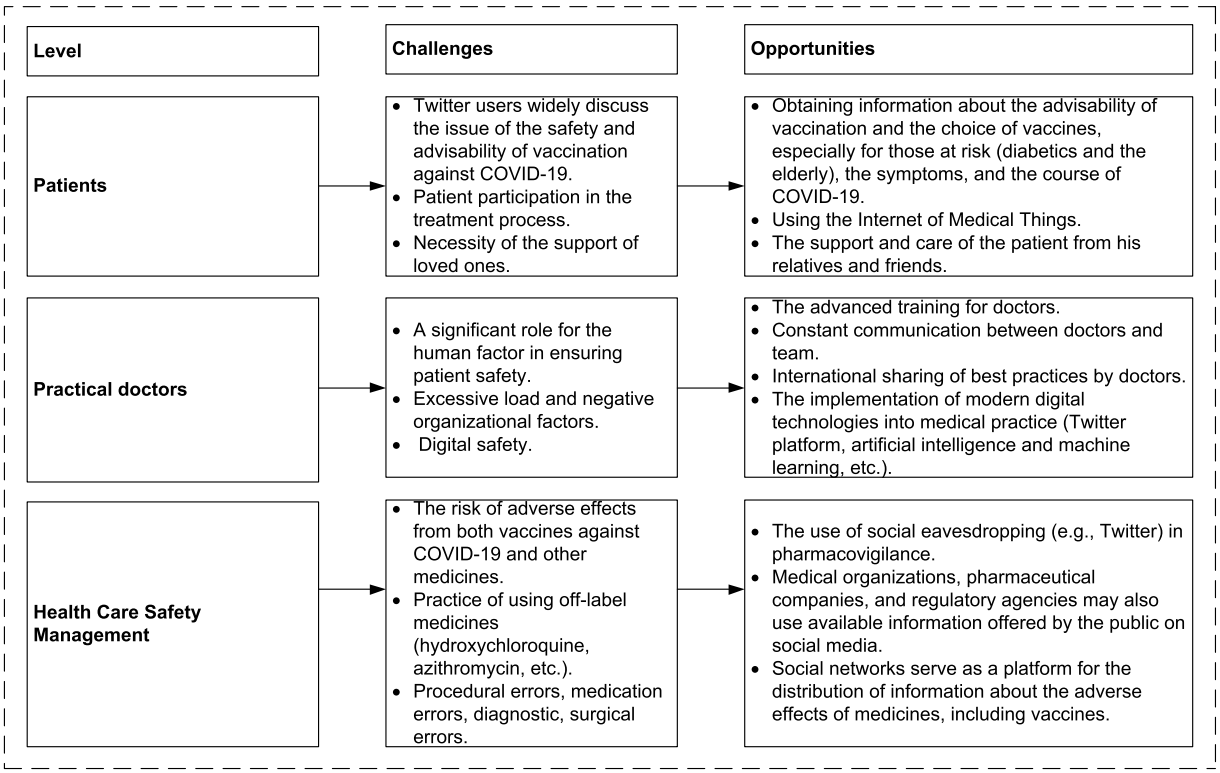

FIGURE 6
Summarized approaches to reduce the risks of adverse events reflected in the #PatientSafety discussions on Twitter.

Summarized approaches for patient safety promotion can be used in other pandemics and for patient safety management in clinical practice.

The study has several limitations. Firstly, we only analyzed one hashtag used in Twitter discussions. Secondly, Twitter users are not representative of the entire population, and the collected data only indicate the opinions and reactions of online users possessing Twitter accounts. In this context, it is of interest to study data from other Internet platforms (for example, Facebook, Instagram, YouTube, etc.) and analyze their correlation. It is also promising to focus on discussions shared in different languages to analyze the reactions of the populations in specific countries. In future studies, it would be promising to include German, French, and other languages for analysis in order to obtain a global perspective. Notably, studies of online discussions are time-sensitive (e.g., in the present study the tweets were collected in a specified time period). In summary, with the careful consideration of existing limitations, Twitter data overall represent a valuable source of information for real-time gain of knowledge based on user-generated content related to patient safety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

OL: Conceptualization, Investigation, Methodology, Writing – original draft. FM: Writing – review & editing. MM: Writing – review & editing. BZ-K: Writing – review & editing. CT: Writing – review & editing. BS: Writing – review & editing. JS: Writing – review & editing. AA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing – review & editing. HW: Conceptualization, Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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Lessons learned from the COVID-19 response in Sri Lankan hospitals: an interview of frontline healthcare professionals

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Introduction: The COVID-19 pandemic revealed the lack of preparedness in health systems, even in developed countries. Studies published on COVID-19 management experiences in developing countries, including Sri Lanka, are significantly low. Therefore, lessons learned from pandemic management would be immensely helpful in improving health systems for future disaster situations. This study aimed to identify enablers and barriers to COVID-19 management in Sri Lankan hospitals through healthcare workers' perceptions.

Methods: Frontline doctors and nurses from different levels of public hospitals were interviewed online. Both inductive and deductive coding and thematic analysis were performed on the transcribed data.

Result and discussion: This study identified four themes under enablers: preparing for surge, teamwork, helping hands and less hospital-acquired infections. Seven themes were identified as barriers: lack of information sharing, lack of testing facilities, issues with emergency equipment, substandard donations, overwhelmed morgues, funding issues and psychological impact. These preparedness gaps were more prominent in smaller hospitals compared with larger hospitals. Recommendations were provided based on the identified gaps.

Conclusion: The insights from this study will allow health administrators and policymakers to build upon their hospital's resources and capabilities. These findings may be used to provide sustainable solutions, strengthening the resilience of the local Sri Lankan health system as well as the health systems of other countries.

KEYWORDS

COVID-19, healthcare professional, hospital, pandemic, Sri Lanka

1 Background

The COVID-19 pandemic has resulted in a global health and economic crisis (1), emphasising how important it is to be prepared for disasters. The COVID-19 virus was first detected in the city of Wuhan in Hubei Province, China, in late December 2019, and the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 (2). According to data, COVID-19 has been reported in 539 million people and resulted in over 6.3 million deaths globally by 21 June 2022 (3).

The COVID-19 pandemic has placed a tremendous burden on healthcare systems. The pandemic has also illustrated the risks of global overdependence on a single nation (such as China or India) for essential medicines and medical equipment (4). Even developed countries had to struggle to control the infection and to reduce deaths. Unlike in other disasters, developing nations became helpless without support from developed nations because COVID-19

was a global pandemic. Healthcare workers (HCWs) were at great risk of becoming infected through occupational exposure (5, 6). Thousands of HCWs had been infected and a significant number had died across the world (5, 7, 8). Therefore, protecting HCWs was also a priority in reducing the burden on hospitals.

The fear of devastating impacts continued to grow in developing countries. The lower-income countries and countries with less-resourced health institutions have found it disproportionately hard to expand existing capacity for increasing demand (9). The rapid spread of the infection has overburdened health systems of these countries in terms of critical care provision, including beds in intensive care units (ICUs), mechanical ventilation, supplementary oxygen and the ability to protect HCWs (9).

Developing countries in Asia had faced many challenges in their socioeconomic and healthcare systems (10). Although almost all countries in the world had faced challenges because of COVID-19, South Asian countries in particular dealt with enormous challenges. These were mainly the result of their large population, less-resourced health facilities, high poverty rates and low socioeconomic conditions (10). The COVID-19 pandemic rapidly overwhelmed the fragile health systems of these countries (10). For example, India had periods of COVID-19 crisis for several months in 2021 where hospitals were overcrowded with patients, running out of oxygen and capacity was exceeded (11). The government collaborated with nationwide local authorities to combat the situation to ensure adequate hospital beds, oxygen and anti-viral drugs (12). Because of the surge in COVID-19 deaths, hospital morgues and crematoriums were also overwhelmed. Bodies were piled up and some were cremated in family backyards or even in the streets, while some corpses were thrown into rivers (13).

Studies have also reported that the inefficient management of logistics chains, lack of human resources and inadequate laboratory facilities compromised the readiness of healthcare systems in neighboring countries such as Nepal, Bangladesh and Pakistan (14–16).

As a developing country also situated in South Asia, Sri Lanka was also at risk of experiencing a critical situation with the onset of the pandemic. Early preventive strategies taken by the government and the Ministry of Health (MoH) were considered successful in preventing widespread community transmission (17). However, the subsequent second and the third waves of the pandemic put an increased strain on the local health system, overwhelming its capacity (18). From the first reported case on 27 January 2020 to the end of September 2020, there were only 3,363 confirmed cases and 13 deaths over a period of less than 9 months (17). However, by 26 February 2022, the corresponding numbers had increased to 643,072 positive cases and 16,142 deaths (3). It was inevitable that the local health system would be stretched to its maximum capacity and face challenges. Lessons learned from past disasters are of paramount importance when improving health system resilience. However, there has been a scarcity of research on COVID-19 experience in Sri Lankan hospitals.

As frontline responders, doctors and nurses who were actively involved in COVID-19 management in local hospitals were the ideal personnel to explore hospital preparedness to the pandemic. Therefore, this study aimed to identify enablers and barriers to the COVID-19 response in Sri Lankan hospitals through frontline HCWs' experiences. These findings would be helpful in improving the resilience of the Sri Lankan health system to future disasters. The lessons would also be useful in providing sustainable solutions for strengthening the resilience of health systems in other countries.

2 Methodology

2.1 Study design, sampling, and recruitment

A descriptive qualitative approach was used in this study. Because the public health sector is providing universal free health coverage to all citizens in Sri Lanka, almost all COVID-19 cases were managed in public hospitals except for a few cases managed in the private sector. To ensure a generalized understanding, doctors and nurses employed in public sector hospitals in Sri Lanka were recruited, representing both male and female respondents from different categories of hospitals (national hospitals, teaching hospitals, district general hospitals, base hospitals and military hospitals) in different provinces of the country. A snowball sampling technique was employed, leading to the recruitment of different categories of frontline HCWs, representing health administrators (healthcare professionals in administrative roles), consultant physicians, consultant emergency physicians, in-charge nurses and nursing officers.

It was considered that theme saturation would be achieved at approximately 15 interviews which also aligned with the investigators' intention to minimized additional burden to this already busy period for frontline health care workers. Therefore, recruitment email requests were sent to 20 doctors and nurses explaining the purpose and the manner of the study and also requesting their consent for recording the interview. Eighteen agreed to participate in the study by replying to the invitation email.

2.2 Inclusion criteria

Participants were eligible if they were frontline HCWs (doctors and nurses) who had at least 1 month of experience managing COVID-19 patients and more than 5 years of career experience in public sector hospitals and were willing to be interviewed.

2.3 Exclusion criteria

All private and public sector hospitals that did not have a COVID ward were excluded from the recruitment procedure.

2.4 Data collection

The interviews were arranged for a preferred time and date for each participant during their non-work time. All the interviews were conducted online via Zoom from 15 December 2021 to 15 January 2022. Each interview lasted for between 45 and 60 min. The interviews were continued until data saturation was achieved. Altogether, 16 participants were interviewed, at which point data saturation was confirmed. All 11 doctors were interviewed in English and all five nurses were interviewed in the Sinhala language for their convenience.

These interviews were conducted following a semi-structured, interview guide prepared by the researchers. The guide was based on the 4S domains of hospital disaster preparedness: space, stuff, staff and systems (19–21) (Appendix I). It also focused on identifying demographic characteristics of the respondents along with the identification of enablers and barriers to COVID-19 management.

All the interviews were audio-recorded, with the informed consent of the participants. Confidentiality of the data was ensured. All the interviews were conducted by NM (main author), who had previous experience of conducting interviews. The details of the qualitative interview were reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ) guide (22) (Supplementary Appendix II).

2.5 Data analysis

Content analysis was conducted according to the Graneheim and Lundman technique (23). Both inductive and deductive coding and thematic analysis of transcribed data were performed using Microsoft Word.

2.6 Rigor or trustworthiness

The trustworthiness of this qualitative study was achieved by ensuring credibility, transferability, dependability and confirmability (24, 25). Several enhancing strategies were used in the study. To enhance credibility, a diverse group of participants was recruited, including both males and females, with different expertise, from different levels of hospitals, representing several districts in the country. The interview guide was designed by NM and GO and revised by a qualitative research expert. The guide was pilot-tested for clarity and comprehension by interviewing a separate doctor and a nurse in Sri Lanka who did not participate in the study. The interviews were transcribed by a professional transcriber who is fluent both in English and Sinhala. The transcripts were verified for accuracy. All the recordings were listened to carefully numerous times; they were then double-checked for clarity by two independent reviewers (NM and GO). The English transcripts of the nurses' interviews, which were conducted in Sinhala, were checked for clarity by NM, who is fluent in English and whose mother language is Sinhala. All the transcripts were read through several times and coded by two independent reviewers (NM and GO). If any discrepancies occurred, consensus of a third reviewer (PC) was taken to make the final decision. All the codes, categories and themes developed by the independent reviewers were refined by the third reviewer (PC).

To enhance confirmability, member checking was performed, and all the transcripts were sent back to the participants for their opinions and verification of the accuracy of the codes and interpretations. While reporting, evidence was provided using verbatim quotations from the participants.

To enhance dependability, NM made reflexive notes throughout the study, while GO and PC served as auditors and carefully examined the process.

To enhance transferability, the study context was accurately described with the details of participants, sampling methods and procedures of data collection, etc.

2.7 Ethics statement

Ethical approval was obtained from the Monash University Human Research Ethics Committee on 12 October 2021 (Project ID: 29716). Administrative approval was obtained from the MoH, Sri Lanka on 8 October 2021.

3 Findings

The demographic characteristics of the 16 participants are illustrated in Table 1. There were 10 male and six female respondents from different levels of hospitals, namely, the national hospital, two teaching hospitals, four district general hospitals, four base hospitals, the police hospital and two military hospitals, the Army and the Navy. Their career experience ranged from 11 years to 29 years. Almost all had worked on frontline services from the beginning of the pandemic in Sri Lanka; therefore, they had an average of about 18 months' experience by the time of the interview. There were five nursing professionals, including two nursing officers and three in-charge nursing officers. There were 11 doctors, including three consultant emergency physicians, five medical administrators, two consultant physicians and one public health specialist (Table 1).

The analysis yielded 47 codes, 9 categories and 11 themes. Four themes were identified as enablers of the COVID-19 response in Sri Lanka, namely, preparing for surge, teamwork, helping hands and less hospital-acquired infections. These four themes comprised a total of nine categories. Seven themes were identified as barriers, namely,

TABLE 1 Demographic characteristics of the respondents.

Category	Sub-category	Number (percentage)
Gender	Male	10 (62.5%)
	Female	6 (37.5%)
Expertise	Medical administrator	5 (31.3%)
	Emergency physician	3 (18.8%)
	In-charge nurse	3 (18.8%)
	Nursing officer	2 (12.5%)
	Consultant physician	2 (12.5%)
	Public health specialist	1 (6.3%)
Work experience (years)	10–14	4 (25%)
	15–20	5 (31.3%)
	21–25	5 (31.3%)
	26–30	1 (6.3%)
	31–35	1 (6.3%)
COVID-19 management experience (months)	9–12	3 (18.8%)
	13–16	3 (18.8%)
	17–20	10 (62.5%)
Hospital type	National	2 (12.5%)
	Teaching	2 (12.5%)
	District general	4 (25%)
	Infectious disease	1 (6.3%)
	Base	4 (25%)
	Army	1 (6.3%)
	Navy	1 (6.3%)
	Police	1 (6.3%)

lack of information sharing/communication challenges, lack of testing facilities, issues with emergency equipment, substandard donations, overwhelmed morgues, funding issues and psychological impact on HCWs (Table 2). The 'psychological impact on HCWs' theme will be discussed in a separate paper because of the relatively large amount of content pertaining to this barrier (i.e., this theme resulted in multiple codes and categories from the participant interviews). Therefore, this theme is not included in Table 2.

The data analysis identified the enabler themes described in the following sections.

3.1 Preparing for surge

To accommodate a large number of COVID patients, all the hospitals needed to expand available space, the number of beds and other critical care capacities. Three categories were identified under this theme: (i) changes in routine procedures, (ii) rapid development of infrastructure and (iii) training on personal protective equipment (PPE) donning and doffing.

3.1.1 Changes in routine procedures

All the hospitals made considerable changes in routine hospital operational procedures, such as canceling clinics, outpatient department (OPD) and routine surgeries. Triage protocols were modified and treatment protocols and management guidelines were also adopted based on the technical guidance issued by the MoH and the WHO. These changes also included the provision of hand-washing and sanitising facilities at the entrance of all the units, limitation of the number of visitors, maintenance of physical distancing and frequent cleaning of the hospitals.

An administrator from a national hospital described the changes that occurred in his hospital:

> We discharged non-urgent patients, cancelled elective surgeries, stopped outpatient treatments and routine clinics. However, we established a system to send the drugs to clinic patients by post, ensuring their safety and providing continuous supply of medicines. We limited the point of entry to the facility. Further, we modified our standard triage system as well. We prepared a general roster for COVID management including all the doctors in the hospital.

3.1.2 Rapid development of infrastructure

All the hospitals rapidly converted some of their wards, transformed existing spaces or abandoned wards for COVID treatment areas and isolation facilities. The ICUs and high dependency units (HDUs) were newly built or upgraded, if already existing. The government provided the necessary logistics and financial resources to these hospitals through the MoH. Further, these hospitals were supported by external donations, and manpower was increased by the voluntary participation of military personnel and the public.

An emergency physician from a district general hospital explained:

> Initially, it was a big challenge for us to allocate existing ICU beds to manage COVID patients. But we had a separate hospital, which was not open for the public at that time. Its ICU was not functioning. With the ministerial approval, we established a separate 'fever corner', an isolation area and a six-bedded ICU. Now, it is fully dedicated for COVID patients.

A nursing officer from a district general hospital described how they successfully expanded space and bed capacity:

> This unit, initially, was a rehabilitation centre. We quickly transformed this into a COVID ward. Gradually, we expanded it up to 300 beds. Then, the ICU was started with three beds. Finally, we could start a treatment centre and a 24 bedded HDU as well.

3.1.3 PPE donning and doffing training

The study participants received PPE training from various platforms, ranging from online videos to hands-on training. The majority of the participants received training at the Infectious Disease Hospital (IDH) in the capital city, Colombo. A small group of frontline doctors, nurses and supporting staff of most of the hospitals were sent to the IDH for a short-term training program on PPE.

A nurse in charge of a COVID ICU in a base hospital described:

> We, a team of nurses, sisters and minor staff, had a two-day training at IDH. In addition, our infection control unit also conducted some training for nurses on PPE donning and doffing. The trained staff, then, trained the other staff.

However, some hospitals mostly developed their knowledge and skills through virtual platforms. An emergency physician from a teaching hospital explained how they trained the staff virtually:

> We learned, PPE donning and doffing, totally from the online resources like YouTube. Also, we conducted virtual training program for our staff.

3.2 Teamwork

All the participants highlighted that during the crisis, everybody worked as a team. The important decisions were made through discussions and regular meetings; everybody supported each other more than ever before. Two categories were identified under this theme, namely, dedicated staff and regular meetings.

3.2.1 Dedicated staff

The respondents highlighted how the frontline workforce was dedicated to their duties by sacrificing the most important life events, social and personal events, the New Year and religious festivals. They were not limited only to their designated duties, but extended full support to cover duties of other categories of staff, when needed. They put their own life at risk to protect others and were fully dedicated to their duties.

An administrator from a military hospital described:

> Some members of the staff could not even attend … their mother's funeral because of … COVID duties. I also had to stay in the East for about 3 months for supervising my team and I was away from my family. We all were fully engaged with our duties.

TABLE 2 Identified codes, categories and themes of enablers and barriers.

Codes	Categories	Themes
Enablers		
1. Modified triage 2. Cancel clinic, OPD, routine surgeries 3. Modified rosters	1. Changes in routine procedures	1. Preparing for surge
4. Transformed spaces 5. Improve oxygen supply 6. Improve ICU/HDU facilities	2. Infrastructure development	
7. On site/online training 8. Training of trainers	3. PPE training for emergency staff	
9. COVID Cell meetings 10. Key stakeholders' discussion 11. Decision-making as a team	4. Regular meeting	1. Teamwork
12. No demarcations 13. Supporting each other 14. Take the risk 15. Sacrifices	5. Dedicated staff	
16. Volunteering 17. Construction of ICC and wards 18. Support transportation 19. Disposal of bodies	6. Military support	2. Helping hands
20. Donate PPE and medical equipment 21. Sending food for patients/staff 22. Providing dry rations	7. Community support	
23. Frequent sanitising 24. Wearing mask/PPE 25. Hand washing	8. Strictly followed precautions	4. Less hospital-acquired infection
26. Government's vaccination efforts 27. Priority for health staff	9. Successful vaccination	
Barriers		
28. Multiple reporting 29. Lack of timely update 30. Lack of IT facilities 31. Delayed and poor information sharing		5. Lack of information sharing
32. No PCR machine 33. Few standard laboratories 34. Delayed result		6. Lack of testing facilities
35. Shortage of equipment 36. Poor knowledge of functionality 37. Shortage of consumables		7. Issues with emergency equipment
38. Used items 39. Broken items 40. Hidden agendas of donors		8. Substandard donations
41. Lack of mortuary staff 42. Lack of morgue capacity 43. Problems with cremation		9. Morgue capacity exceeded
44. No accountants 45. Inability to manage monetary donations 46. Prolonged time for processing 47. Lack of funds		10. Funding issues

HDU, high dependency unit; ICC, intermediate care centre; ICU, intensive care unit; IT, information technology; OPD, outpatient department; PCR, polymerase chain reaction; PPE, personal protective equipment.

An administrator from a national hospital described how dedicated their staff was:

> It's very sad to say, in some ICUs all the supporting staff had to be quarantined and all their work had to be done by the nurses and nurses had a very bad time. However, they did a great job. Even though we had loads of challenges, we all worked together towards the goal of saving lives. We did not have any conflicts. So, everybody worked as a team.

A physician from an infectious disease hospital explained:

> We had to improvise our own way of doing the ward rounds without exposing the full staff. Normally, we used to do ward rounds with doctors, medical student, nurses and minor staff. But now, I go to the patients alone, to prevent exposing others. Sometimes, I had to take samples for PCR.

3.2.2 Regular meetings

Almost all the respondents described that they had regular meetings with key personnel in the hospital to discuss issues, progress and to make decisions. All the hospitals had a weekly meeting called 'COVID Cell'; in addition, larger hospitals had daily administrative meetings.

An emergency physician from a district general hospital described:

> Actually, we had weekly COVID meetings in our hospital, it's called COVID Cell and we took most of the critical decisions during this meeting, it's a multi-disciplinary meeting representing all categories of staff. I represented the emergency department.

A hospital administrator from a teaching hospital explained:

> Every morning, we had administrative meetings with the directors, deputy directors, chief nursing officers, accountant and all the key personnel. We were updated with current situations and future plans. We also had twice a week meeting with physicians, surgeons and in charge nurses. All these meetings gave us the strength and we felt that we were together.

3.3 Helping hands

The COVID response of most of the hospitals, as well as the national response, was highly supported by the military forces and the public. Two categories were identified under this theme: support from the military and community support.

3.3.1 Support from the military

All the respondents highlighted the contribution of the military to the national response, mainly through the COVID Task Force. Specifically, Army personnel contributed greatly to infrastructure establishment and maintenance of intermediate care centres (ICC) and treatment centres. They also supported the vaccination program, providing voluntary medical teams for some hospitals.

An administrator from a military hospital explained:

> We had full deployment of all the staff and they were working 24/7. We provided manpower to the civilian hospitals and heavily involved in vaccinations. As most of the ICC were in faraway places, we had to transport patients and the bodies. The COVID Task Force is also headed by the commander of the Army. The coordination of the health sector and all the other sectors were handled by this task force. Also, almost all the quarantine process was mainly handled by the army, with the support of Air Force and the Navy. Most of the COVID treatment facilities were also developed by Military Engineering Troops.

3.3.2 Community support

All the participants highly valued and appreciated the various forms of support given by the community.

An emergency physician from a district general hospital described how the community helped the hospital:

> Our health system is entirely free of charge but compared with the health budget allocated by the government, it is impossible to cater all the facilities for this surge of patients. However, we received donations from the community including medical equipment, PPE, oxygen supply systems worth millions, also dry rations, cloths, food and sanitary items. Sometimes, they provided meals for our staff. Without these donations I do not think we could battle this pandemic.

3.4 Less hospital-acquired infection

The other enabler identified was the smaller number of hospital-acquired infections among the staff. Two categories were identified under this theme as contributing factors for success, namely, strictly following precautions and successful vaccination.

3.4.1 Strictly following precautions

All the respondents highlighted that all categories of HCWs carefully followed the precautionary measures. Even though there was a lack of PPE at some stages of the pandemic, they made sure to protect themselves, paying for the cost of PPE by themselves.

A nursing officer from a district general hospital described:

> We are directly contacted with the infection, but most of us did not contract the disease. We were very keen on our protection and strictly followed the precautionary measures. Frequent hand washing, sanitising, proper wearing of PPE helps to reduce the transmission of infection among the staff. Only a very few staff members become positive in our ICU, but the origin of the infection was found to be outside sources, not from the hospital.

3.4.2 Successful vaccination

These respondents also appreciated the government initiatives for successful vaccination programs, which involved expediting the procurement process and improving vaccine administration, with the support of the military medical teams.

A nursing officer from a base hospital explained:

> Actually, the vaccination program of the country was very successful. Health workers were given priority and we have already completed three doses of Pfizer. Now, we feel like we are fully immune. Therefore, the staff aren't scared to work as before.

The data analysis identified the barriers (not including the theme, psychological impact on HCWs) described in the following sections.

3.5 Lack of information sharing/ communication challenges

Participants experienced a lack of timely updates on information related to COVID-19. They also found some challenges in accessing that information via online platforms because of several reasons, including the lack of a user-friendly website and the lack of communication infrastructure and IT facilities.

An administrator from a base hospital described:

> Poor information sharing was a main problem. There was much delay in receiving management protocols from the Ministry. It was difficult to trace the latest version of the protocol from the Ministry website as the indexes were not updated. Also, we had to prepare multiple reports to inform our daily statistics to several institutions. This reporting was an extra burden with the limited staff and lack of IT facilities.

A nursing officer expressed the lack of IT facilities in a district general hospital:

> We do not have a computer in our ICU, no WhatsApp facilities or other IT facilities for us to communicate. When the director's office is closed, we have to wait until it opens, even to get a printout.

3.6 Lack of testing facilities

Initially, most of the hospitals had challenges with testing facilities. They had to send samples to Colombo or to laboratories in other locations. Those labs were overwhelmed with samples from all over the country. Therefore, it took an average of 3 to 5 days to obtain the result. However, later, most of the hospitals received polymerase chain reaction (PCR) machines and other test kit facilities to overcome this barrier.

A nursing officer from a district general hospital explained:

> Actually, we had to face a lot of trouble even to do our PCRs. We did not have a PCR facility and had to send the sample to Karapitiya. It takes about 4 days to get the result.

An administrator from a base hospital described:

> Initially, we had to take the samples and send to whatever the available laboratory. Some laboratories sent the reports very late. After few months, we got a PCR machine.

3.7 Issues with emergency equipment

At the initial stage, almost all the hospitals experienced a shortage of emergency equipment. Even though the MoH provided them with some equipment, it was not sufficient to manage the huge influx of patients. The community also donated much equipment; however, this was not enough. Some hospitals received adequate equipment, but they did not receive proper guidance or training on the functionality and maintenance of the equipment ("poor knowledge of functionality" to be interpreted as suboptimal training / orientation / in-service in the use of emergency equipment). Further, the participants highlighted that some equipment could not be used because of the unavailability of consumables. Conversely, respondents from the police and military hospitals reported having an adequate amount of emergency equipment, including PPE and other essential supplies.

A nursing officer from a base hospital described:

> We received a lot of monitors, CPAP (continuous positive airway pressure) and Bi-PAP (bilevel positive airway pressure) machines as donations. Only the ETU (Emergency Treatment Unit) staff had training on this equipment. Nurses from different units were allocated for each shift at the COVID wards and they were not trained. Therefore, the majority had poor knowledge on the functionality and the protection of the equipment.

A nursing officer from a district general hospital described why some equipment became unusable:

> The business community and well-wishers have given us many equipment worth millions, ventilators, syringe pumps, high flow machines, defibrillators etc. However, some equipment could not be used because of lack of parts to replace, for example, we have defibrillators with sticky pads, these pads are not available in the country because of increased demand.

3.8 Substandard donations

Some interviewees complained about donations. Some donations were substandard, while some were purely for publicity. This created an unnecessary burden for the administrators.

An administrator from a base hospital described:

> Some community donations were either used or not having service agents in the country. Some were broken and just piling up as garbage in our hospital. As we must keep the inventories of all the donations, getting rid of them is an extra burden. The Ministry should regulate such poor-quality donations.

Another administrator from a different base hospital expressed:

> Some donations were tricky, because some people donated a few items and they just wanted to get huge publicity. They needed to take photos and videos and put them on social media or other media for publicity. This type of donation makes unnecessary trouble for us.

3.9 Morgue capacity exceeded

The majority of the participants described that they could manage the morgue at their hospital through the rapid cremation of bodies within 24–48 h. However, a few hospitals faced a situation where morgue capacity was exceeded.

An administrator from a base hospital described how the morgue of his hospital was overwhelmed.

> We got several bodies from the community, but we have only four coolers. We were overwhelmed by home deaths. A negative PCR was needed if a post-mortem was required on a death. Initially, we did not have a PCR machine. So, it took several days to get the report. So, we had to keep the body outside for about a day, once a cooler was available, we put them into the freezer. Sometimes, bodies were decomposed partially and we were blamed. Anyway, we had to care for the living rather than the bodies.

The same hospital faced a serious problem because of overstretched morgue capacity.

> We had an issue with the swapping of two bodies; the relatives were given the wrong bodies. This happened because of a checking mistake of one of the minor staff members and the supervising person. This was partially because of the problem with our staff and also because of the overwhelming of our morgue capacity. This became a big issue and was highlighted in all the media.

Another emergency physician from a teaching hospital described:

> Actually, our mortuary capacity was exceeded and we had to keep the bodies outside the mortuary for about 1 day. However, the army personnel assisted us to quickly remove the bodies, arranging cremations.

3.10 Funding issues

Financial resources were a great challenge in all the hospitals. Unlike the hospitals governed by the MoH (e.g., the national, teaching and district hospitals), the provincial hospitals, which are governed by provincial ministries, faced many difficulties with financial resources. Respondents described the complicated and time-consuming procedure of the approval of costs at the provincial level. The main barrier to maintain a contingency fund was the unavailability of an accountant in the provincial hospitals.

An administrator from a base hospital described why he could not maintain emergency funds:

> We cannot maintain any funds at the base hospital levels as we do not have an accountant. We have to request funds from the RDHS (Regional Director of Health Services) and it takes so much time to process. I did not entertain monetary donations because there is no proper system to manage funds within our type of hospitals.

Another administrator from a different base hospital highlighted the same issue:

> Lack of funds is the main challenge in managing a disaster in provincial setup. Even though the line ministry issues funds quickly in emergency situations, the provincial setup takes a long time. I have only 5,000 rupees for my petty cash and 20,000 rupees for emergency drugs. That's the only funds I have. We do not have an accountant.

4 Discussion

To the best of our knowledge, this is the first study in Sri Lanka to examine the enablers and barriers to COVID-19 management through the perceptions of both doctors and nurses in the frontline of the healthcare system. This study identified several enablers and enormous challenges faced by frontline HCWs in battling the 'perfect storm' of the COVID-19 pandemic in Sri Lanka. The study revealed four main themes of enablers of the COVID-19 response: preparing for surge, teamwork, helping hands and less hospital-acquired infections. Seven themes were identified as main barriers: lack of information sharing/communication, lack of testing facilities, issues with emergency equipment, substandard donations, exceeded morgue capacity, funding issues and psychological impact on HCWs. The last theme was not included in this discussion, as explained earlier.

The Sri Lankan government's key interventions included the establishment of the National Task Force to coordinate the COVID response; imposing island-wide lockdowns at an early stage of the pandemic; closure of all ports of entry, schools and universities; mandatory face mask-wearing; social distancing measures; intense contact tracing; strict 14-day quarantining and disinfecting public places. These interventions helped keep the first wave in Sri Lanka under effective control (26). The quick establishment of designated quarantine centres with the support of military personnel was also immensely helpful for the public as all the facilities were provided free of charge.

This study reported that the government's well-organized and coordinated national response was highly successful in controlling disease transmission as well as improving hospital surge capacity nationwide. This response was primarily handled by the MoH, in collaboration with the National COVID Task Force (17). The response was also supported by the WHO, many other private and public organizations and the general public. In preparing for surge, almost all the hospitals successfully converted their existing wards or other available spaces into COVID wards within a short period of time. A reserved pool of military personnel was quickly mobilized and these rapid transformations were supported by voluntary contributions. The government expedited the process by providing necessary logistics and financial support through the MoH. Further, some hospitals established or upgraded their existing ICUs and HDUs. Most of the hospitals developed COVID-19 treatment protocols and management guidelines based on the technical guidelines issued by the MoH and the WHO.

However, frontline HCWs also struggled with multiple challenges because of inadequate preparedness at hospital level. Base hospitals were the smallest hospitals included in this study and they were managed by the provincial ministries. This study highlighted that base hospitals had more difficulties than bigger hospitals because of lack of

resources. It was also revealed that these hospitals faced multiple challenges because of lack of efficient financial management systems.

However, the military and the police hospitals were better prepared in terms of all resources compared with other hospitals. This success may be because of the separate governance of these hospitals by the Ministry of Defence, and also because of the better funding system and their more positive mindset thanks to training.

As found in this study, the lack of IT facilities was a huge barrier in communication and information sharing in most of the hospitals in Sri Lanka. In contrast, effective use of technology in the digitalisation of healthcare, such as in contact tracing, surveillance, sharing real-time data, laboratory networking and coordinating with other stakeholders, were key in the successful pandemic management of other countries (27). For example, the South Korean government disclosed real-time COVID-19 information through mass media, dedicated websites, phone messages and mobile apps (28, 29).

Communication is of paramount importance in a disaster response to enable effective coordination and collaboration within the hospital as well as with external stakeholders. Many countries shifted to virtual communication during the pandemic to ensure effective communication, fast learning and knowledge updating (30). Even though people were physically distancing, these platforms kept them more connected socially than ever before. Some countries also introduced telemedicine practices, ensuring the safety of both patient and the practitioner while keeping face-to-face contact. Therefore, the accelerated expansion of telehealth became one of the most important changes in the delivery of healthcare during the pandemic (31).

Further, to draw meaningful insights, it is vital to have timely access to real-time data, especially in a pandemic situation. However, in Sri Lanka, health information systems were found to be inadequate and underfunded. The lack of IT facilities and the lack of an appropriate central health database system hampered health information sharing among hospitals (28). Our study highlighted that the smaller hospitals were most affected by the poor communication of real-time updates on COVID-19.

Sri Lankan hospitals still have a manual documentation system. As highlighted by our study, the preparation of multiple documents and daily reporting to several places were an extra burden for the limited staff, especially with poor IT facilities. In contrast, with the surge of COVID-19 patients, the emergency departments of developed countries adopted multiple electronic health record process improvements to reduce the burden of documentation (32). Other countries also provided technologies to facilitate communication between patients and their families by video conferencing (32). They found this to be beneficial for both patients and their families.

This study found that the lack of dedicated laboratories and testing facilities severely compromised the efforts of battling the pandemic in Sri Lanka. Improving testing capacities was one of the first priorities to control the spread of the disease in every country. For example, Australia, with a population of 25.4 million, conducted over 63,000 daily PCR tests in June 2020 (33). However, during the same period, for an almost similar population of 21.5 million (34), the total PCR testing capacity of Sri Lanka was 2,526 per day (35).

The WHO recommends that highly infectious samples should be tested at biosafety level (BSL) 3/4 type laboratories (36). These are highly sophisticated facilities that require specialized expertise. At the beginning of the pandemic, there were no such facilities functioning in Sri Lanka. Therefore, the laboratory staff had to conduct COVID testing in high-risk, routine laboratory environments. The Medical Research Institute (MRI), Colombo, established a BSL3 laboratory decades ago; however, it had not been in operation since 2002 (37). Several other BSL2 laboratories are located in medical colleges and universities. The lack of expertise in this field was a major barrier. However, at the beginning of 2020, the MoH had taken initiatives to mobilize resources to implement a BSL3 laboratory at MRI (37). At the same time, the Interim Biosafety Guidelines for Laboratories were issued by the MoH to inform the laboratory staff on safety precautions while handling samples (38). However, Sri Lanka's ability to fight the pandemic was compromised by limited testing facilities.

This study also identified that local hospitals were short of emergency equipment during the peak of the pandemic; this was similar to many countries around the world. The demand for emergency medical equipment quickly exceeded supply, leading to critical shortages, especially, ventilators and PPE. Some countries adopted creative and timely strategies to overcome this challenge. They relaxed the regulations imposed on manufacturing and promoted local production. As an example, the US Food and Drug Administration provided maximum regulatory flexibility for manufacturing to increase the availability of ventilators, other respiratory devices and accessories (39). This flexibility encouraged manufacturers and increased local production. To increase the number of existing ventilators, these guidelines also recommended that hospitals use ventilators beyond their shelf life and also to use ventilators intended for other purposes (39, 40). For instance, they allowed ventilators normally used at home or during transport to be used in hospitals for the long term. They also advised the use of non-invasive breathing equipment for stable patients. This type of flexibility could be adopted by the Sri Lankan government to improve the availability of emergency equipment in its hospitals. In addition, this study found that substandard donations imposed an extra burden on hospitals.

This study also emphasized the lack of morgue capacity in hospitals. During the peak of the pandemic, hospital morgues across the globe became overwhelmed. However, hospitals in developed countries expanded their morgue capacity using large portable refrigerator units as makeshift morgues (41). Because of the high infectivity, the WHO recommended following certain guidelines when handling COVID-19 bodies (42). The WHO also stressed that morgue staff must be trained to use appropriate PPE, and effort should be made to ensure the timely and reliable identification, documentation and traceability of the dead (42). However, it is questionable whether resource-poor countries could adopt such guidelines. Generally, in such countries, untrained or minimally trained staff handled dead bodies. As revealed in our study, Sri Lanka also experienced some mishaps in the handling of dead bodies because of staff shortages, inadequate morgue capacity and lack of documentation and supervision.

Adequate financing is of paramount importance for maintaining a strong and resilient health system and also for continuing essential health services in any disaster (43). As a middle-income country, Sri Lanka has many socioeconomic problems. In addition, the country's main income sources were also severely affected by the global pandemic (44). Therefore, the country had to mount its response to the pandemic with limited financial resources. Many capacities that are crucial to preparedness can only be built over time and require sustained commitment and funding (43).

According to our findings, most of the base hospitals experienced financial barriers, and these were largely caused by the inefficient system of financial management at the provincial level. Although decentralization has given the provinces the power to formulate their own statutes in Sri Lanka, there is a high degree of financial dependence on the central government. Certain processes were affected by the additional administrative layers at the provincial level, resulting in unnecessary delays. Therefore, generally, most provincial councils were not as efficient and effective in their service delivery as the central ministry.

Many studies have acknowledged the psychological impact of COVID-19 on HCWs (45–49). However, limited studies have focused on how other aspects of hospital preparedness, such as donations, communication, laboratory facilities and morgue capacity, have affected the COVID-19 response, as examined in our study. Similarly to our findings, a few studies have reported that lack of training, limited PPE, lack of testing facilities and funding were barriers to managing COVID-19 in most of the health systems around the world, including developed countries (50–52).

This study identified that very few HCWs had hospital-acquired infections because of adherence to strict precautionary measures at the hospital level. This is confirmed by a study conducted in a base hospital in Sri Lanka, where only 28% of infected HCWs of that hospital acquired COVID-19 from the hospital setting (53).

A study conducted in the United Kingdom (UK) on the COVID-19 management experience of HCWs reported that the redeployment of staff to ICU duties heightened the feeling of being unprepared as PPE simulation was the only training they received (50). Our participants experienced the same situation because of moving non-trained staff to the emergency department to address severe staff shortages. However, UK staff had opportunities to access online training to improve their capacity. In contrast, the majority of our study participants did not even have free access to the internet, resulting in further barriers to improve their knowledge and skills.

Many countries highlighted the importance of community support received during the COVID-19 response (54–56). Our study also identified community support as an enabler; however, sometimes, the donations became additional burden for Sri Lankan hospitals because of the poor-quality or substandard donations they received. This was a significant finding of our study, which was not reported in other COVID-19 studies. Similar incidents were also reported in Sri Lanka during the tsunami of 2004. The uncoordinated and substandard donations resulted in negative impacts on the relief and recovery process (57).

Studies have also reported that information overload was a common problem experienced by HCWs in other countries (51, 58). In contrast, lack of information sharing was a significant finding in our study context. This may be because of the lack of communication facilities and IT facilities in most of the rural hospitals.

5 Recommendations

To ensure that the Sri Lankan health system is more disaster-resistant, the Ministry of Health, health planners, policymakers and hospital administrators are encouraged to take appropriate action with regard to the following;

- Improve communication infrastructure in the hospitals and implement new technologies to enhance information-sharing through appropriate platforms.
- Strengthen the IT systems of local hospitals. Specifically, the healthcare workers in base hospitals and district general hospitals should be provided with internet access.
- Provide regular training and simulation exercises to ensure the capacity building of staff.
- Improve laboratory facilities and train laboratory staff.
- Promote local production of PPE and emergency equipment and improve the quality and availability of these equipment in local hospitals.
- Introduce an appropriate regulatory mechanism to coordinate and monitor donations, and to prevent substandard donations to hospital
- Find ways to expand mortuary capacity and conduct the appropriate training of morgue staff.
- Allocate adequate funding for capacity building, surveillance, information management, risk communication and essential logistics requirements.
- Provide the administration with the required expertise and authority for handling a contingency fund in provincial hospitals.

6 Limitations

The participants of this study were restricted to the frontline doctors and nurses in hospitals. Thus, the experience of other categories of frontline HCWs in hospitals, such as paramedics, laboratory staff, mortuary staff, kitchen staff, waste management staff, radiology department staff, etc., were not included in this study. Moreover, community HCWs were not included. The interviews were conducted at one point in time and respondents' attitudes can change over time.

7 Conclusion

The Sri Lankan government's multi-disciplinary team approach and well-coordinated response to COVID-19 was highly successful in controlling the spread of the disease during the initial stage of the pandemic.

This study identified some positive impacts of the pandemic through a concerted national response, community engagement, support and donations to frontline workers. The HCWs also demonstrated much dedication and unity. An extremely low prevalence of hospital-acquired infections among the health staff was observed, possibly resulting from close adherence to precautionary measures and a successful immunization program.

However, significant gaps were also identified because of the lack of emergency training, inadequate testing facilities, poor information sharing and morgues exceeding capacity. In addition, poor-quality donations imposed an unnecessary burden on some hospitals. Moreover, inadequate IT facilities and communication infrastructure hindered information sharing, communication and access to online

resources for the staff in smaller hospitals. Further, because of a lack of funds and a flexible funding management system, the provincial hospitals faced multiple challenges.

Such barriers should be addressed to better prepare hospitals for future disasters. These lessons may serve as a starting point for crafting new plans and recalibrating existing plans. Further research is needed to gain a deeper understanding of the enablers and barriers at different levels of hospitals across the island.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Monash human research ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NM: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. GO: Conceptualization, Methodology, Formal analysis, Supervision, Writing – review & editing. PC: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1280055/full#supplementary-material

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Symptoms and medical resource utilization of patients with bronchiectasis after SARS-CoV-2 infection

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Background: The impact of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on patients with bronchiectasis in terms of symptoms, self-management and medical resource utilization was unknown.

Objective: To describe the impact of infection by SARS-CoV-2 on fluctuation of symptoms, self-management and medical resource utilization of patients with bronchiectasis during the pandemic of COVID-19.

Methods: This was a single-center cross-sectional questionnaire study performed in Peking University Third Hospital. An online questionnaire investigation addressing the impact of SARS-CoV-2 infection on respiratory symptoms, self-management and medical resource utilization was conducted among patients with bronchiectasis during the COVID-19 surge in December 2022 in Beijing, China.

Results: Five hundred patients with bronchiectasis, with 285 (57%) females, and a mean ($\pm SD$) age of 57.9± 15.1 years, completed the telephone questionnaire. The reported prevalence of COVID-19 was 81.2% (406/500). Of the 406 COVID-19 patients, 89.2% experienced fever lasting mostly for no more than 3 days, 70.6 and 61.8% reported exacerbated cough and sputum production respectively, and 17.7% reported worsened dyspnea. Notable 37.4% of the patients with COVID-19 experienced symptoms consistent with the definition of an acute exacerbation of bronchiectasis. However, 76.6% (311/406) of the infected patients did not seek medical care but managed at home. Of the patients who visited hospitals, 26.3% (25/95) needed hospitalization and 2.1% (2/95) needed ICU admission. Multi-factors logistic regression analysis showed that younger age ($p = 0.012$) and not using a bronchodilator agent($p = 0.022$) were independently associated with SARS-CoV-2 infection, while a history of exacerbation of bronchiectasis in the past year ($p = 0.006$) and daily use of expectorants ($p = 0.002$) were associated with emergency visit and/or hospitalization for patients with bronchiectasis after SARS-CoV-2 infection.

Conclusion: During the COVID-19 surge, the infection rate of SARS-CoV-2 in patients with bronchiectasis was high, and most of the patients experienced new-onset or exacerbated respiratory symptoms, but only a minority needed medical visits. Our survey results further underscore the importance of patients' disease awareness and self-management skills during a pandemic like COVID-19.

KEYWORDS
bronchiectasis, SARS-CoV-2, medical resource, symptoms, infection

1 Introduction

Bronchiectasis is defined as abnormal dilation of the bronchi, typically presenting with symptoms such as chronic cough with sputum production, dyspnea, and recurrent respiratory exacerbations. It represents the third most frequent chronic inflammatory diseases of the airways, after asthma and chronic obstructive pulmonary disease (COPD), and is an increasingly common disease in China, with an estimated prevalence of 174.45 (137.02, 211.88) per 100,000, which increased 2.31-fold from 2013 to 2017 (1), posing a high social and economic burden (2, 3).

Acute exacerbations (AE) of bronchiectasis are associated with increased airway and systemic inflammation (4), worse quality of life (5), progressive lung damage (6, 7) and more medical resource utilization. Respiratory viruses can be identified during exacerbations in up to 50% of patients with bronchiectasis (8, 9) and have been postulated to disturb the balance between chronic bacterial colonization and host-defense response, leading to outgrowth of bacteria and heightened inflammatory responses which resulted in acute exacerbation. The coronavirus (CoV) was one of the most common viruses detected in nasopharyngeal swab or sputum in patients with bronchiectasis experiencing an exacerbation (10).

Coronavirus disease 2019 (COVID- 19), caused by the novel severe acute respiratory syndrome CoV 2 (SARS-CoV-2), has spread rapidly worldwide since December 2019 (11). During the pandemic, the impact of COVID-19 on the management of chronic diseases has received much attention, which, for airway diseases, was concentrated mostly on risks of SARS-CoV-2 infection in patients with asthma and COPD (4, 5, 7, 12, 13), but the impact on patients with bronchiectasis in terms of respiratory symptoms, self-management and medical resource utilization is not known. A UK COVID -19 population study (13) showed that the diagnosis of bronchiectasis was associated with a risk of hospitalization (HR 1.34) and of death (HR 1.12) with COVID-19. In contrast, a nationwide retrospective cohort study in China showed that, after adjustment for age, sex, and other systemic comorbidities, patients with bronchiectasis were not more likely to need invasive ventilation, admission to intensive care unit, or to die at day 30 after hospitalization, compared with those without (6). However, because most people with COVID-19 had not been admitted to hospital, selecting only hospitalized patients for cohort entry often led to enrollment bias. Up till now, SARS-CoV-2 infection and its natural course in the population with clinically diagnosed bronchiectasis have been rarely studied.

In the early December of 2022, the strict measures for preventing COVID-19 were lifted in Beijing, and a large population experienced SARS-CoV-2 infection. Therefore, we undertook a survey to investigate the prevalence of SARS-CoV-2 infection and the symptoms, self-management and medical resource utilization in patients with bronchiectasis during this pandemic surge.

2 Method

2.1 Study design

This was a cross-sectional questionnaire study performed in Peking University Third Hospital. All subjects had been confirmed to have bronchiectasis by chest HRCT in Peking University Third Hospital. An online questionnaire investigation addressing the impact of SARS-CoV-2 infection on patients with bronchiectasis and self-management and medical resource utilization was conducted.

The study was approved by the Ethics Committee of the Peking University Third Hospital (registry M2021-428). All the procedures were performed in accordance with the guidelines of the authors' institutional ethics committee and adhered to the tenets of the Declaration of Helsinki.

2.2 Criteria for inclusion and exclusion

The criteria for inclusion: patients with bronchiectasis who had visited Peking University Third hospital between 1 January 2018 and 30 November 2022; adult status (18 years or more); residence in Beijing.

The criteria for exclusion: refusal to participate in the study.

The survey was conducted by telephone call. Initially, 995 patients were identified as potential interviewees, of whom 398 failed to be connected, 84 refused to participate, and 13 died before the study onset. Finally, 500 patients finished the questionnaire. The flowchart of our study was shown in Figure 1. According to the principles of sampling for a cross-sectional survey, the sample size needed to be 5–10 times the questionnaire items (14). The number of questionnaire items in this study was 25, and therefore 500 participants met the needs of statistical analysis.

2.3 Structured questionnaire and measurements

An online administered questionnaire consisting of several parts was constructed. The introduction of the questionnaire described the background and purpose of the survey and stated that the questionnaire would be answered anonymously and voluntarily following informed consent. Basic demographic information included age, gender, body mass index (BMI), and smoking habits. Baseline data related to bronchiectasis consisted of the disease course, main manifestations, exacerbation times in the past year, underlying etiology and stable stage therapy of bronchiectasis, comorbidity and vaccination history. Questions about COVID-19 included SARS-CoV-2 infection status, methods of diagnosis, symptoms, self-management and medical resource utilization.

The symptoms of COVID-19 were defined as those emerging or aggravating on pre-existing symptoms such as fever, cough,

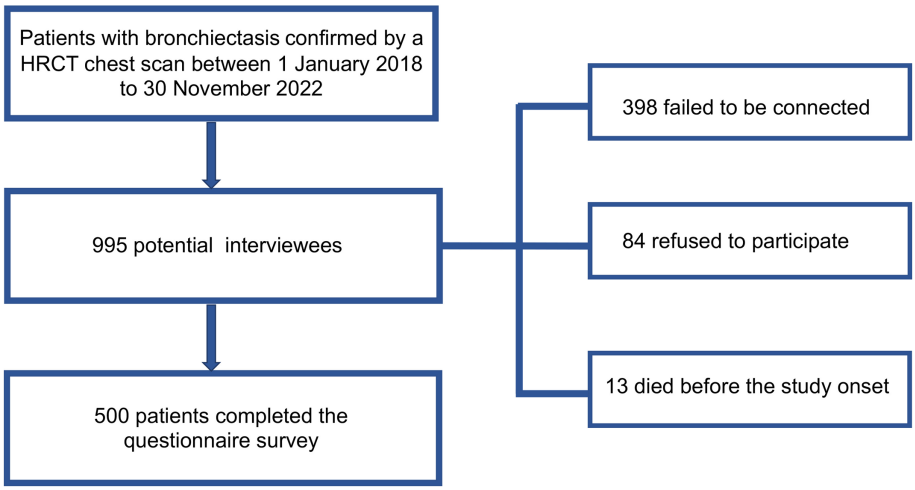

FIGURE 1
Flowchart of study. HRCT, high-resolution computerized tomography.

expectoration, dyspnea (shortness of breath, chest tightness, and wheezing), loss of appetite, and fatigue.

2.4 Analyzed variables

2.4.1 Baseline variables

The following baseline variables were analyzed: age, gender, BMI, smoking history, age at diagnosis of bronchiectasis, chronic symptoms of bronchiectasis, and pharmacological treatment of bronchiectasis.

2.4.2 Exacerbation history

An exacerbation of bronchiectasis (15–17) was defined as the presence of three or more of the following symptoms worsening for more than 48 h: cough, volume and/or consistency of sputum, purulence of sputum, dyspnea and/or intolerance of exercise, asthenia and/or general malaise, and hemoptysis, as well as a need for a change in treatment, for example as the need of antibiotics, and exclusion of other causes of clinical deterioration.

2.4.3 SARS-CoV-2 infection

The methods of diagnosis of SARS-CoV-2 infection included laboratory confirmation of SARS-CoV-2 by a nucleic acid test, or a positive self-administered antigen test, or consistent symptoms and epidemiology. The following variables were analyzed: the prevalence of infection of SARS-CoV-2, the symptoms (and duration) caused by COVID-19, medical visits, medicines used, hospitalization and intensive care admission.

2.5 Statistical analysis

Data were expressed as mean ± standard deviation or median (interquartile range, IQR) for continuous variables depending on whether or not they followed a normal distribution, while categorical variables were expressed as counts and percentages. Both parametrical (Student's t-test for repeated measurements) and non-parametrical (Wilcoxon) tests were used to compare the quantitative variables depending on the variable distribution. In the case of qualitative variables, proportions were compared by means of the chi-square test, as well as Fisher's exact test, where necessary. Logistic regression was used to analyze the associated risk factors. A two-tailed value of p of <0.05 was considered statistically significant. Missing values were not imputed. All analyses were performed using SPSS version 20 Armonk, NY.

3 Results

3.1 Baseline characteristics of the patients

Of the 500 patients who completed the telephone questionnaire, 285 (57%) were female, and the mean ($\pm SD$) age was 57.9 ± 15.1 years (Table 1). Most respondents (388/500, 77.6%) had been vaccinated against COVID-19 (Table 1). The prevalence of cough, sputum production, dyspnea and/or exercise intolerance, hemoptysis at baseline (i.e., stable stage before having COVID-19) was 62, 59.2, 12.0, and 18.0%, respectively. 140 (28%) patients reported at least one AE, of whom 32.9% (46/140) with at least one AE needing hospitalization, in the past year (Table 1). 4.6% (23/500) of the patients were treated with ICS, 14% (70/500) received long-acting β-agonists (LABA) or/and long-acting muscarinic antagonists (LAMA), while 4.2% (21/500) received ICS plus a LABA (Table 1). In terms of the potential etiologies for bronchiectasis, post-infection accounted for 22.8% (114/500), post-tuberculosis for 16.0% (80/500), and those with unknown causes for 61.2% (306/500).

3.2 The prevalence of SARS-CoV-2 infection

81.2% (406/500) of the patients reported infection by SARS-CoV-2, of whom 82 (20.2%) were confirmed by nucleic acid tests, 281 (69.2%) by antigen tests, and 107 (26.3%) were verified by typical

TABLE 1 Demographic and baseline characteristics of patients with bronchiectasis.

	n = 500
Age (mean ± SD)	57.9 ± 15.1
Sex (male, %)	215 (43.0)
BMI (mean ± SD)	21.7 ± 6.8
Cigarette Smoking (No., %)	129 (25.8)
COVID-19 vaccination doses (mean ± SD)	3.2 ± 1.3
Chronic symptoms before lifting of COVID-19 control measures (No., %)	
No symptoms	126 (25.2)
Cough	310 (62.0)
Sputum	296 (59.2)
Hemoptysis	90 (18.0)
Dyspnea	60 (12.0)
Wheezing	57 (11.4)
Maintenance therapy (No., %)	153 (30.6)
Bronchodilators	70 (14)
ICS	23 (4.6)
Expectorants	71 (14.2)
Acute exacerbation in the past year (No., %)	140 (28)
Comorbidity (No., %)	
Hypertension	87 (17.4)
COPD	41 (8.2)
Asthma	41 (8.2)
Diabetes	43 (8.6)
Malignancy	17 (3.4)

COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease.

symptoms and a history of close contact with family members with SARS-CoV-2 infection.

3.3 Symptoms and clinical course of patients with bronchiectasis after SARS-CoV-2 infection

Of the 406 COVID-19 patients, 1.47% (6/406) had no symptoms, while 70.6% experienced cough (Figure 2A), 61.8% had expectoration (Figure 2B), 17.7% complained of dyspnea (Figure 2C), and 89.2% (400/406) had fever which lasted mostly for no more than 3 days (Figure 2D). It was notable that 37.4% (152/406) of the patients with COVID-19 experienced symptoms consistent with the definition of an acute exacerbation of bronchiectasis.

3.4 Self-management and medical resource utilization of patients with bronchiectasis after SARS-CoV-2 infection

Of the 406 bronchiectasis patients with COVID-19, 76.6% (311/406) did not seek medical treatment but managed by themselves. Antipyretic drugs (49.1%, 153/311) and oral antibiotics (15.8%, 49/311) were the two most commonly used drugs at home. The main reason (92.6%, 288/311) for not seeking medical care was that the patients believed that the symptoms were mild and could resolve spontaneously, while the remaining (7.4%, 23/311) responded that they had difficulty in seeking medical treatment. Of the patients who sought medical care, 26.3% (25/95) needed hospitalization and 2.1% (2/95) needed ICU admission.

3.5 Differences in demography and clinical characteristics between COVID-19 and non-COVID-19 patients with bronchiectasis

Compared with COVID-19 patients with bronchiectasis, non-COVID-19 patients with bronchiectasis were older (62.7 Vs. 52.8 years, $p = 0.001$), with a higher prevalence of hypertension (24.5% Vs. 15.8%, $p = 0.045$), with a higher proportion of long-term drug treatment for bronchiectasis (39.4% Vs. 28.6%, p = 0.04) and bronchodilator treatment (26.6% Vs.11.1%, $p < 0.001$), Table 2. Multivariable logistics analysis including age, hypertension, long-term drug treatment and bronchodilator treatment showed that older age [0.473 (0.264, 0.846), $p = 0.012$] and using a bronchodilator agent [0.514 (0.290,0.910), $p = 0.022$] were independently negatively correlated with SARS-CoV-2 infection, Table 3.

3.6 Risk factors for emergency visiting and/or hospitalization

The demographic and clinical characteristics of COVID-19 patients and the risk factors for emergency visiting and/or hospitalization were shown in Tables 4, 5. In group comparison and univariate risk analysis, age, COVID-19 vaccination times, daily symptom of sputum, dyspnea, wheezing, and regular use of bronchodilators, expectorants, and acute exacerbations in the past year, comorbidity of COPD and diabetes were risk factors for emergency visit and/or hospitalization after SARS-CoV-2 infection. However, multivariable analysis showed that only acute exacerbation in the past year ($p = 0.006$) and long-term use of expectorants ($p = 0.002$) remained to be significant risk factors.

4 Discussion

There have been several studies, mostly retrospective, investigating the impact of COVID-19 on bronchiectasis in hospitalized patients (4, 6), or comparing the difference between COVID-19 patients with and without bronchiectasis (13, 18–20). However, there was a lack of study on the epidemiological and clinical data, self-management and medical resource utilization of bronchiectasis patients infected with SARS-CoV-2 during the COVID-19 pandemic. The COVID-19 pandemic resulted in the public recognition of social distancing and mitigation measures that reduced person-to person interactions. There was a significant reduction in the frequency of reported exacerbations of bronchiectasis during the lockdown period (21–23). For example, an observational, multicenter study in Spain showed that

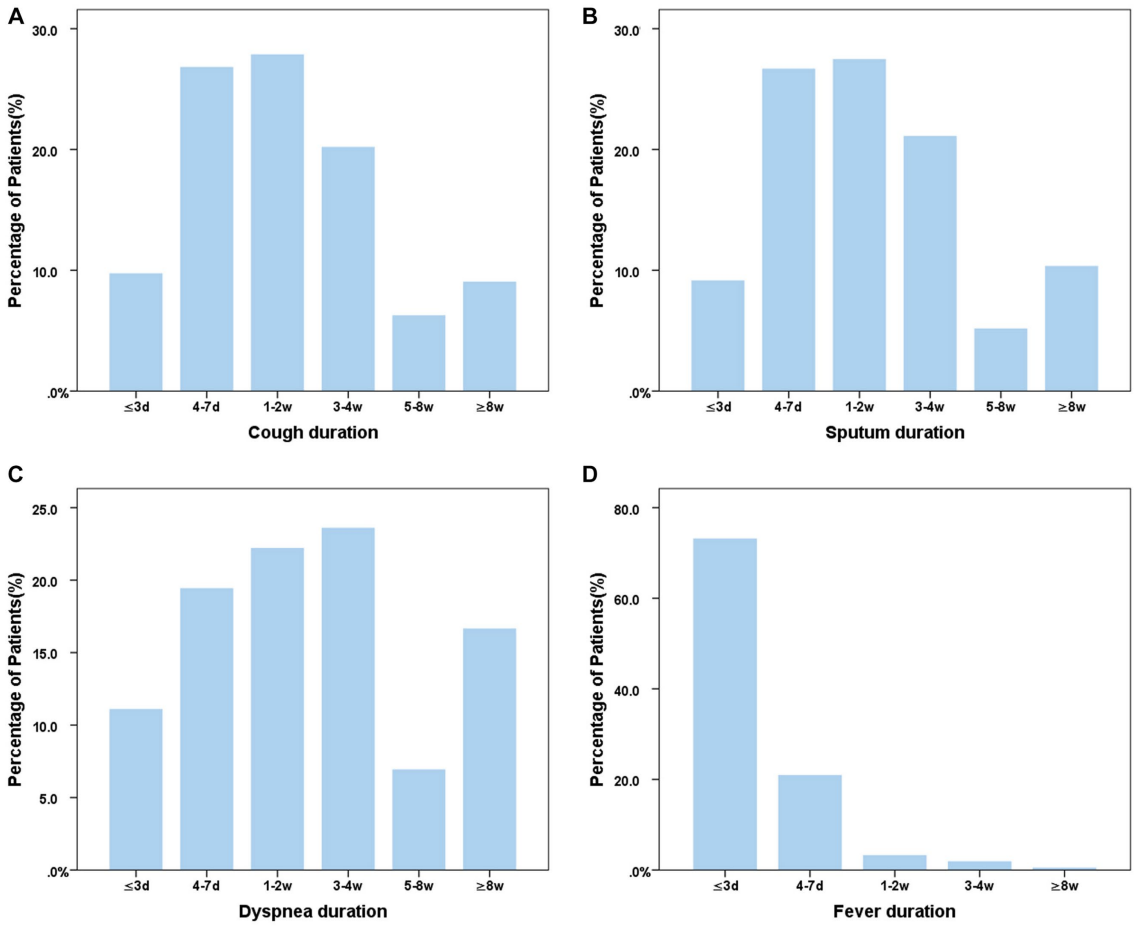

FIGURE 2
Distribution of main symptom duration in bronchiectasis patients with COVID-19. **(A)** Cough duration of bronchiectasis patients with COVID-19; **(B)** Sputum duration of bronchiectasis patients with COVID-19; **(C)** Dyspnea duration of bronchiectasis patients with COVID-19; **(D)** Fever duration of bronchiectasis patients with COVID-19. ≤3d, 4-7d, 1-2w, 3-4w, 5-8w, ≥8w means the course of symptom ≤3d, 4-7d, 1-2w, 3-4w, 5-8w, ≥8w means the course of symptoms was less than 3 days, 4-7 days, 1–2 weeks, 3-4 weeks, 5–8 weeks and more than 8 weeks, respectively.

the proportion of patients without any exacerbations increased from 22.6% in the pre-pandemic period to 63.1% in the pandemic ($p < 0.001$) (22). However, after the lift of COVID-19 lockdown, the prevalence and the impact of SARS-CoV-2 infection on patients with bronchiectasis was not clear.

The present study, to our knowledge, was the first to describe the infection rate, respiratory exacerbation and medical resource utilization in patients with bronchiectasis during a COVID-19 surge in China. We found that the infection rate of SARS-CoV-2 in bronchiectasis patients was 81.6%. Of the bronchiectasis patients infected by SARS-CoV-2, 37.4% experienced symptoms consistent with the definition of an acute exacerbation of bronchiectasis. The common symptoms of bronchiectasis patients with COVID-19 included fever and new-onset or exacerbated respiratory symptoms, such as cough, expectoration and dyspnea. The duration of fever was short (≤ 3 days), while respiratory symptoms (such as cough, expectoration, and dyspnea) lasted much longer (4 days to 4 weeks). Notably, 76.6% patients did not need immediate medical care but successfully managed at home. Of the patients who sought medical care, 26.3% needed hospitalization and only 2.1% needed ICU admission. We also noted that, compared with the uninfected patients, those infected by SARS-CoV-2 were younger and were less likely to receive bronchodilator therapy.

Bronchiectasis patients with SARS-CoV-2 infection reported a wide range of symptoms on presentation. Similar to other population studies (11, 16, 24–26), fever was the most frequent symptom in our cohort. The frequency of fever (89.2%) in the present study was similar to most previous studies (11, 25, 26), but higher than the data from a system review on clinical characteristics for COVID-19 (37.0%) (16).

Cough was another common symptom in COVID-19 patients (11, 16, 25–27). The incidence of cough (71.6%) in our study was similar to that reported in other studies (11, 26, 27), but higher than the data from a systematic review of COVID-19 (25.4%) (16). The frequency of dyspnea (17.7%) in our patients with SARS-CoV-2 infection was mostly similar to, or higher than that reported elsewhere (11, 26, 27), although lower than that from patients visiting emergency departments (32%) (25). These respiratory symptoms persisted from 4 days to 4 weeks, and the duration was longer in those who had chronic symptoms at baseline (data not

TABLE 2 Comparison of characteristics between bronchiectasis patients with and without COVID-19.

	COVID-19 *n* = 406	Non-COVID-19 *n* = 94	*p* value
Age (mean ± SD)	56.8 ± 15.0	62.7 ± 14.8	0.001*
Sex (male, %)	175 (43.1)	40 (42.6)	0.923
BMI (mean ± SD)	21. 7 ± 7.0	21.8 ± 5.6	0.913
Cigarette Smoking (No., %)	106 (26.1)	23 (24.5)	0.676
Maintenance therapy (No., %)			
Bronchodilators	45 (11.1)	25 (26.6)	<0.001*
ICS	17 (4.2)	6 (6.4)	0.36
Expectorants	57 (14)	14 (14.9)	0.831
Acute exacerbation in the past year (No., %)	115 (28.3)	25 (26.6)	0.736
Comorbidity (No., %)			
Hypertension	64 (15.8)	23 (24.5)	0.045*
COPD	33 (8.1)	8 (8.5)	0.903
Asthma	34 (8.4)	7 (7.4)	0.768
Diabetes	36 (8.9)	7 (7.4)	0.658
Malignancy	14 (3.4)	3 (3.2)	0.901

COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease.

TABLE 3 Risk factors for COVID-19 in patients with bronchiectasis.

	Single-factor logistic		Multi-factorl logistic	
	OR with 95% CI	*p* value	OR with 95% CI	*p* value
Age(>56)	0.359 (0.209,0.616)	<0.001*	0.473 (0.264,0.846)	0.012*
Hypertension	0.578 (0.336,0.992)	0.047*		
Maintenance bronchodilators	0.379 (0.219,0.654)	<0.001*	0.514 (0.290,0.910)	0.022*

OR, odd ratio; CI, confidence interval; *$p < 0.05$.

TABLE 4 Comparison of characteristics between patients who needed and those who did not need emergencycare and/or hospital admission.

	Emergency care and/or hospital admission (*n* = 39)	No emergency care and/or hospital admission (*n* = 367)	*p* value
Age (mean ± SD)	65.7 ± 16.0	55.8 ± 14.6	0.001*
Sex (male, %)	18 (46.2)	157 (42.8)	0.686
BMI (mean ± SD)	21. 7 ± 4.8	21.8 ± 7.2	0.991
Cigarette smoking (No., %)	14 (35.9)	92 (25.1)	0.143
COVID-19 vaccination doses (mean ± SD)	2.5 ± 1.4	3.3 ± 1.2	<0.001*
Chronic symptoms before lifting of COVID-19 control measures (No., %)			
No symptoms	4 (10.3)	100 (27.2)	0.034*
Cough	29 (74.4)	219 (59.7)	0.074
Sputum	30 (76.9)	204 (55.6)	0.01*
Hemoptysis	10 (25.6)	67 (18.3)	0.263
Dyspnea	10 (25.6)	38 (10.4)	0.005*
Wheezing	10 (25.6)	36 (9.8)	0.003*
Maintenance therapy (No., %)			
Bronchodilators	12 (30.8)	37 (10.1)	<0.001*
ICS	3 (7.7)	14 (3.8)	0.466
Expectorants	19 (48.7)	38 (10.4)	<0.001*
Acute exacerbation in the past year (No., %)	21 (53.8)	94 (25.6)	<0.001*
Comorbidity (No., %)			
Hypertension	7 (17.9)	57 (15.5)	0.694
COPD	10 (25.6)	23 (6.3)	<0.001*
Asthma	2 (5.1)	32 (8.7)	0.441
Diabetes	8 (20.5)	28 (7.6)	0.007*
Malignancy	3 (7.7)	11 (3.0)	0.127

COVID- 19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease.

shown). Our finding that 37.4% of the symptomatic patients met the criteria of an acute exacerbation was consistent with the notion that viral infection could lead to acute exacerbation of bronchiectasis (8, 9, 11), possibly with secondary bacterial infection playing a role at a later stage (9, 28).

We also looked at the potential risk factors for SARS-CoV-2 infection in patients with bronchiectasis. Our survey showed that younger age and not using a bronchodilator were independently associated with SARS-Co-2 infection. There was evidence showing that patients with SARS-Co-2 infection were mostly younger than 60 years (29). Bronchodilators were recommended for patients with shortness of breath according to guidelines of bronchiectasis (15, 30–33). It was speculated that the elderly patients and patients using bronchodilators may take stricter measures for COVID-19 prevention, thus reducing the risk of being infected. For example, mask-wearing, even with the use of non-medical masks, has a substantial impact on outbreak control of COVID-19 (34). Interestingly, the odds of an individual being observed to wear a mask was higher in older adults than younger individuals (23). There are conflicting evidences on whether patients with bronchiectasis are more susceptible to COVID-19. A single-center case–control study using nationally representative data from the COVID-19 cohort and matched cohort in South Korea (20) showed that the incidence of COVID-19 was relatively higher in patients with bronchiectasis than those without bronchiectasis, and COVID-19 patients with bronchiectasis, as compared to those without, were also more likely to have pulmonary comorbidities including asthma and COPD, as well as extra-pulmonary comorbidities, such as hypertension, diabetes mellitus and heart failure. Recently, a multi- center retrospective cohort study (35) showed that bronchiectasis was not

TABLE 5 Risk factors for emergency care and/or hospital admission.

	Single-factor logistic		Multi-factor logistic	
	OR with 95% CI	*p* value	OR with 95% CI	*p* value
Age (>56)	2.548 (1.176, 5.520)	0.018*		
COVID-19 vaccination doses (>2)	0.279 (0.140, 0.554)	<0.001*		
No symptoms	0.305 (0.106, 0.880)	0.028*		
Sputum	2.663 (1.230, 5.769)	0.013*		
Dyspnea	2.985 (1.350, 6.600)	0.007*		
Wheezing	3.170 (1.429, 7.034)	0.005*		
Bronchodilators	3.964 (1.853, 8.478)	<0.001*		
Expectorants	8.225 (4.035, 16.764)	<0.001*	3.818 (1.652, 8.824)	0.002*
Acute exacerbation in the past year	3.388 (1.731, 6.633)	<0.001*	2.904 (1.358, 6.212)	0.006*
COPD	5.157 (2.241, 11.870)	<0.001*		
Diabetes	3.124 (1.312, 7.439)	0.01*		

COVID- 19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease OR: odd ratio; CI: confidence interval; *$p<0.05$.

significantly associated with COVID-19 [pooled HR 0.78 (95% CI, 0.41–1.49)], but there were still no data related to the severity of the disease.

It is worth noting that most of our patients did not make medical visits but successfully managed by themselves after infection with SARS-CoV-2. Of the patients who visited hospitals, nearly 25% needed hospitalization. It was similar to a previous population cohort study in England (8,256,161 patients) showing that 25.5% of patients with chronic respiratory diseases needed to be hospitalized with SARS-CoV-2 infection, far higher than the hospitalization rate of patients with COVID-19 in the overall population (2.2%) (13). However, our study further demonstrated the necessity of health education to enhance patients' disease awareness and self-management skills, particularly during a pandemic like COVID-19 when medical resource was allocated to emergency response.

In an outbreak of pandemic like COVID-19 when medical resources are limited, it is imperative to identify patients with exacerbated respiratory diseases who may need emergency care. Therefore, we analyzed the risk factors for emergency visit and/or hospitalization in our patients. Our results showed that these patients were more likely to be older, to have chronic symptoms of sputum production and dyspnea, to receive treatment with bronchodilators and/or expectorants, to have comorbidities including COPD and diabetes, and to have a history of acute exacerbation of bronchiectasis in the past year. A history of acute exacerbation of bronchiectasis in the past year and the use of daily expectorants were independently associated with emergency visit and/or hospitalization for patients with bronchiectasis infected with SARS-CoV-2. This result was consistent with a previous study on the impact of the COVID-19 pandemic on exacerbations and symptoms of bronchiectasis (21). The daily use of expectorants may be an indicator of frequent cough and sputum production as a manifestation of a more severe disease.

There were several limitations to our study. First, as a single-center telephone survey, the sample size was relatively small, and there may be recall bias. Second, there may be survivor bias. However, of the 995 patients who received our telephone call, 13 had died before the surge of COVID-19 in early December 2022. It is speculated that there was little impact of deceased patients on the outcomes of this survey. Third, because the patients were recruited retrospectively, and due to the time limit of a telephone survey, data related to assessment of bronchiectasis severity and etiology were not complete, such as data on the scale of dyspnea, sputum culture results, lung functions, and investigations into rarer causes for bronchiectasis which may explain the higher proportion of cases with unknown etiology in our patients. Another limitation was that of the patients who were identified as having COVID-19, 26.3% had no confirmation by a positive viral test, but only reported consistent symptoms and a history of close contact with family members with SARS-CoV-2 infection.

5 Conclusion

In conclusion, during the COVID-19 surge in December 2022 in Beijing, the infection rate of SARS-CoV-2 in patients with bronchiectasis was high. After SARS-CoV-2 infection, the majority of our patients experienced new-onset or exacerbation of respiratory symptoms (cough, expectoration and dyspnea) which lasted for a longer time. However, most of the patients infected with SARS-CoV-2 successfully managed at home. A history of exacerbation of bronchiectasis in the past year and daily use of expectorants were independently associated with emergency visit and/or hospitalization for patients with bronchiectasis after SARS-CoV-2 infection. Our survey results further underscore the importance of patients' disease awareness and self-management skills during a pandemic like COVID-19.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Peking university Third Hospital (registry M2021-428). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JunW: Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. JR: Writing – review & editing, Data curation, Investigation. XL: Writing – review &

editing, Data curation, Investigation. JuaW: Investigation, Writing – review & editing. CC: Writing – review & editing. LS: Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YS: Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The spread in time and space of COVID-19 pandemic waves: the Italian experience from mortality data analyses

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Introduction: Italy was the first European country affected by COVID-19. Thanks to governmental containment measures (9 March 2020), the spread of COVID-19 was limited. However, in this context, accurate data assessment is crucial and mortality is a more reliable indicator of the virus spread compared to the count of positive cases. This study aimed to retrospectively evaluate the impact of the pandemic in different areas of Italy using the time series analysis of official deaths and excess COVID-19 deaths.

Methods: Mortality data (23 February–30 April 2022) by Istituto Nazionale di Statistica (ISTAT) were analyzed, including four waves of COVID-19. Previous mortality data (January 2015–November 2019) were used to estimate a Poisson regression model of the pre-pandemic mortality pattern and derive the excess COVID-19 deaths as the difference between the actual deaths number and the extrapolation of the previous mortality pattern to the pandemic period, separately for Northern, Central, and Southern Italy, to compare the impact of mortality across time periods and geographical areas.

Results: Estimated excess compared with official COVID-19 mortality shows that, during the first wave, there was an underestimation of deaths. COVID-19 mortality rate almost doubled the official rate in the North (1.60‰ vs. 0.86‰) and nearly tripled it in the South (0.22‰ vs. 0.08‰). In late 2020-early 2021, official and estimated mortality curves are closer, displaying just a small gap at the start of the second wave. During the fourth wave (end of 2021-early 2022), Northern and Central Italy show reasonable agreement; the South presents a large relative underestimation of deaths (+90% increase), with a large increase in its excess deaths national quota, 9% in the first wave to 42% in the fourth.

Discussion: The results provide a measure of the COVID-19 excess deaths and an unbiased estimate of Italian mortality rates. In the first wave, the gap between official COVID-19 and excess mortality was particularly high and lockdown measures may have reduced the spread of the infection. In the fourth wave, the gap for the South increases again, probably because the healthcare system may not have coped with the prolonged pressure of the pandemic, or for a decreased compliance with the official paper-based mortality surveillance system that could be overcome in the future by digitalizing the process.

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KEYWORDS

COVID-19, mortality, containment measures, Italy, pandemic, EuroMOMO

1 Introduction

Coronavirus disease 2019 (COVID-19), started in China, rapidly became a global emergency, and was declared a pandemic by the World Health Organization (WHO) on the 11th of March 2020 (1). The pandemic was then declared to be ceased on the 5th of May 2023 (2).

Over 770 million confirmed cases, and nearly 7 million deaths have been recorded in the world.

Italy was the first European country to be affected with very high rates of contagion and death, especially in the North of the country. In continental Europe, Italy ranked third with about 26 million as number of cumulative cases, after France and Germany with about 38 million each. According to WHO's Coronavirus Dashboard, as of 5 May 2023, after the official declaration of the pandemic ending, considering mortality, Italy ranked first with more than 190.000 cumulative deaths followed by Germany with more than 174.000 and France with approximately 168.000 (3).

At the start of the pandemic, due to the rapid spread of the disease overwhelming the healthcare system, the Italian government imposed a nationwide lockdown on the 9th of March 2020 which ended on the 3rd of May 2020 (4). Thanks to the containing measures implemented by the government, the disease was thus limited, and the healthcare system was mostly able to deal with the emergency, although approximately 250,000 confirmed cases and 35,000 deaths were reported in the first wave, which occurred mainly in the north of Italy (5).

The accurate assessment of data is crucial for monitoring the spread of any viruses and informing the public and the policymakers and to direct actions toward individual and collective decisions aimed to control the pandemic (6). During the COVID-19 pandemic, there was much debate about surveillance systems and monitoring data. Different types of data (count of reported COVID-19-positive cases, number of infected and hospitalized patients, patients admitted to intensive care units (ICUs), and number of deaths) have been used, depending on the specific objective being pursued, bearing in mind that there are advantages, and disadvantages to any surveillance system that need to be taken into account when interpreting the data: the number of new positive cases recorded per day heavily depends on the number of tests administered to the population which varies with the spread of the disease (7); the relative number of unreported cases (e.g., cases identified by the individual but not reported to public health authority) increased with the increasing COVID-19 contagiousness but also with the reduction of symptoms related to the diffusion of vaccinations making the number of official daily or weekly cases even less reliable. Hence, mortality data may represent an alternative and reliable source also for COVID-19 as it is for seasonal influenza surveillance (8–10). It is however of extreme importance to precisely identify and detect the specific COVID-19 mortality contribution.

All these considered, monitoring the mortality trends of COVID-19 in the population is still important today to control for the possible onset of new virus variants, which can act as an alert for public health policymakers.

Previous study on excess mortality has been conducted both on Italian data (11–15) and data from other countries (16) and comparing mortality across countries (17, 18), mostly focusing on the first COVID-19 waves in 2020 (12–15, 18, 19) and looking at socio-demographic determinants/correlates of mortality (11).

In this context, our study aimed to investigate COVID-19 Italian mortality data, estimating the excess mortality due to COVID-19 and comparing it with the official mortality during all four Italian waves, up until 30 April 2022. An additional aim was to assess the relationship between COVID-19 mortality and national lockdown/restrictions imposed during the first, second, and third waves of the epidemic in different Italian geographic areas, namely, Northern, Central, and Southern Italy, seeking any novel insight through these data on the general performance of the Italian public health system across time and geographic areas of the pandemic.

2 Materials and methods

The first (23 February 2020–30 April 2020), the second (6 October 2020–5 January 2021), the third (1 March 2021–23 May 2021), and the fourth (1 November 2021–30 April 2022) COVID-19 waves have been studied separately with the same analysis procedure. We used data provided by the Italian National Statistical Institute (ISTAT Istituto Nazionale di Statistica) publicly available on their site. Mortality statistics are submitted to the Civil Status Offices of the municipalities. Data refer to the period 1 February 2020–31 July 2022, and the analysis has been performed using data from 23rd February (start of the first wave) up to 30 April 2022 (end of the fourth wave) (20). After the statistical analysis, the results are compared with the official laboratory-confirmed COVID-19 deaths provided by Istituto Superiore di Sanità (ISS) (21). Mortality data by ISS were collected during the pandemic in addition to the ISTAT death forms flow. Indeed, considering the exceptional nature of the pandemic and the state of emergency that has arisen, the Italian Ministry of Health issued the note 0007922 (22), commissioning the ISS to build a collection and review system on a sample of medical records transmitted to the Institute by the Regions to evaluate the main characteristics of COVID-19 deaths. The software used to perform the statistical analysis is *ROOT* (23).

From ISTAT data, the mortality due to COVID-19 was identified and enucleated from all other causes as in a counting process with the identification and discrimination of "signal" and "background" components. The COVID-19 deaths represent the signal, while any other source of mortality represents the background. The background contribution is subtracted from the total observed mortality using statistical methods, based on a maximum-likelihood fit, and it is called in the following as the "baseline." To determine the baseline an approach similar to the one employed for the analysis of European mortality by EuroMOMO (24) is performed. This is summarized by the following regression model for counts:

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$$b[i] = offset * (1 + slope * i) + amplitude * \cos((i + phase) * 2\pi / 365)$$

where $b[i]$ is the estimated number of deaths for day i from 01/01/2015 to 30/11/2019; the seasonal component is parameterized by a cosine curve with a period of 1 year, and the amplitude, the phase, and the offset are estimated from data. The offset is multiplied by a linear function to account for possible year-dependent mortality variations due to changes in the age structure of the population. The parameters of this model have been estimated from pre-COVID data corresponding to periods which do not overlap with influenza and heat waves, that is, April–May and September–November of 2015, 2016, 2017, 2018, and 2019 years.

This baseline fitted contribution has been then extrapolated to the COVID-19 wave periods and subtracted from the data to obtain the estimate of the COVID-19 excess of deaths.

$$excess[i] = n[i] - b[i]$$

where $n[i]$ is the number of deaths for day i. The fit of the baseline has been made for Italy as a whole and for the Northern, Central, and Southern Italy breakdowns.

Mortality rates (per 1,000) are calculated as the number of deaths divided by the resident population. The uncertainties of the death excess are evaluated taking into account the Poissonian error on n [i] (i.e., $\sqrt{n[i]}$) and the statistical uncertainty from the fit of baseline estimation $b[i]$.

This methodology is applied to data with different breakdowns: nationwide, Northern, Central, Southern Italy, regional, and provincial levels. These estimated numbers are then compared with the official laboratory-confirmed COVID-19 deaths (21).

3 Results

The number of deaths for the whole dataset used by the analysis is shown in Figure 1. The periods used for the baseline fit and the fit results are also overlaid. The different excesses due to influenza and heat waves and the COVID waves for the years 2020–2022 are clearly visible.

In Table 1, the results for the floating parameters in the fits are detailed, then the resulting subtracted distribution is shown in Figure 2. A dashed red line is shown at zero to better visualize the extent of the daily excess of mortality once the background has been subtracted. The excess is compared with the official laboratory-confirmed COVID-19 deaths.

The death rates for Italian provinces obtained by using the same approach for the first wave only of COVID-19 are shown in Figure 3.

A detailed description by geographical area (North, Centre, and South Islands, as Italy is usually geographically classified) of the four different waves is shown in Figures 4–6. On the graphs, the pattern of the excess mortality is compared with the pattern for the official deaths (blue).

The comparison of the mortality excess with official numbers shows that, during the first wave, there has been an underestimation of COVID-19 deaths, particularly at the beginning of the pandemic and in Northern Italy (Figure 4). The excess of mortality for the first wave started at the end of February 2020, when the first Italian case of

TABLE 1 Results for the floating parameters of the fit to the number of deaths in Italy vs. time shown in Figure 1.

	Fitted values ± 1SE
Offset	1685.9 ± 3.1
Slope	−3.3 ± 1.7
Amplitude	173.3 ± 3.9
Phase	−30.22 ± 0.58

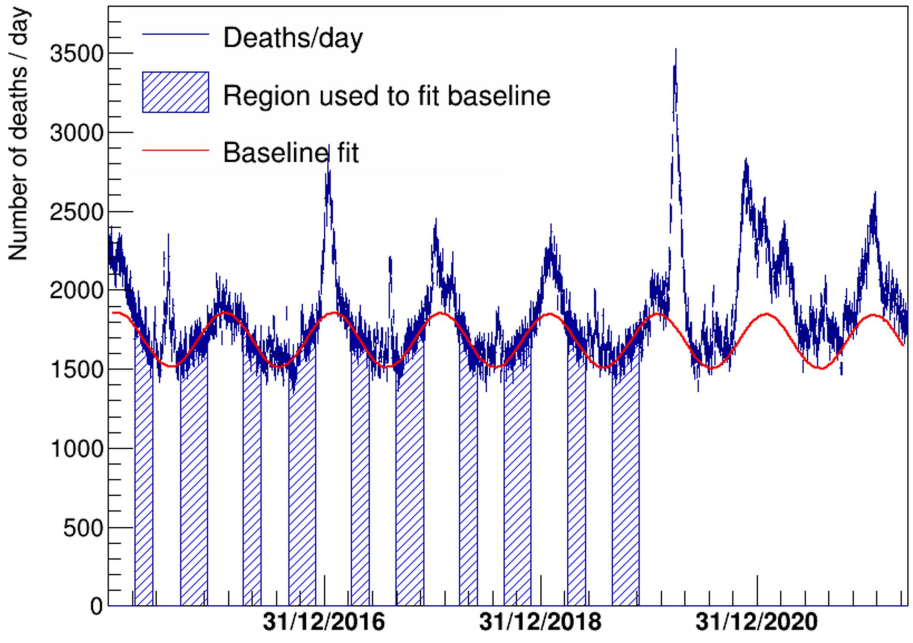

FIGURE 1
Deaths per day in Italy since 1 January 2015 shown with a blue histogram. The fitted function to describe the baseline is also shown with a continuous red line. The periods used to fit the baseline correspond to the blue regions, where the impact of influenza and heat waves is negligible.

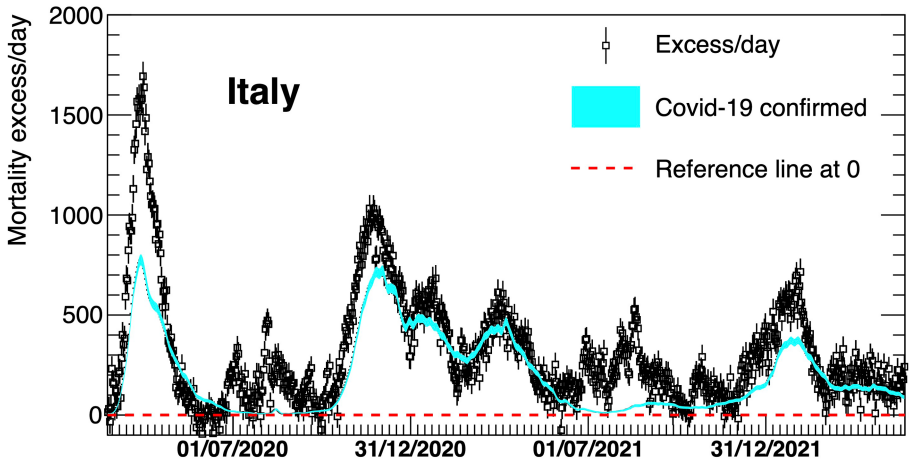

FIGURE 2
Excess in deaths per day in Italy 23 February 2020–30 April 2022. Results are compared with the official COVID-19 deaths (light blue line). Death excesses are shown with respect to zero, represented with a red dashed line.

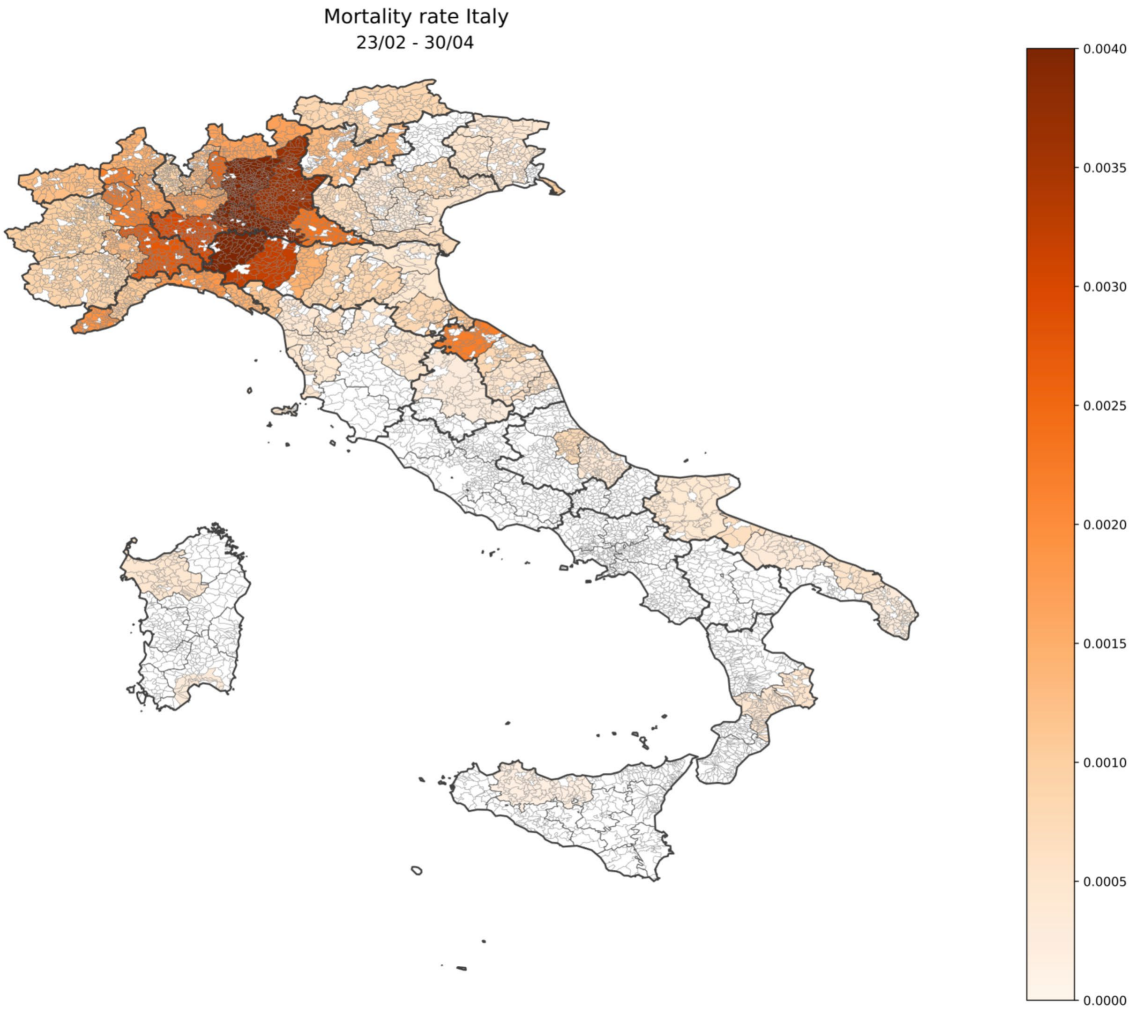

FIGURE 3
Geographical distribution of Italian mortality excess rate during the first wave of COVID-19 (23 February 2020–30 April 2020) shown in the heat map.

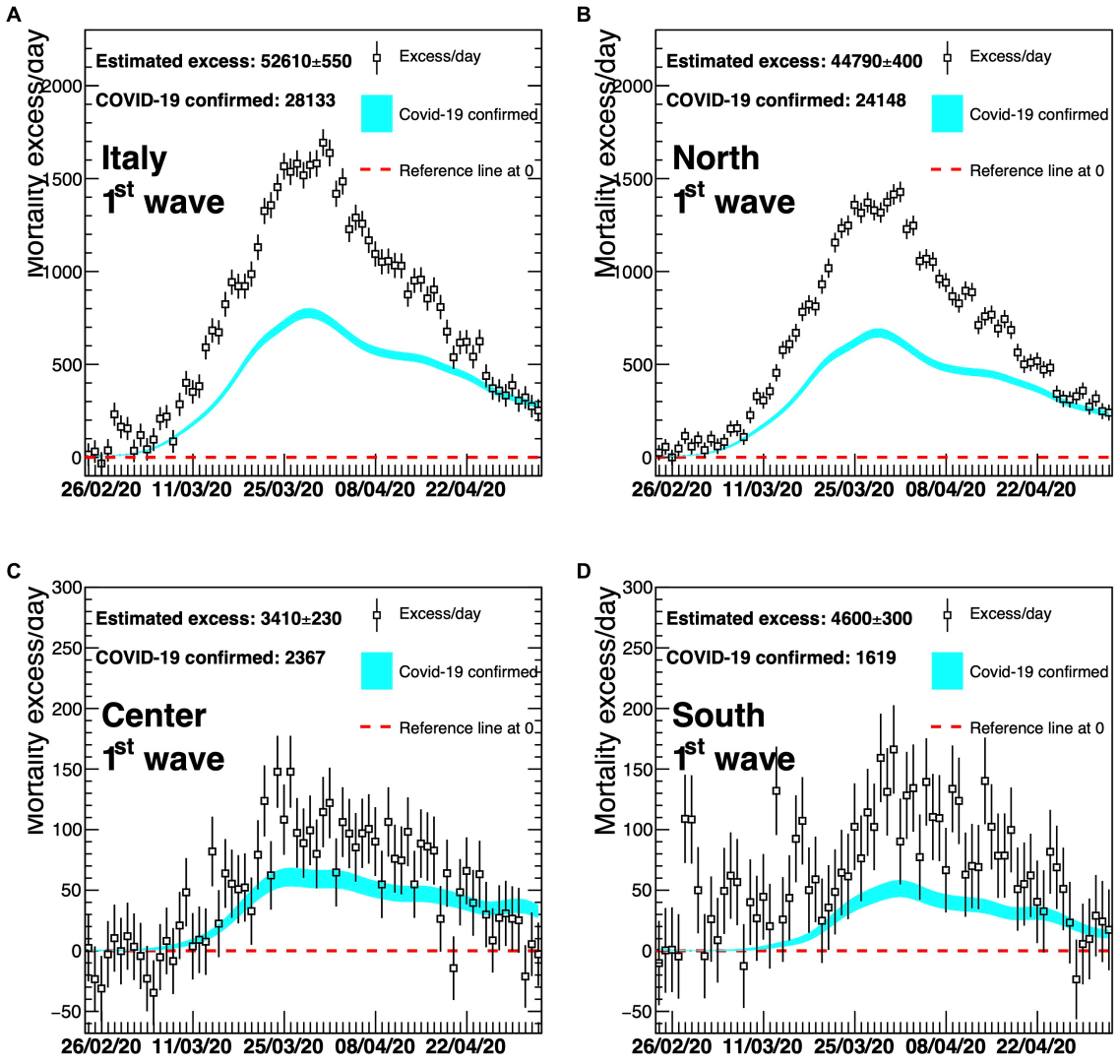

FIGURE 4
Excess in deaths per day for the first wave of COVID-19 (23 February 2020–30 April 2020) for the whole of Italy **(A)**, Northern Italy **(B)**, Central Italy **(C)**, and Southern Italy **(D)**. Results are compared with the official COVID-19 deaths (light blue line). Death excesses are shown with respect to zero, represented with a red dashed line. The vertical axis defining mortality excess/day uses a scale up to 2300 in the two top graphs **(A,B)** and a scale up to 300 in the two bottom graphs **(C,D)**.

COVID-19 was officially reported, and then rapidly increased indicating that, at the beginning of the outbreak, a large fraction of deaths was not identified by the official monitoring system.

Later, the two curves tend to be closer to each other, suggesting that the identification of COVID-19 deaths has improved with time (Figures 5, 6). In particular, Figure 5 reveals a much better agreement between the dotted (excess/day) and the light blue (COVID-19 confirmed) lines although a delay in the time of the official monitoring system is still present at the beginning of the second wave. There is a slightly worse agreement for the Southern part of Italy.

Finally, Figure 6 represents the fourth COVID-19 wave. In this case, Northern and Central Italy show a reasonable agreement, while a large relative underestimation of almost a factor 2 is present for the Southern part of the country, during most time of this wave.

The gap between the curves of the national estimated and officially registered mortality rates shown in panel (A) of Figures 4–6 reflects the geographical deviations described above.

Results in Table 2 indicate that the estimated COVID-19 mortality rate almost doubled the official rate in the first wave for the North (1.60‰ vs. 0.86‰) and nearly tripled it in the South (0.22‰ vs. 0.08‰) even if in the South the magnitude of deaths estimated and occurred was much smaller in absolute values.

During the second and third waves, there was no big difference between estimated and official mortality rates, whereas during the fourth wave not only did the South of Italy display comparatively a very substantial discrepancy (+90%), but was also characterized in this case by a high absolute excess mortality which rose to 42% of the total excess of deaths in Italy from 9% of the first wave.

4 Discussion

Accuracy, precision, and reliability are key elements of disease estimates, especially during pandemics when many articles (often

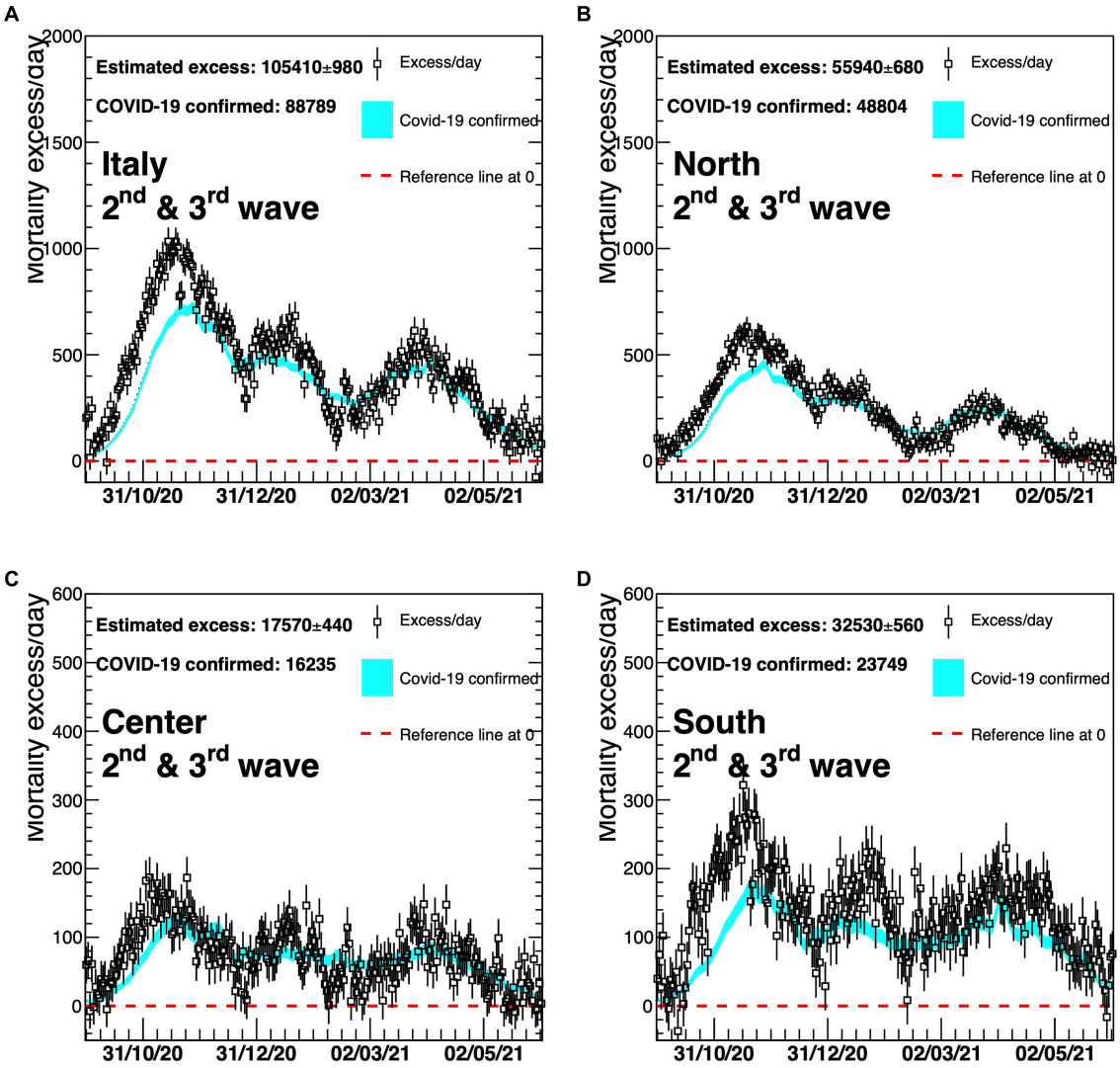

FIGURE 5
Excess in deaths per day for the second and third waves of COVID-19 (6 October 2020–23 May 2021) for the whole of Italy **(A)**, Northern Italy **(B)**, Central Italy **(C)**, and Southern Italy **(D)**. Results are compared with the official COVID-19 deaths (light blue line). Death excesses are shown with respect to zero, represented with a red dashed line. The vertical axis defining mortality excess/day uses a scale up to 2,000 in the two top graphs **(A,B)** and a scale up to 600 in the two bottom graphs **(C,D)**.

without peer review) might lead to the dissemination of flawed studies (25). In dealing with contagious and transmissible diseases, the correct estimate of the extent of deaths is very important for public health professionals and policymakers in order to mitigate the effect of transmission. In the recent COVID-19 pandemic, there was no consensus about which data were more reliable for developing containment measures such as lockdowns, quarantine, isolation, and cordon sanitaire, especially considering the possible negative implications (e.g., on mental health and on children's education) of such public health policies.

At the beginning of the pandemic, some studies reported crude numbers of COVID-19 deaths as published by National Health Authorities (21), while others expressed doubts about the observed or estimated rates connected to the emergency, the overload of the healthcare system, the avoidance of hospital care because of fear, and the absence of a diagnosis because of dying at home or in nursing homes without a microbiological diagnosis (26, 27).

The results in this study provide a measure of the COVID-19 excess deaths, extending up until 30 April 2022 previous results consistent with ours which were published, using different but comparable excess mortality techniques, on the initial 2020 wave of COVID-19 across Italy or in some specific region (12–15, 18, 19); in particular, our analyses provide novel unbiased estimates of the Italian regional mortality rates across four pandemic waves, based on time series modeling previously adopted also by EuroMOMO (24).

During the first wave, mortality turned out to be much higher than that based on official data, especially at the beginning of the outbreak. In Northern Italy, the excess of mortality was higher than in Central and Southern Italy, but all curves show a very similar shape over time. In each curve, the position of the maximum, a direct consequence of the lockdown is, as expected, very similar, and corresponds to the end of March 2020, that is, approximately 15 days after the enactment of lockdown. Thanks to this containment measure,

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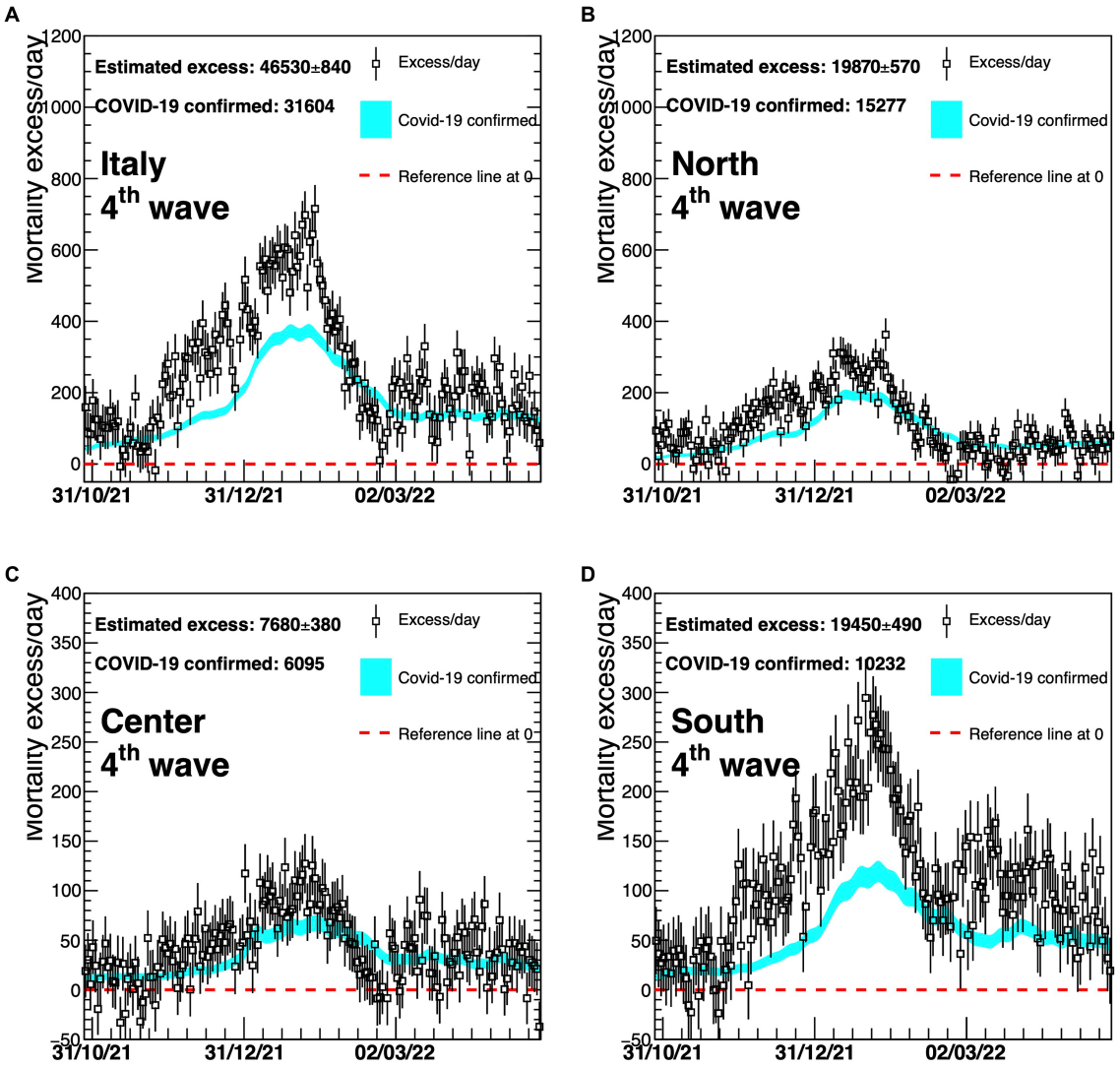

FIGURE 6
Excess in deaths per day for the fourth wave of COVID-19 (1 November 2021–30 April 2022) for the whole of Italy **(A)**, Northern Italy **(B)**, Central Italy **(C)**, and Southern Italy **(D)**. Results are compared with the official COVID-19 deaths (light blue line). Death excesses are shown with respect to zero, represented with a red dashed line. The vertical axis defining mortality excess/day uses a scale up to 1,200 in the two top graphs **(A,B)** and a scale up to 400 in the two bottom graphs **(C,D)**.

larger numbers of deaths could be prevented, even though the virus was already circulating and causing deaths in Central and Southern Italy, showing the effectiveness of this difficult policy decision at that moment, to avoid the health system collapse.

Figures 2, 5, 6 show that COVID-19 deaths decreased over time along the second and third waves; a slight rise is observed during the fourth wave coinciding with the Christmas and New Year holiday period, which in Italy are traditionally celebrated with family and friends, circumstances that could have facilitated virus spreading. Moreover, although the time profile of official and estimated mortality data looks almost the same for the second and third waves, there is a delay of roughly 10 days in the observed official data, corresponding to the difference between the maxima of the two distributions. This delay depends on the surveillance system itself which allows some days of delay after death for official communication.

In the fourth wave (Figure 6), there is a difference between the estimated and official deaths as observed in panel (A), probably due to the same gap displayed in panel (D) for Southern Italy. This could be related to different hypotheses: First, the healthcare system may not have coped with the prolonged pressure of the pandemic; second, there could have been an underreporting of official data, once the emergency period was over and vaccinations together with new COVID-19 treatments eased the pandemic fear.

A recommendation for the future could be to implement an Italian computerized statistical death form to avoid the delays connected to the use of paper forms for official death communication to the mortality surveillance system. Moreover, this tool could be more user-friendly than the paper one, helping the physician throughout the data compilation process with specific message boxes.

Finally, our study presents some limitations: There are possible potential biases represented by either a wrong baseline subtraction or

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TABLE 2 Summary of the death excess results compared with official COVID-19 mortality.

		Estimates of COVID-19 excess of deaths (± uncertainty)*	Official deaths	Estimated COVID-19 mortality rates (per 1,000) (± uncertainty)*	Official mortality rates (per 1,000)	Ratio between estimated and official rates (± uncertainty)*
First wave	North	44,790 ± 400	24,148	1.60 ± 0.02	0.86	1.85 ± 0.02
	Central	3,410 ± 230	2,367	0.28 ± 0.02	0.20	1.44 ± 0.10
	South	4,600 ± 300	1,619	0.22 ± 0.02	0.08	2.84 ± 0.19
	Italy	52,610 ± 550	28,133	0.87 ± 0.01	0.47	1.87 ± 0.02
Second and third waves	North	55,940 ± 680	48,804	2.00 ± 0.02	1.74	1.15 ± 0.01
	Central	17,570 ± 440	16,235	1.47 ± 0.04	1.36	1.08 ± 0.03
	South	32,530 ± 560	23,749	1.62 ± 0.03	1.19	1.37 ± 0.02
	Italy	105,410 ± 980	88,789	1.75 ± 0.02	1.47	1.19 ± 0.01
Fourth wave	North	19,870 ± 570	15,277	0.71 ± 0.02	0.55	1.30 ± 0.04
	Central	7,680 ± 380	6,095	0.64 ± 0.03	0.51	1.26 ± 0.06
	South	19,450 ± 490	10,232	0.97 ± 0.02	0.51	1.90 ± 0.04
	Italy	46,530 ± 840	31,604	0.77 ± 0.01	0.52	1.47 ± 0.03

*The uncertainty related to the estimated excess of deaths and rates is due to the Poissonian error in the counting and the statistical uncertainty of the background subtraction.

by the impact of other causes of death, which can be correlated with the presence of COVID-19; however, the latter does not look dominant, because the baseline-subtracted distributions show the typical exponentially-growing, Gompertz-like shape as for the official ones. In addition, the ratio between mortality excess and official data does not seem to depend on the mortality rate, as it would happen if there was a correlation with the spread of the virus: For instance, in the first wave, this ratio was larger for Southern Italy than for Northern Italy. If such a correlation had been present, we would have observed the opposite effect, as the impact of the virus had been much weaker in Southern Italy.

In future, the spread of transmissible diseases could take advantage of the use of Artificial Intelligence (AI) software support to interpret health data coming from wearables (e.g., breath or cough sounds assessment and saturation analysis) to faster detect individual infections and exploit this information to promptly alert the public health surveillance systems. This shade of digital public health can also be very useful to put into action faster mitigation measures aimed at minimizing the number of cases and deaths, during any future health threats, i.e., not only in the rare case of future relapses of COVID-19, but also for pandemics that may develop in the near future from other viruses, such as Influenza viruses or any new virus that may spillover and that cannot be clearly foreseen at the moment we are writing the article.

In conclusion, the methods we used are to be considered as tools for Public Health professionals to monitor mortality and help detect future emergency scenarios, avoiding the lack of preparedness that characterized the COVID-19 epidemic in Italy.

For Figures 4–6, panel (A) corresponds to upper left, panel (B) to upper right, panel (C) to bottom left, panel (D) to bottom right.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.istat.it/it/archivio/240401.

Author contributions

DR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Visualization, Writing – original draft. LP: Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. PM: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft. LS: Formal analysis, Software, Visualization, Writing – original draft. ML: Formal analysis, Supervision, Writing – original draft. MA: Formal analysis, Supervision, Writing – original draft, Writing – review & editing. MC: Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Field based research in the era of the pandemic in resource limited settings: challenges and lessons for the future

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The coronavirus pandemic that began in December 2019, has had an unprecedented impact on the global economy, health systems and infrastructure, in addition to being responsible for significant mortality and morbidity worldwide. The "new normal" has brought along, unforeseen challenges for the scientific community, owing to obstructions in conducting field-based research in lieu of minimizing exposure through in-person contact. This has had greater ramifications for the LMICs, adding to the already existing concerns. As a response to COVID-19 related movement restrictions, public health researchers across countries had to switch to remote data collections methods. However, impediments like lack of awareness and skepticism among participants, dependence on paper-based prescriptions, dearth of digitized patient records, gaps in connectivity, reliance on smart phones, concerns with participant privacy at home and greater loss to follow-up act as hurdles to carrying out a research study virtually, especially in resource-limited settings. Promoting health literacy through science communication, ensuring digitization of health records in hospitals, and employing measures to encourage research participation among the general public are some steps to tackle barriers to remote research in the long term. COVID-19 may not be a health emergency anymore, but we are not immune to future pandemics. A more holistic approach to research by turning obstacles into opportunities will not just ensure a more comprehensive public health response in the coming time, but also bolster the existing infrastructure for a stronger healthcare system for countries.

KEYWORDS

COVID-19, field research, remote research, telephonic survey, digital health, LMICs

Introduction

In December 2019, the city of Wuhan in China reported the first human case of the novel coronavirus infection caused by the SARS-CoV2, a disease that we now know as COVID-19. The outbreak spread globally soon after, with the World Health Organization (WHO) declaring COVID-19 a global pandemic on March 11, 2020 (1). Three years on, the total number of confirmed COVID-19 cases (as of March 10, 2023) worldwide are

more than 676 million, while the total number of confirmed deaths stand close to 6.9 million (2). The pandemic has resulted in huge economic losses, a breakdown of the fragile health infrastructure especially in the lower- and middle-income countries, and a significant increase in poverty and unemployment, above and beyond the high mortality and morbidity rates in the affected populations (3–7). The effects of COVID-19 have thus been far-reaching, and we continue to grapple with multiple concerns encountered in this "new normal".

One of the greatest unrivaled challenges faced by the medical and scientific communities has been the disruption of non-coronavirus related clinical and public health research activities with trials and field studies getting delayed or prematurely concluded (8–11). Protocols like maintaining physical distancing, restricting travel and avoiding gatherings and meetings to lower the risk of transmission of this highly infectious viral disease, as well as redirection of existing funds for pandemic research, have made field-based research work involving human participants in healthcare settings like hospitals and clinics as well as in the community rather challenging (10, 11). Although non-COVID research took a hit across countries, low-middle-income countries (LMICs) have suffered a greater impact due to amplification of existing difficulties (12). As a response to this, researchers across the globe have shifted to virtual or remote methods of collecting study data during the pandemic (13, 14). This involves telephonic and tele-conference methods, as well as web-based applications to communicate with the participants, while ensuring the wellbeing of everyone involved in such studies. Digital approaches and the use of technology have thus gathered immense momentum in the last 2 years since they allow people to participate without worrying about exposing themselves to the infection. Such methods make it easier for the researchers to continue their work safely, while adhering to COVID-19 appropriate mandates. Various remote methods have been in use in high-income countries, such as interactive voice response (IVR), computer-assisted telephone interviews (CATI), short message service (SMS) and video conferencing (via zoom/skype), for both qualitative and quantitative purposes (13, 15). Due to lower levels of education and internet access and availability issues in spite of extensive use of mobile phones in low and middle income countries (LMICs), telephonic methods are more common and preferred over online internet-based methods (16). However, such approaches come with their own set of complications, especially in developing nations. Such challenges have been further augmented by COVID-19 (17).

Our paper aims to document the significant impediments to epidemiological research amidst the pandemic, in a resource-limited setting, based on our experience of conducting a hospital-based observational study in North India, substantiating them with existing evidence in this regard. We also propose ways to address some of these setbacks and suggest feasible solutions. Our research study is an ongoing prospective cohort involving in-person recruitment of patients on statins from the cardiology outpatient department of a tertiary care hospital in Delhi, and subsequent remote data collection telephonically, for a 2 year follow-up period with data obtained at baseline, and at the end of the first and second years.

Barriers to conducting field-based research during the COVID-19 pandemic

Economic constraints, lack of awareness and skepticism

The health system in the LMICs comprises of both private and public health care facilities and a significant proportion of the population opts for private health centers (18, 19). According to a few published reports, the private sector accounts for a considerable share of healthcare services in developing economies and caters to the lower income groups as well (40%, 57% and 62% in the African, South-East Asian, and Western Mediterranean regions) (20–22). The population groups that cannot afford private healthcare services are thus dependent on large public tertiary care centers offering medical care at a highly subsidized cost (18, 19, 23). Thus, in developing nations, a significant proportion of the patients at tertiary care centers belong to the lowest socio-economic strata.

The literacy levels in patients are also rather low, with studies reporting a 30%—45% prevalence of low to no education across LMICs (24–28). This in turn leads to a sub-optimal level of health literacy, i.e., their understanding and knowledge of their disease condition and medications. Limited awareness of clinical research and its relevance have also been reported as deterrents to research interest and participation in a few studies (29–34).

The pandemic has exacerbated this challenge. Remote interactions are now more feasible and safer as compared to in-person interactions, and it is difficult to explain things telephonically and convey the point across as effectively as one would, in a face-to-face setting (35). Gaps in communication act as hindrances to data collection. Also, building trust without an in-person interaction requires both patience and time, since a phone call doesn't offer the same personal touch (13, 36).

Unavailability of digital records and the use of paper-based prescriptions

Large government/public hospitals have a high burden of patients, a heavy footfall in their Out Patient Departments (OPD) and limited resources (37, 38). The existing infrastructure makes it difficult to establish and maintain digital records or online databases for admitted patients and OPD patients in most such facilities. Unlike the west, the implementation and use of electronic medical record (EMR) systems in the LMICs remains rather minimal, and is limited to a handful of private tertiary care centers, while an overwhelming majority in the private and public sector still work with paper-based records (39–44). Additionally, the paper-based prescriptions are usually available only with the patient (45). Prescriptions and other documents like test reports and discharge summaries tend to get lost, torn or misplaced, and unavailability of records makes it impossible to track patients or obtain their history remotely (46).

Ensuring correctness of contact information

Since remote modes of data collection are largely dependent on establishing contact through a mobile phone in resource limited settings, the contact information provided to the researcher is of prime importance. However, the numbers provided for the call may turn out to be erroneous or out of service, leaving the investigators with no choice but to drop the participant. At times the contact number may stop functioning due to inability of patients/caregivers to recharge/top up the talk time given the financial constraints exacerbated by the pandemic. This also gives rise to the need for multiple contact points within the participant's family, so that if the primary phone number turns out to be incorrect or non-functional, contact can still be established through alternate numbers. This is a time-intensive activity since the respondents' family/friends need to be contacted first, in order to be able to communicate with the participant (36).

Dependence on smart phones and instant messengers

Remote data collection methods involve the use of a smartphone with an internet connection and instant messaging apps like WhatsApp. This can be used to obtain drug prescriptions, biochemical test reports, scans and other such source documents from the patient. According to a 2023 report, more than half of the world's current population, now owns a smartphone, with 4.3 billion users (47). WhatsApp messenger is also gaining momentum for use in population-based surveys and provides new opportunities for enhanced communication and engagement during fieldwork (48). However, its use is currently limited in LMICs and both its potential and concerns with respect to data collection in health research need further exploration (49). Also, roughly 3 billion people, about 38% of the world population, despite living in mobile broadband network areas, do not use the Internet (47). Therefore, participants with limited means, especially those in the older age groups, may not possess a smart phone/WhatsApp, or may not be well versed with its functioning and correct usage (50, 51). In such cases, gathering data becomes an arduous task (36, 52).

Connectivity and network issues in rural areas

The economy has taken a massive hit as a result of the pandemic. This has led to a significant increase in unemployment, which in turn has pushed the working class into poverty. Consequently, a large number of people belonging to the lower socio-economic strata had to migrate back to their ancestral homes often in remote rural locations (53–55). This has inevitably affected data collection procedures adversely. Network and connectivity play a major role in carrying out remote research work. City outskirts, suburban and rural areas may not have adequate network coverage which results in weak signals, call drops and patchy internet connectivity (13, 16). Each interview with a participant residing in such a location takes longer and usually involves more than one call making it a time-intensive endeavor. These disturbances and interruptions also hamper the overall quality of the data collected during remote telephone-based interviews (36). Virtual modes of collecting research data have compounded the already existing digital divide, putting the economically weaker participants at a disadvantage in many aspects (14, 56).

Decreased patient footfall in the hospitals

There is often a dearth of tertiary care health services in low- and middle income countries (LMICs). Tertiary care hospitals even when available, are present only in the major cities (57, 58). Hence, they cater to patients not just from the same city, but also from various neighboring cities and regions across the country. In the wake of COVID-19, health related travel went down, unless there was a medical emergency or a health condition that required immediate attention. This could be to avert the risk of infection and to avoid spending money on inter-city travel at a time when finances are rather limited. As a consequence, the total number of patients visiting these health facilities was much lesser than it used to be pre-pandemic (59–62).

Lesser footfall means a smaller sampling frame to choose from. This leads to longer periods of recruitment and contributes to delays in study conduct. Progress of studies requiring in person follow ups can be expected to be hampered similarly. Transport and distance related concerns have always been barriers to participating in field based research that have been further compounded during the pandemic times (32).

Issues with privacy

Unlike in-person interviews, where the investigator can choose an appropriate setting for the patient to be in, interviews conducted remotely do not offer the same flexibility in terms of the surrounding environment of the participant (63). Often, participants when called, are at home, sitting with their family members. Space constraints and overcrowding with several people living together makes it almost impossible to talk to the participant privately. Sometimes participants find a place outside their homes where they may be joined by a neighbor or a friend (13, 14). In face-to-face settings, the researcher has significant control on the environment and can ensure privacy at all times. However, this onus is placed on the participants in remote research (13). Such situations act as obstacles to data collection which ideally requires a silent area. It thus becomes difficult to ensure confidentiality and accuracy of responses which affects validity of the data and continued participation (34).

Ethical challenges

Conducting research during a pandemic is essential as well as necessary, but the appropriateness of the same may be debatable. Subjecting the participant to an extensive interview or survey during unprecedented times when people are struggling with a deadly virus, monetary losses and other peculiar disruptions in the wake of a global pandemic could pose a moral dilemma. Additionally, obtaining verbal consent in remote research work comes with its own set of challenges, in terms of maintaining a record of the consent obtained, while being mindful of privacy and mitigating the risk for coercion, in order to maintain the voluntary participation requirement. This becomes an even more important consideration when dealing with vulnerable groups or studies involving sensitive topics (17). Remote data collection may also put a greater responsibility on the participants, in terms of getting their phones recharged, figuring out the use of WhatsApp or other remote data collection apps, and finding an appropriate space at home to respond to the investigator's calls. On the contrary, such methods relieve the participants of the burden associated with spending time and the opportunity cost to travel to the study setting/hospital, and in many cases, missing out on their daily wages. Such issues often find themselves at the center of debate and discussion. The pros and cons of this conundrum need to be weighed for every research study, following which it should be dealt with in a manner that is sensitive, does no harm to participants while also ensuring that science and biomedical research are not unduly hampered by the pandemic (13).

Increased frequency of non-response and higher attrition rates

Conducting research using remote methods like mobile phones can lead to a higher non-response rate in the study population (64, 65). Response rates ranging from 40 to 55% for telephonic surveys and interviews have been previously reported in literature (66–70). Higher non-response has been correlated to older, less affluent and less educated individuals, and is found to be affected by connectivity and low internet bandwidth issues too (65–68, 71). This becomes even more relevant when it comes to living in small crowded spaces, joint phone ownership in the family and limited availability of resources to maintain digital connectivity, along with mistrust in unknown numbers and misconstruing calls as being phishing/spam (13, 16). Also, the older adults are sometimes uncomfortable speaking over the phone and prefer a face-to-face discussion which could be a reason for their refusal to participate. At times, this translates to women and the aged being under-represented owing to lack of autonomy and independence in the household (13). In some patriarchal settings, the male spouse may choose to respond on behalf of the female which affects the accuracy of the answers (13, 72). Moreover, since mobile phones are the predominant mode of communication, tracking participants down for follow-up investigations and interviews is an uphill task too. Once they are aware of how the telephonic survey would go, some of them stop taking follow-up calls saying they don't have time for another round of interview, or that they don't understand the reason for a second call (13, 16). Also, a majority of mobile phone users subscribe to prepaid connections (73, 74), which are more likely to get discontinued, and thus could immediately cut the participant off from the researcher. Thus, remote surveys might run the risk of a higher dropout rates and greater loss to follow-up, as compared to in-person studies (75). It is possible that such studies have a slight overrepresentation of people belonging to the higher socio-economic groups, those with access to individual smartphones and ability to use the internet, those with higher literacy and those living in relatively less crowded homes (13, 76).

Maintaining respondent engagement and interest

Ensuring the interest and attention of the respondents over a phone call is rather demanding. Additional efforts need to be made to keep participants engaged since this can affect the overall quality and accuracy of the collected data (64). This pertains to very young and very old individuals, who may get bored or lose interest and hang up in the middle of the interview, leaving responses incomplete. Longer interactions/questionnaires may further fatigue or distract the participants, leading to the information captured being unreliable and/ or invalid (16, 36).

Possible solutions for conducting field based research in a pandemic scenario

Clinical research is vital to reducing disease burden, enhancing health, and increasing the overall quality of life in populations. It also provides insights into disease pathology and epidemiology that can help scientists and researchers tackle new diseases and improve patient outcomes (77, 78). Thus, research becomes even more essential during a public health crisis. Even as the COVID-19 pandemic subsides, the challenges of conducting research, especially remotely, continue to exist. We have provided insights based on our experience with quantitative research. However, the restrictions that come with a pandemic have equally affected qualitative research as well (79–81). In fact, there are several overlapping issues affecting both the approaches to health research conduct, while some remain unique to each methodology (82). The following section describes possible solutions to address some of the barriers highlighted above (Table 1).

Improving health literacy

The World Health Organization defines health literacy as 'the achievement of a level of knowledge, personal skills, and confidence to take action to improve personal and community health by changing personal lifestyles, and living conditions' (83). In other words, it is the ability of a person to make sense of health related information so as to implement the same in their routine activities, and augment their quality of life (84). Health literacy rates in the developing countries are significantly low, owing to inadequate

TABLE 1 Selected barriers and possible solutions for conducting field research during a pandemic.

Barriers	Possible solutions
Economic constraints, lack of awareness and skepticism	Optimized fund allocation Improving health literacy Encouraging science communication Enhancing participation in scientific research
Unavailability of digital records and the use of paper-based prescriptions	Digitization of patient health records
Ensuring correctness of contact information	Digitization of patient health records
Decreased patient footfall in hospitals	Digitization of patient health records and establishing robust remote research systems
Issues with privacy and ethical challenges	Reminding participants of research context Ensuring flexibility in timing of communication Transparency regarding risks involved and process of data collection and utilization
Increased frequency of non-response and higher attrition rates	Improving health literacy Encouraging science communication Enhancing participation in scientific research Optimized fund allocation Utilizing technological advancements
Maintaining respondent engagement and interest	Improving health literacy Encouraging science communication Enhancing participation in scientific research Addressing research hesitancy and building trust

education, economic constraints, and other socio-cultural barriers (84, 85).

Improving health literacy among populations can enable people to play a more active role in their treatment and overall health. Targeted health interventions focused on populations with limited or no health literacy can improve their understanding of their health, reduce skepticism toward scientific research, enhance treatment compliance and strengthen doctor-patient relationships (86). This would ultimately augment interest in research participation and support remote research activities in the long term. Better knowledge of their own health, clinical care and the relevance and need for research could improve response rates and encourage willingness of the participants to contribute both in-person and virtually.

This would require improvements in the existing health infrastructure to support access to relevant health information, more manpower for engagement with medical professionals as well as the general public, and encouraging the practice of science communication in healthcare for communicating information to the patients in a language and manner they understand. Easy to read infographics, posters and pamphlets prepared in local languages, training health educators for interacting with communities, integrating health literacy in the educational curriculum in schools, and sensitizing researchers, scientists and medical professionals about this issue have been shown to be effective in this regard (84, 87). However, it is important to note that health literacy is a complex issue which is a function of various systemic factors like linguistic, social and cultural barriers, poverty and lower standards of living, gender disparities, as well as shortcomings of the current education system, which in turn result in lack of basic education and sub-optimal literacy levels overall (88–92). Addressing these fundamental concerns through policy level changes and national reforms, with various stakeholders working synergistically, is a starting point that would eventually contribute to improved health literacy levels as well.

Encouraging science communication

Science communication (SciComm) has gathered a lot of momentum over the years, as a result of growing interest of educators, scientists and communication experts in this field. It is based on the broad concept that distinguishes information availability and accessibility. Readily available medical information in research papers, textbooks, newspapers, may not be accessible to the layperson. Also, accessibility itself does not ensure usability. Technical jargon, unfamiliar vocabulary and complex texts can act as major hindrances to uptake of information by the general population. Science communication aims to bridge this knowledge gap, by making important information available and accessible to the public, through simpler narratives translated in multiple languages, for easier consumption (93–96). A good example of SciComm is clinicians communicating information about a disease condition to a patient (explanation of their illness, the treatment regimen, adverse-effects if any, and precautions to be taken) in a simplified manner and in the vernacular language specific to that region. It is an ecosystem that encompasses numerous stakeholders, each with a designated role, and involves multiple communication pathways -digital, verbal, visual amongst others (93, 97).

Changes at the individual as well as the policy level can contribute to improved health literacy through SciComm. There is a dearth of literature on the effect of various interventions on health literacy rates in resource limited settings, warranting the need for extensive research to understand economic implications of low literacy rates and the cost-effectiveness of various interventions- traditional/learning based (booklets, pamphlets), art based (storytelling), interaction based (peer-support programs) and technology based (digital devices and websites) (88, 98, 99). However, evidence from the developed world settings does suggest that higher literacy could prove to be cost-effective since lower health literacy levels are associated with higher medical costs (100, 101).

Digitization of patient health records

An electronic health record (EHR) is a collection of medical records of a person that are created during a clinical event and get accumulated over their lifetime. Maintaining an electronic database helps keep a record of important medical information and history of the patient, avoid repeat investigations and improve the overall therapeutic experience for both care providers and receivers. The public sector IT system needs improvements in terms of internet speed and connectivity issues. Apart from data protection concerns, setting up infrastructure for digital systems is resource intensive and requires personnel (102). Other challenges

that hamper the broader implementation of digital record systems in healthcare include limited financial backing, lack of processes for data integration, inadequate training and capacity building, low education levels, legislation and policy gaps, and concerns with cyber security laws, ethics and regulatory bottlenecks (103–106). Filling these lacunae is a herculean task and would require concerted efforts over time but can have a substantial positive impact on public health research and contribute to more robust evidence synthesis. Digital records become even more essential in remote research where participants might be required to furnish information through mobile phones. Availability of medical documents and other records in an online format could enable easy access for participants as well as easy sharing with the study investigators, ensuring completeness of the medical data obtained from each participant.

As part of the above, shifting to e-prescriptions can make doctor-patient consultations a much more seamless experience. Paper based prescriptions are prone to errors, can have handwriting issues, and run the risk of getting lost or misplaced, leading to permanent loss of crucial patient information and disease history (107–109). Some physicians have also suggested incorporating printed terms for "Morning," "Afternoon," and "Evening" in different local languages on the prescription sheet to overcome the language barrier (110). Keeping a scanned copy of the patient prescription with the consulting doctor/hospital is also believed to be a useful way of ensuring that a record of the patient history exists with the hospital in case the patient loses or forgets to carry it with them (110). Additionally, there is literature evidence to show that hospitals with electronic patient health records incur lower costs due to fewer errors and a more streamlined management system (111).

However, one needs to remember that the transition from paper based records to electronic records can only happen in phases, with establishments gradually shifting to a hybrid mode before operating in a paperless fashion. Even then, the paper based approach has its own advantages that cannot be overlooked or rendered redundant and while digital technology is the future, offline documentation can always serve as a backup repository for data storage.

Enhancing participation in scientific research

People's willingness to participate in a study, whether hospital-based, field-based or remote, is one of the most pivotal aspects of clinical research. Acknowledging systemic and individual level hurdles in this regard is the first step toward enhanced participation rates at the start of the study and reduced attrition while it is ongoing. Systematic reviews conducted in the past have suggested a few factors that could effectively favor participation in research (34, 95, 96, 112).

Providing clarity regarding short-term or long term benefits for the participant

Patients are found to be more likely to participate in research studies if they are convinced that the output will benefit their health. It is essential to be transparent as well as realistic with participants in terms of what they can expect from their involvement (34, 95, 96, 112). Additionally, efforts should be made to make them understand that research is not the same as medical care and immediate treatment benefit may not be a possibility (95).

Instilling a sense of altruism

The feeling of being able to contribute to collective good has been found to influence patients' decision to participate in research in some cases. Making them aware of the larger goal of improved therapeutic experience and enhanced clinical care for future patients could serve as an impetus for participation (113, 114).

Sharing details of any risks involved

Adequately informing participants of any major or minor risks involved can ensure greater trust in the research process, which in turn could positively impact participation rates. This requires detailed patient information sheets and availability of the study team/personnel for answering questions and addressing apprehensions (34, 96).

Maintaining transparency in data collection and utilization processes

Various approaches to garner greater confidence in the research and its findings have been suggested in literature, including sharing of study data where applicable, dissemination of results among the participants, and keeping them updated about the study progress along with other stakeholders (34, 95, 96, 112). The language and terminology used for communicating such information plays a crucial role in communication (34, 95, 96, 112).

Facilitating access to the healthcare provider

In tertiary care public health facilities, the doctor-patient ratio is highly skewed, resulting in heavy patient loads in most outpatient as well as inpatient departments. Making efforts to provide participants better access to therapeutic care, especially where the clinician researcher is leading the study, could also serve as a significant impetus to continued participation and retention in the study (34, 95, 96, 112).

Addressing research hesitancy

Tackling skepticism about research among the patients is paramount. Alleviating their concerns with empathy and establishing the importance of their participation through regular engagement and communication can help avoid feelings of distrust and apprehension toward research (34, 95, 96, 112).

Building patients' trust in the researchers

Rapport building is an essential component of any clinical research study. Being available for the patients, providing them with a contact number they could use and setting aside some time to

address any queries they may have, related to the ongoing research or the clinical care, could be a source of validation for them, lowering their reluctance to engage with the investigators over the course of the study (34, 95, 96, 112).

Further, remote data collection brings along some peculiar issues pertaining to privacy, the participant's overall understanding of the setting (since they are usually in their homes), establishment of initial contact, and internet and connectivity hassles. The following ways could ensure greater willingness to participate in such studies and lower the risk of attrition (14, 115).

Reminding them of research context

Remote research involves participants attending interviews from their homes, instead of being present in a formal setting. This can lead to them forgetting the purpose or context of the investigator's call. In such cases, reminding them of the purpose of the study can improve data quality while allowing participants to speak comfortably (14, 115).

Offering alternative times for communication

Participation in research while being at home means less stringent schedules for investigators to operate within. Additionally, pandemic related disruptions can further interrupt people's daily routines and data collection may not always happen as planned. Sending a reminder beforehand, as well as providing a different time slot based on the participant's convenience saves the researchers' time and the flexibility keeps the participant interested (14, 115).

Working closely with their friends/family

Establishing more than one level of contact could help minimize drop outs and loss to follow ups. Efforts to obtain contact information of a family member, or friend who is either a caregiver, accompanies the patient for their hospital visits or is involved in any other aspect of their treatment becomes important if access to the patient is getting difficult (14, 115). Communication with a family member could also ensure greater trust from their end.

Optimizing fund allocation

Since remote research involves much lesser travel to the hospital/clinical setting, provisions could be made to divert that component of the study grant toward providing call and internet services to the participants (14, 115). Enhanced access to technology through resource optimization can streamline the process of study data collection considerably and ensure continued participant engagement (14, 115).

Utilizing technological advancements

A remote research setting may not always allow immediate communication with the participant. Technological features like voice notes in WhatsApp can come in very handy in situations when a voice call is not feasible. Besides, text reminders for upcoming or missed follow-up calls can be helpful in ensuring participant availability at scheduled times (14, 115). This could foster continuity in research and can help keep the participants engaged during follow-ups.

Conclusion

The pandemic has significantly altered the world we live in, bringing in a multitude of changes in various aspects of our routine lives. This has inevitably affected the way we conduct field-based research activities as well. Some of the challenges are unfamiliar, while others have just resurfaced or been magnified. However, the myriad of issues associated with carrying out primary research also bring opportunities to work differently and perhaps improve and strengthen the existing systems in place.

Remote research comes with its own set of concerns, but can also be highly effective in organizing routine surveillance measures for timely capture of health-related data. Addressing the barriers highlighted above through leveraging technology, investing in health infrastructure, and facilitating greater awareness can modify our overall approach to research.

The worst of the COVID-19 pandemic has come to an end, but we are not immune to threats of future epidemics (116–120). Further, the lessons learned during this period can elevate existing research processes as a whole, fostering greater opportunities for scientific advancements in the coming time. Even when traditional methods of face-to-face research are possible, remote methods can help save time and money that could be employed elsewhere to improve the efficiency of field-based research. This transition may not be straightforward and would require being more receptive to incorporating newer ideas into our usual ways of conducting health research. However, the outcomes would be rather rewarding and worth the effort in the long run.

Author contributions

RM: Conceptualization, Investigation, Methodology, Resources, Writing—original draft. TL: Methodology, Project administration, Supervision, Writing—review & editing. SG: Methodology, Project administration, Supervision, Writing—review & editing. HI: Methodology, Supervision, Writing—review & editing. RD: Methodology, Supervision, Writing—review & editing. AK: Conceptualization, Methodology, Resources, Supervision, Writing—review & editing.

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The effects of the first wave of COVID-19 restrictions on physical activity: a longitudinal study from "step into health" program in Qatar

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Introduction: The COVID-19 pandemic led to restrictions that prevented physical activity in public places. This study sought to conduct a comprehensive longitudinal analysis of how lockdown policies in an Arabian Gulf country influenced the patterns of physical activity during first wave.

Methods: In a longitudinal study design, members of the ongoing "Step into health" community-based health promotion program who provided valid pedometer data from January to August 2020, covering pre, during and post-covid first wave period met the inclusion criteria.

Results: 420 (76.7% men, 13.8% ≤40 years) were included in the study. Overall, significant decline in daily step counts was recorded (–1,130 ± SE302) after the implementation of lockdown policies ($p < 0.001$). When the restrictions were removed, the steps per day were still lower compared to pre-covid for men (–910 ± SE610, $p = 0.017$) and among individuals with normal BMI (–1,304 ± SE409, $p = 0.004$). The lockdown in Qatar did not significantly affect women and individuals with obesity who already had lower daily steps pre-covid.

Discussion: The present study confirms immediate decline in daily steps imposed indirectly through the COVID-19 lockdown measures. Participants with higher physical activity levels pre-covid experienced significant decline in step count during and even after restrictions were uplifted.

KEYWORDS

physical activity, pedometer, COVID-19, pandemic, lockdown, longitudinal study

1 Introduction

At the onset of the first wave of the coronavirus disease (COVID-19) in the State of Qatar, the Ministry of Public Health implemented a nationwide lockdown and restrictive measures that included social distancing, quarantine and self-isolation. Although lockdowns were essential to limit the spread of the disease, they brought about important changes in lifestyles and behaviors that had undeniable consequences on mental (1) and physical health (2). With the closure or limited access to work places, educational institutions, outdoor spaces, or fitness/sports centers, people spent most of their time confined at home, either working or engaging in leisure screen-based activities (3). In addition, many adults were also presented with increased household and childcare commitments. As a result, a general decline in physical activity was reported in most studies in different parts of the world (4) as well as an increase in sedentary behaviors during COVID-19 lockdown (5, 6).

The World Health Organization (WHO) recommends adults to engage in a minimum of 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity per week for substantial health benefits (7). Engaging in regular physical activity is crucial for maintaining good health, preventing chronic non-communicable diseases, and improving mental health and well-being (8). Being active has also been linked to lowering the detrimental impact of COVID-19 measures on health as well as reducing the gravity of the infection (9, 10).

As the COVID-19 pandemic continued, the WHO and other international organizations issued specific physical activity guidelines for times of lockdown (e.g., home-based exercises), urging people to remain active and break up sedentary behavior (11). In addition, the most reported barrier to physical activity (i.e., lack of time, (12) was no longer a concern for some people for which an increase in physical activity was observed during lockdown (13, 14)). However, despite the fact that some were presented with new opportunities to remain or become physically active, a general decline in all intensity levels of physical activity (15) and increase in sedentary behaviors were still observed for various populations including children and medical patients (16).

Four studies from the Arabian Peninsula also indicated such declines in physical activity. For instance, 52% of the 2,255 adult participants from Saudi Arabia reported a decrease in their physical activity levels, which was significantly associated with gains in weight (17). In UAE, (18) revealed that 38.5% of the 1,012 adult participants did not engage in physical activity and 36.2% of them spent over 5 hours per day on screen-time activities for entertainment. Additionally, a third of adults living in the State of Kuwait reported engaging in less than 30 min of physical activity or exercise per week during the COVID-19 lockdown (19). Finally, a study conducted in Qatar found that the COVID-19 quarantine also negatively impacted physical activity levels, resulting in a decrease in physical activity (especially moderate-intensity), increase in sitting time, and fewer walking days of at least 10 min per week (20). However, to our knowledge, all studies from the Gulf Peninsula region used subjective measures (i.e., self-reported questionnaires and surveys), lacking objective assessment of physical activity patterns.

In response to the challenges posed by the COVID-19 pandemic, many countries have closely monitored national public health programs. The 10,000 Steps Australia program that included more than 400,000 participants showed that the detrimental effects of lockdown on step count were consistent across age groups and genders (21) and disappeared after the ease of restrictions. Another longitudinal study from Japan found decreases in average step count during the lockdown period, mostly affecting women and non-older people (22). The Step Into Health (SIH) program in Qatar is one such initiative, engaging the community to adopt a more active lifestyle by promoting walking (23). The availability of pedometer data from the Qatar's SIH program offers a rare opportunity to gain an objective understanding of the impacts of the COVID-19 pandemic on physical activity. Therefore, the purposes of the present study were to: objectively assess changes in daily steps during the first wave of the COVID-19 pandemic and lockdown in Qatar and identify the population characteristics associated with these changes. In Qatar, half of the population do not engage in regular physical activity, while 82% of middle-aged women do not engage in any form of physical activity (24). However, it is important to mention that participants in such studies are usually considered "diligent" as formulated by (22) or motivated to use pedometers on a daily basis and regularly upload their records. Therefore, the analysis of a specific "health-conscious" part of the population with daily step counts higher than reported averages in the general population (21, 22) would provide unique insights into the impact of the pandemic policies on a relatively active group. The value of the findings will reside in the ability to use the information to inform policy in case of future pandemics and/or limitations in public sports activities.

2 Materials and methods

2.1 Study design and population

This is a longitudinal study which aims to assess the changes in daily steps during the first wave of the COVID-19 pandemic and lockdown in Qatar and identify the population characteristics associated with these changes. SIH, a community-based program, was launched in 2012 to promote physical activity among the residents of Qatar (23). The program was publicized nationwide through outreach advertisement campaigns within different settings (workplaces, campuses, and malls). This program encourages participants to increase their overall steps up to 10,000 steps per day or more. Upon registration, participants were provided with a free of charge pocket-sized Omron HJ-324 U pedometer (Omron Healthcare, Co., Ltd., Kyoto, Japan) linked to a web-database that records their activity levels. During the study period of interest, there were 1,409 registered pedometer users in the program that were active.

2.2 Study measures and participants

Demographic and anthropometric data were extracted from the database, including age, gender, nationality, and Body Mass Index (BMI) based on self-reported height and weight. As for physical activity assessment, daily and aerobic step counts of pedometer records from the database were extracted for the studied period. Participants were included in this study if they provided daily pedometer data between 1st of January and 30th August 2020, (marking pre, during and post COVID-19 wave 1 outbreak phase).

Individuals who did not upload physical activity data were excluded. To ensure valid wear time, only observations with step counts ranging from 500 to 60,000 were included (23).

2.3 Ethical considerations

Participants were asked to sign a disclaimer upon registration to the SIH program, agreeing to the use of their data for program evaluation and research. The data was anonymized prior to analysis and personal information was treated with confidentiality. The study adhered to ethical guidelines and was approved by the Institutional Review Board of Aspire Zone Foundation (E202104021).

2.4 Timeline of wave 1 of COVID-19

On February 29, 2020, the first case of COVID-19 involving a Qatari male returning from Iran was confirmed. Lockdowns were implemented on March 12, 2020, leading to the closure of various public venues like theaters, children play areas, gyms etc. In the initial phase of lifting of restrictions, starting from June 15, mosques opened with precautions, along with 40% capacity granted to selected private healthcare facilities. Malls partially resumed operations while maintaining limited access, and outdoor sports were permitted within restricted park areas. Workplaces were allowed to function with 20% capacity, adhering strictly to health protocols. From July 1, the second phase commenced, permitting small gatherings of up to 10 people. Further openings for mosques were initiated, alongside a 60% operational capacity for private health clinics. Parks, Corniche, and beaches were made accessible, with malls operating under restricted hours and capacity. Additionally, 50% workplace capacity was permitted with stringent health precautions. Moving into the third phase starting from August 1, medium-scale gatherings of up to 40 people were allowed. Mosques were open for Friday prayers, and private health clinics were permitted to function at 80% capacity. Professional sports training was allowed in open spaces and large halls, with a limit of five people. Health clubs, gyms, pools, beauty and massage parlors, and barber shops operated at 50% capacity. All malls were open for full hours, and restaurants began operating with limited capacity, gradually increasing over time.

2.5 Data analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) v21.0. Descriptive statistics, including means, standard deviations were used to represent daily step count. Participants age were grouped into two categories (i.e., age $\leq$ 40/>40 years) based on distinct health and fitness goals and varying prevalence of age-related chronic conditions from earlier reports in Qatar (25). The participants were also categorized into four regional groups according to the World Health Organization classified regions (WHO). BMI Status was calculated and categorized into three categories (i.e., $\leq$25 normal, >25 to <30 overweight, and $\geq$30 Obese). To study the changes in daily step count, a moving average of 7 days was used on a time series graph to visualize the changes by age, gender, BMI status and region. To isolate the impact of COVID-19-related lockdowns from climatic conditions on daily physical activity, we conducted a comparative analysis of daily step counts during equivalent months or periods in the years 2019 (as a reference) and 2020. Linear mixed models were used to assess the changes in steps per day during and after COVID-19 lockdown, compared to baseline assessment, based on independent factors such as sex, age, and obesity status. All factors and their interaction with factor time were included in the linear mixed model. By adding subject id as a random effect with a random intercept we accounted for individual-level variation and within-subject correlation. Unstructured covariance structure was found to be the best fit. Region could not be included in the above model due to small sample size of some groups especially the participants from the African continent. Separately a linear mixed model was designed that included time and region interactions.

3 Results

Four hundred and twenty individuals (average age 50.0 ± 9.4 years) met the inclusion criteria in this study. A significant majority of the participants, accounting for 86.2% of the total sample were older than 40 years.

The study comprised predominantly male participants, (76.7%). Regarding BMI categorization, a substantial portion of the sample (46.0%) fell within the overweight category and 21.4% were obese. Geographically, the majority of the participants hailed from the Southeast Asian region (60.2%), followed by the Middle Eastern region at 31.9% (Table 1).

Table 2 presents the changes in the steps per day during and after the COVID-19 lockdown, compared to the baseline step count according to the participant characteristics.

After lockdown restrictions were implemented, the step count steeply fell and average steps thereafter increased even before the lifting of restrictions (15 Jun 2020) throughout the lockdown until the beginning of Ramadan, the month of fasting (see Figure 1).

TABLE 1 Characteristics of the participants.

Variables		Frequency	Percentage
Age group			
	≤40 years	58	13.8%
	>40 years	362	86.2%
Sex			
	Females	98	23.3%
	Males	322	76.7%
BMI group			
	≤25 kg/m^2	137	32.6%
	25–30 kg/m^2	193	46.0%
	>30 kg/m^2	90	21.4%
Region			
	African	7	1.7%
	Middle Eastern	134	31.9%
	Southeast Asian	253	60.2%
	Western	26	6.2%

TABLE 2 Linear mixed model: steps per day (mean ± SE)* and changes in steps per day during and after COVID-19 lockdown compared to pre-covid.

	Pre-covid	During COVID lockdown	Post lockdown	During vs. pre (Percentage of change)	*p*-value	Post vs. pre (Percentage of change)	*p*-value
Overall	7,969 ± 376	6,915 ± 421	7,275 ± 371	−1,054 ± 309 (−13.2%)	0.002	−694 ± 293 (−8.7%)	0.054
Sex							
Female	7,686 ± 591	6,922 ± 651	7,320 ± 570	−763 ± 442 (−9.9%)	0.235	−366 ± 413 (−4.8%)	0.758
Male	8,253 ± 388	6,908 ± 441	7,230 ± 393	−1,345 ± 319 (−16.3%)	<0.001	−1,023 ± 299 (−12.4%)	0.002
Age group							
≤40 years	7,472 ± 546	6,000 ± 625	6,572 ± 590	−1,472 ± 530 (−19.7%)	0.017	−900 ± 509 (−12.0%)	0.215
>40 years	8,466 ± 348	7,830 ± 386	7,978 ± 333	−636 ± 250 (−7.5%)	0.034	−489 ± 231 (−4.8%)	0.102
BMI Status							
≤25 kg/m2	9,313 ± 543	7,858 ± 599	7,826 ± 525	−1,454 ± 407 (−15.6%)	0.001	−1,487 ± 377 (−16.0%)	<0.001
>25 to <30 kg/m2	7,620 ± 476	6,537 ± 533	7,199 ± 469	−1,083 ± 359 (−14.2%)	0.008	−421 ± 335 (−5.5%)	0.507
≥30 kg/m2	6,976 ± 629	6,350 ± 709	6,800 ± 619	−626 ± 480 (−9.0%)	0.476	−176 ± 450 (−2.5%)	0.972

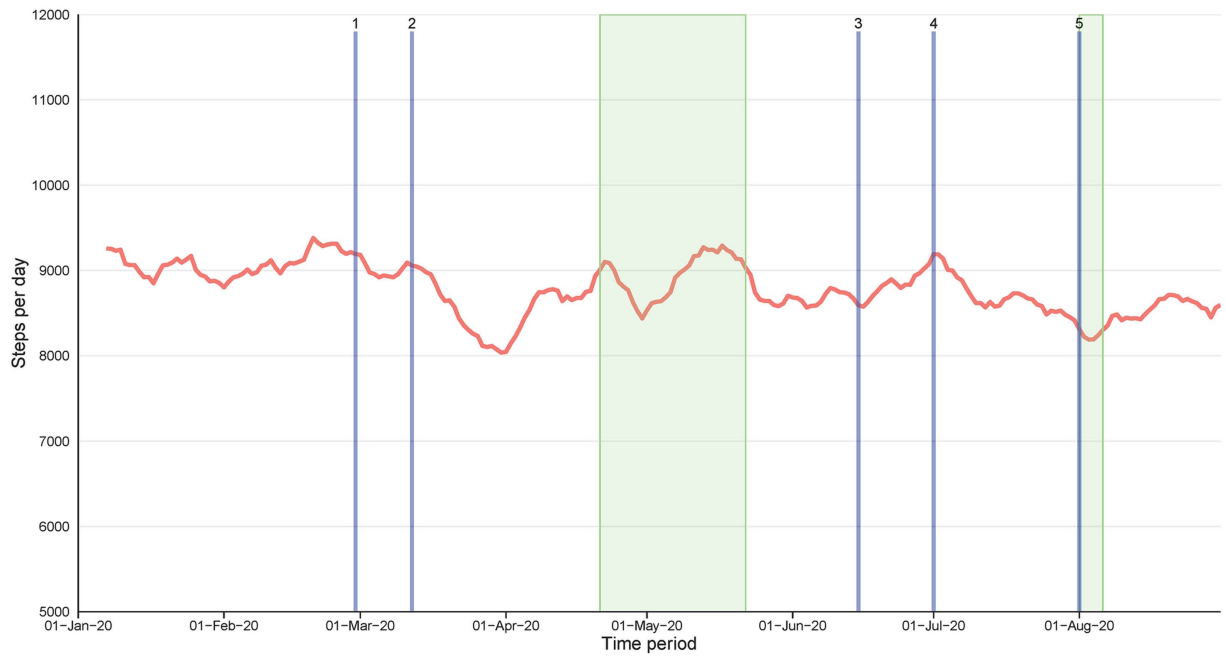

FIGURE 1
The moving average (7 d) steps per day among the participants from January 2020 to 31 August 2020. The wide, green-shaded area represents the month of Ramadan (23 April 2020–23 May 2020) and the narrow, green-shaded area represents Eid al-Adha observation (30 July 2020–6 August 2020). For all figures, the description of the timepoints is as follows: (1) First COVID-19 case in Qatar; (2) Qatar imposes lockdowns; Gradual lifting of lockdown (3) Phase 1; (4) Phase 2; (5) Phase 3.

Compared to the pre-pandemic step count, during the lockdown step count was reduced by −1,054 ± 309 steps (13.2%, $p = 0.001$). By contrast, the after-pandemic step count was still lower 694 ± 293 steps, but this difference was not statistically significant ($p = 0.054$) (Table 2). Before the pandemic, men were generally more active than women. At the beginning of the lockdown, a decrease in steps was evident fell in women (−763 ± 442 steps) [albeit not reaching statistical significance with $p = 0.235$] but was larger and statistically significant in men (−1,345 ± 319steps [16.3%, $p < 0.001$]). Compared to the pre-pandemic step count, the after-pandemic step count in men was still lower by −1,023 ± 299 steps (12.4%, $p = 0.056$) and in women but not statistically significant (4.8%, $p = 0.974$) (See Figure 2A). An unexpected finding was that the younger individuals in the SIH cohort (i.e., <40 years old) were less active than older individuals (i.e., ≥40 years old) before, during, and after the pandemic (See Figure 2B). The decrease in step count during the pandemic versus before the pandemic in the <40 years age group was (−1,472 ± 530, $p = 0.017$) and in the ≥40 years age group was (−636 ± 250, $p = 0.034$).

Significant differences were also identified between the activities of individuals who were classified as normal weight (BMI: 18.5–24.9),

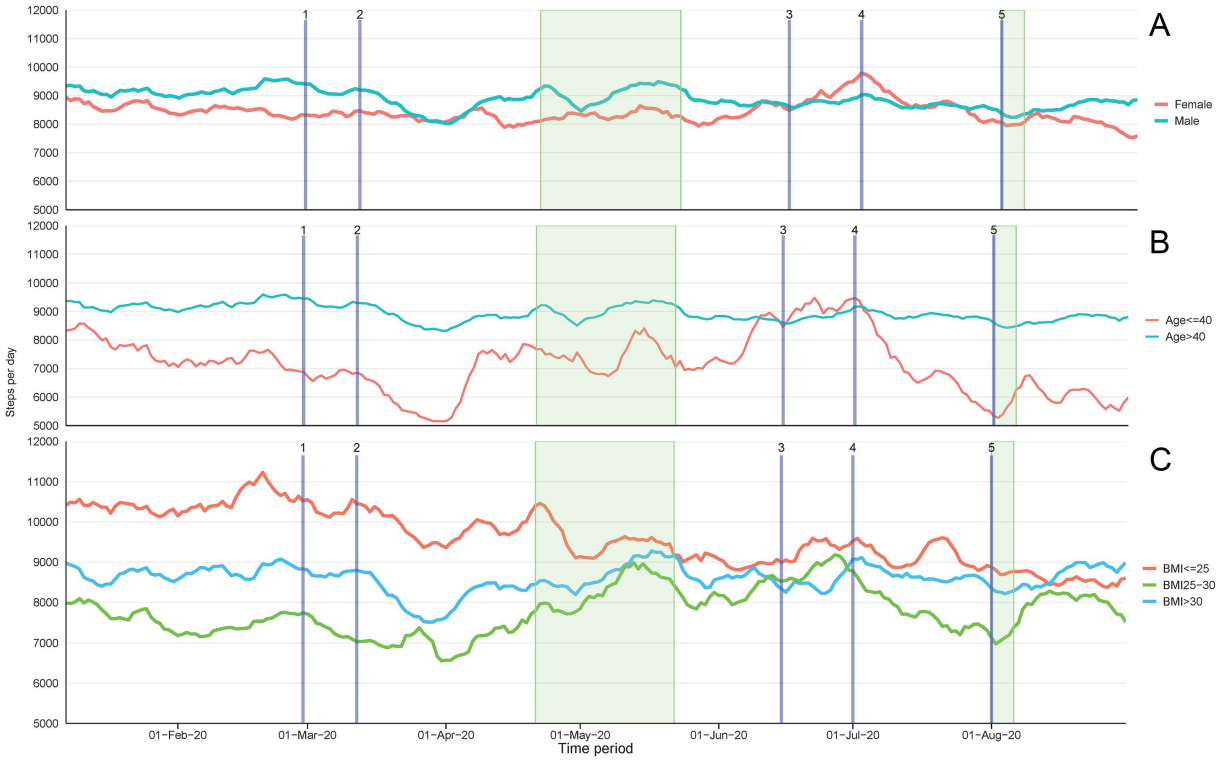

FIGURE 2
The moving average (7 d) steps per day among the participants, based on sex, age group, BMI status, from January 2020 to 31 August 2020. The wide, green-shaded area represents the month of Ramadan (23 April 2020–23 May 2020) and the narrow, green-shaded area represents Eid al-Adha observation (30 July 2020–6 August 2020). The description of the timepoints is as follows: (1) First COVID-19 case in Qatar; (2) Qatar imposes lockdowns; Gradual lifting of lockdown (3) Phase 1; (4) Phase 2; (5) Phase 3.

overweight (BMI: ≥25 to <30), and obese (BMI: ≥30). The step count pre-covid was lower in individuals with higher BMI (see Figure 2C). During the pandemic, compared to before the pandemic, the step count decreased significantly by −1,454 ± 407 steps in normal weight people and by −1,083 ± 350 steps in overweight people ($p = 0.001$ and $p = 0.008$, respectively). In the obese group, the step count decreased by −626 ± 480 steps, but this difference was not significant ($p = 0.476$). The after-pandemic step count in the normal weight group was still lower post pandemic restrictions (−1,487 ± 377 $p < 0.001$) but remained similar in other groups as clustered by BMI status.

During the lockdown and during the lifting of restrictions, the activity level of the Middle Eastern individuals and the Southeast Asian individuals did not change substantially. By contrast, the activity level in Western individuals increased during the lockdown, however, it decreased with each phase of the lifting of COVID-19 restrictions. Due to small group sizes of ethnicity, region could not be included as a factor in the multivariate linear mixed models shown in Table 2. In a univariate analysis, only looking at the effect of time period on step count by regions, it is shown that average step count during the pandemic was significantly reduced in Southeast Asian group (−1,247 ± 230, $p < 0.001$) and this remained significantly lower during post pandemic restrictions (−876 ± 310, $p = 0.015$). The average steps per day among Western participants remained above 10,000 steps throughout the lockdown period.

By comparing physical activity time series data during the 2020 study period with physical activity of 2019 as a reference we observed distinctive declines in step count during lockdown period (data not shown). This approach allowed us to ensure that observed changes were primarily attributed to the effects of lockdown measures rather than seasonal variations in weather.

4 Discussion

The present study aimed to assess the impact of the first wave of COVID-19 lockdown and fluctuations in daily step counts among citizens and residents of Qatar. It is the first of its kind to use objective pedometer data to measure changes in physical activity during and after the first wave of the pandemic in Qatar. The main result of the study revealed a significant overall decline (i.e., −13.2%) in daily steps during the lockdown period and a recovery with the lifting of the restrictions, which is consistent with previous studies in other parts of the world (21, 22). Although the average decline in step counts was approximately of 1,000–1,500 steps per day, walking an extra 1,000 step per day can reduce risk of cardio-vascular disease and all-cause mortality by 5–21 and 6–36%, respectively (26). Therefore, a relatively small reduction can have marked effects, in particular in individuals which are not particularly active.

Interestingly, a differential impact of the lockdown was observed based on characteristics of subgroups. In fact, step counts of women and individuals with obesity (i.e., BMI ≥ 30) did not vary significantly after the lockdown or after the lifting of restrictions. Conversely, step counts of men and those with normal weight-status (BMI ≤ 25) significantly decreased during that period and remained lower than

baseline consistently across age groups. This first finding might suggest that groups who were the most impacted by the restrictive measures were those who presented higher step counts at baseline. Indeed, many studies demonstrated a larger effect of lockdown on people who were initially more active, including men (13, 27). Conversely, while all age groups were significantly affected by the lockdown, the older group (i.e., > 40 years) who was initially more active than the younger one (i.e., < 40 years) was less severely affected by the lockdown and the lifting of restrictions. Although this finding might seem counter-intuitive for this "more vulnerable" group, it aligns with what was found in an Australian study (21). Authors argued that the older individuals have a higher emotional stability and lower reliance on team-based activities, use of gyms and sporting facilities, which allowed them to maintain their step count. It is also assumed that the older group tended to engage is leisure-time activities that would include walking and was more health conscious to potential health risks of reducing their physical activity level (28). These findings have important implications for informing future public health policies and interventions during times of crisis that should not only focus on the most vulnerable and sedentary subgroups (i.e., older or obese individuals or women), but also on individuals with high activity levels which experience the larges change in activity behaviors.

These results are somehow similar in what was reported in a British cohort where most of the participants <35 years of age did not report sufficient physical activity during the social distancing policy implementation phases (27). Two other studies reported a much larger reduction in PA in males when compared to females in Greece and in the USA. The significant decrease in physical activity observed by these authors (13, 29) in men but not in women during the COVID-19 pandemic may be attributed to various factors. Indeed, understanding gender differences in choices and motivations toward physical activities might offer a good insight. As compared to women, men tend to engage in more outdoor, team-based, high-intensity and competitive physical activities and sports which were more restricted during the pandemic due to social distancing guidelines (13, 30). Women, on the contrary, tend to engage in physical activities for reasons that are more related to weight management or physical appearance as found in a study from Greece (13). Furthermore, men tend to have more demanding work schedules and may have faced additional work-related stressors during the pandemic, leading to decreased physical activity levels (31). Additionally, lockdown and social distancing policies might have determined increased responsibilities for men at home, such as caring for children or older people, which could have limited their time for physical activity observed in our and other studies.

The time-series analyses were able to depict further important fluctuations with the different key events and variations between behaviors of sub-groups during this eight-month period in Qatar. Generally, after the steep decline in step counts due to lockdown, step counts started increasing only a few weeks later and before the start of the first phase of lifting of restrictions (3) (Figure 1). Figure 2 show higher baseline step count for men, normal weight individuals, older and western sub-groups with differences remaining consistent during the full period. However, large variations are seen in men (*vs* women) and the younger group (*vs* older) / [obese group (*vs* normal weight) and western group (*vs* other regions)] at different stages that relate to the lifting of restrictions, Ramadan or holidays (Eid Al-Adha) potential indicating efforts to remain active or regain activity level. The higher fluctuations are also indicative of more responsiveness or sensitivity to changes in the social and environmental context and therefore a higher vulnerability to key events happening.

From our previous analysis in this settings (23), we are aware the climate does play a role in impacting daily physical activity behavior, hence by looking at daily physical activity in a year without lockdowns (2019) and comparing it to the corresponding periods in a year with lockdowns (2020) we found that the observed declines in step counts were specifically associated with lockdown implementations rather than being influenced by temperature and humidity conditions.

The study is the first of its kind to investigate the impact of the COVID-19 pandemic on physical activity in Qatar during and after quarantine using objective pedometer. The use of pedometers provided accurate and objective data relative to physical activity. The study had a large sample size for a country the size of Qatar and a longitudinal design, which allowed for the evaluation of changes in physical activity over time. The use of time series was also a key factor for assessing variation in steps around the main events.

Certain limitations also exist and are important to mention. The study was conducted in a specific geographic region and may not be generalizable to other socioeconomic contexts. The sample consisted of participants who were already enrolled in a health promotion program (SIH) revealing a more motivated and health-conscious population, which may limit the generalizability of the findings to the wider population of Qatar. Additionally, the study did not collect data on other factors that may have influenced physical activity, such as socio-demographic characteristics or access to recreational facilities. Considering the limitations of self reported measures to determine BMI, previous work has indicated that BMI computed from self-reported weight and height is a valid measure in adult men and women (32). Future studies should focus on identifying the specific factors contributing to decreased physical activity levels among the most affected sub-groups during pandemics and lockdowns and developing targeted interventions to promote and facilitate physical activity during and after the pandemic.

5 Conclusion

The present study is unique in that it uses pedometer data from the "Step into Health" walking program to objectively measure physical activity levels before, during and after quarantine in Qatar, reporting the first evidence in the Gulf Peninsula region. The results show that step counts steeply fell during lockdown and continued to be lower than pre-pandemic levels even after restrictions were lifted. While several studies showed greater impact of lockdown on physical activity levels of women and obese populations, the present study provides new and different insights. Indeed, we observe a larger impact of the lockdown for men, normal-weight and older groups as compared to women, obese and younger groups. This indicates the need to address specific sex, weight-status and age-related differences in physical activity levels during the COVID-19 pandemic according to the context. Strategies to promote physical activity during the pandemic should be tailored for all individuals to have opportunities to maintain their physical activity levels. Findings of this study can inform future health policies and interventions during crises to focus not only on the more vulnerable groups (e.g., obese and women) but

also on those who are active at baseline and potentially more sensitive to such lockdown measures. Additionally, exploring factors contributing to the resilience observed in certain groups may guide the development of effective strategies for maintaining physical activity levels in diverse populations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involved humans and was approved by the Institutional Review Board of Aspire Zone Foundation (E202104021) (Doha, Qatar). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants due to study involving the analysis of pre-existing data and the data being anonymized. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because Patient consent was waived due to study involving the analysis of pre-existing data and the data being anonymized.

Author contributions

AA-M: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. AF: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – review & editing. AS: Investigation, Resources, Validation, Writing – review & editing. AG: Investigation, Resources, Validation, Writing – review & editing. SA-H: Investigation, Methodology, Resources, Writing – review & editing. LM: Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft. SS: Conceptualization, Investigation, Methodology, Resources, Validation, Writing – review & editing. MC: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1333546/full#supplementary-material

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Long-term reduced functional capacity and quality of life in hospitalized COVID-19 patients

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Background: Persistent symptoms and exercise intolerance have been reported after COVID-19, even months after the acute disease. Although, the long-term impact on exercise capacity and health-related quality of life (HRQoL) is still unclear.

Research question: To assess the long-term functional capacity and HRQoL in patients hospitalized due to COVID-19.

Study design and methods: This is a prospective cohort study, conducted at two centers in Brazil, that included post-discharge COVID-19 patients and paired controls. The cohort was paired by age, sex, body mass index and comorbidities, using propensity score matching in a 1:3 ratio. Patients were eligible if signs or symptoms suggestive of COVID-19 and pulmonary involvement on chest computed tomography. All patients underwent cardiopulmonary exercise testing (CPET) and a HRQoL questionnaire (SF-36) 6 months after the COVID-19. The main outcome was the percentage of predicted peak oxygen consumption (ppVO2). Secondary outcomes included other CPET measures and HRQoL.

Results: The study sample comprised 47 post-discharge COVID-19 patients and 141 healthy controls. The mean age of COVID-19 patients was 54 ± 14 years, with 19 (40%) females, and a mean body mass index of 31 kg/m^2 (SD, 6). The median follow-up was 7 months (IQR, 6.5–8.0) after hospital discharge. PpVO2 in COVID-19 patients was lower than in controls (83% vs. 95%, $p = 0.002$) with an effect size of 0.38 ([95%CI], 0.04–0.70). Mean peak VO2 (22 vs. 25 mL/kg/min, $p = 0.04$) and OUES (2,122 vs. 2,380, $p = 0.027$) were also reduced in the COVID-19 patients in comparison to controls. Dysfunctional breathing (DB) was present in 51%. HRQoL was significantly reduced in post COVID patients and positively correlated to peak exercise capacity.

Interpretation: Hospitalized COVID-19 patients presented, 7 months after discharge, with a reduction in functional capacity and HRQoL when compared

to historical controls. HRQoL were reduced and correlated with the reduced peak VO2 in our population.

KEYWORDS

CPET cardiopulmonary exercise testing, COVID-19, long COVID, HRQOL, functional capacity

Introduction

The COVID-19 pandemic declared in March of 2020 resulted in a massive number of cases in several countries (1). SARS-Cov-2 infection overloaded healthcare systems and was responsible for over 450 million cases worldwide (2). Viral pneumonia is the hallmark of hospitalized COVID-19 patients, and, in severe forms, progress to acute respiratory distress syndrome (ARDS), the most worrying presentation with a high mortality rate and associated with long-term disabilities (3).

Experience from the previous severe acute respiratory syndrome (SARS-CoV-1) epidemic, suggests that pulmonary function at rest and exercise capacity could be profoundly impaired, either by the virus action or because of post-intensive care syndrome, but its long-term impact is unknown (4–6). Studies conducted in patients who recovered from COVID-19 have related a myriad of symptoms, including chest pain, fatigue, dyspnea, leg pain and weakness (7, 8). A case-control study conducted at 2–3 months from disease onset showed that a significant proportion of hospital discharged patients reported symptoms such as breathlessness, fatigue, depression and limited exercise capacity (9). Furthermore, cross-sectional studies performing cardiopulmonary exercise testing (CPET), the gold-standard for functional capacity assessment, elucidated some exercise limitation pathophysiological mechanisms (10, 11). Studies conducted 3 months after discharge had shown reduced functional capacity in 33 to 50% of patients post COVID-19 (12, 13). However, these studies only evaluated short-term physical impairment after COVID-19 infection, with uncertainty about causality, mechanisms of limitation and persistence of this limitation. Possible underlying mechanisms for these persistent complaints can include cardiac, pulmonary and peripheral (oxygen extraction) limitations, with either two or more combined.

The impact in health-related quality of life (HRQol) have been shown to be impaired in patients post COVID-19 (14). Countless patients affected by COVID-19 are returning to their work activities, and the real burden of this disease is still being discovered. Therefore, the aim of this study was to assess long-term functional capacity and HRQoL, among survivors of hospitalization due to COVD-19, comparing the results with those of historical controls matched by age, sex, body mass index, and comorbidities.

Methods

This is a prospective cohort study of COVID-19 patients who required hospitalization due to respiratory symptoms between June 2020 and December 2020 and paired historical controls. Participants were recruited from a previous cohort, in which adult patients ($\geq$18 years) were eligible if admitted with signs or symptoms suggestive of COVID-19 (cough, fever, or sore throat) within 14 days of onset and hospitalized in the prior 2 days (15). All patients were hospitalized at a private hospital in Porto Alegre, southern Brazil. This private institution is the reference hospital in the care of COVID-19 cases in Porto Alegre, RS, Brazil, with 372 infirmary beds, and 113 ICU beds.

Between six and nine months after hospital discharge, patients with confirmed COVID-19 by RT-PCR and pulmonary involvement on chest computed tomography were contacted by telephone to perform a CPET and a clinical evaluation through a HRQoL questionnaire. A physician assessed the presence of persistent symptoms during the clinical evaluation. Exclusion criteria were inability to perform CPET due to musculoskeletal limitation, absence of radiologic pulmonary involvement and patient refusal. The project was submitted to the local ethics committee and complied with both the National Health Council Resolution 466/12 and the Declaration of Helsinki. All patients signed an informed consent.

Data collection

All data were collected prospectively including demographic, symptoms at admission, comorbidities, need for oxygen support, supplemental ventilatory support type, need for intensive care and length of stay. Oxygen support therapy was defined as the therapy used with the highest oxygen concentration supply and invasiveness during hospital admission. Patients were also classified according to the World Heart Organization COVID-19 severity classification: mild (symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia); moderate (adults with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 $\geq$ 90% on room air); severe (adults with clinical signs of pneumonia plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air); and critical patients with acute respiratory distress syndrome (ARDS) or sepsis or septic shock (16). At the follow-up visit, patients were interviewed to assess persistent symptoms, medications in use, current exercise activity and other clinically relevant information.

Cardiopulmonary exercise testing

CPET was performed on a treadmill (General Electric T-2100, GE Healthcare, United States) with breath-by-breath gas analysis (Metalyzer 3B, Cortex, Leipzig, Germany) between January 2021

to March 2021. Symptom-limited maximal exercise testing with an individualized ramp protocol was used to yield fatigue-limited exercise duration of 8 to 12 min. Peak VO2 was determined by the higher measure of 20 s averaging of breath-by-breath values. Other prognostic variables were also measured, such as first and second ventilatory thresholds, which were defined by V-slope for first ventilatory threshold and ventilatory equivalent method to confirm first and determine second ventilatory threshold, minute ventilation-carbon dioxide output relationship (VE/VCO2 slope), oxygen uptake efficiency slope (OUES) and resting end tidal carbon dioxide tension. Maximal effort was considered when respiratory exchange ratio (RER) was equal to or above 1.05. Before each test, brief spirometry was performed before each test, to assess forced vital capacity (FVC) and forced expiratory volume in the 1st second (FEV1). Maximal voluntary ventilation (MVV) was estimated by FEV1x 37.5 (17). Peak VE was also compared as a percentage of maximal predicted using a validated equation (18). For the percentage predicted peak VO2 (ppVO2) both the Wasserman's and Hansen algorithm and FRIEND equations were used (19). Dysfunctional breathing (DB) was defined by pattern recognition as described by previous studies (20, 21). For this classification, we considered the graphs of minute ventilation (VE) versus time, VE/VCO2 slope and respiratory rate (breaths per minute), tidal volume (mL/min) vs. VE (L/min). CPET and spirometry were performed following current guidelines for exercise testing (22).

Quality of life assessment

Short Form36 (SF-36) physical and mental health questionnaire was completed by all post COVID-19 patients. The SF-36 addresses HRQoL in eight domains (general health, physical functioning, physical role function, bodily pain, vitality, emotional role function, mental health, and social functioning) that are summarized in two dimensions: physical and mental. Scores range from worst to best (0–100). The eight different scales scores were calculated and computed. For construction of summary measures, scales were standardized using a *Z*-score transformation, providing both physical and mental composite scores (PCS and MCS). We used national normative data for both z-scores calculations and for comparison purpose with our sample (23).

Selection of healthy controls and pairing

Control subjects were selected from a CPET database of 4,957 test subjects without diagnosed cardiovascular or pulmonary disease, evaluated at an experienced laboratory in the Brazilian Midwest region from 2011 to 2020. CPET were mainly performed for cardiorespiratory fitness assessment and exercise prescription. Test subjects who did not fulfill ventilatory maximality criterion (RER $\geq$1.05) were excluded before pairing. COVID-19 patients were matched with controls by a 1:3 ratio for age, sex, BMI, hypertension and diabetes. A nearest neighbor matching method was applied with a caliper of 0.2 without replacement. After matching, included variables were compared between groups to confirm that there were no significant differences.

Statistical analysis

Continuous data were tested for normality with Shapiro–Wilk test and presented as mean (standard deviation) or median (interquartile range). Categorical data are presented as absolute count and relative frequency. Comparisons between COVID-19 and matched controls were performed by independent samples Student's *t*-test and chi-square test. The effect size was calculated by dividing the mean difference between groups by the standard deviation of the population. Spearman's rank correlation coefficient was performed to test association of HRQoL and CPET data. Non-linear regression with curve fitting was used to examine the relationship between peak VO_2 and PCS of HRQol. We used a generalized linear model to estimate the association of COVID-19 infection in comparison to healthy controls for the ppVO2. An adjusted model including age, sex, height, and weight was also performed. This study used a convenience cohort of patients. We performed a post-hoc power calculation for the observed differences of the ppVO2 among COVID-19 and healthy controls resulting in a power of 89.94% for an alpha value of 5%. Significance was accepted at $p < 0.05$ for all tests. Data were analyzed in SPSS, Version 25.0 for Windows (SPSS Inc., Chicago, IL, United States) and R 4.1.1 statistical software (R: The R Project for Statistical Computing, https://www.r-project.org).

Results

From 110 screened patients with confirmed SARS-CoV-2 infection, 63 were excluded due to an absence of radiological abnormalities at time of admission or did not consent to perform CPET. The flowchart of the study is shown in Figure 1. Our sample comprised 47 previously hospitalized COVID-19 patients with a mean age of 54 years (standard deviation [SD], 14), 19 (40%) females, 24 (51%) with hypertension and 12 (26%) with diabetes. There were no significant differences found in baseline characteristics between cases and the 141 matched controls. COVID-19 patients required supplementary oxygen in 26 (55%) cases, but only 3 (6%) required high-flow nasal cannula, 1 (2%) Bilevel, and 2 (4%) mechanical ventilation. Patients were hospitalized for a median of 7 days (interquartile range [IQR], 4–10) and 5 (11%) required ICU admission. Twenty-six (55%) subjects reported persistent symptoms, being fatigue (46%), dyspnea (38%), and leg pain/weakness (21%) the most common. Table 1 summarizes demographic and clinical data from COVID-19 patients and healthy controls.

Exercise capacity and CPET results

Table 2 and Figure 2 summarize the CPET variables compared between COVID-19 and controls. The median time from hospital discharge to CPET was 7 months (IQR, 6.5–8). The mean FEV1 was 3.34 L [SD, 0.7], and the mean FVC was 4.3 L [SD, 0.9]. Among the patients, 1 presented with a restrictive pattern, while 2 exhibited an obstructive pattern during spirometry. COVID-19 patients showed lower mean ppVO2 by the Wasserman and Hansen algorithm (83% [SD, 15] vs. 95% [SD, 35]; $p = 0.002$), and by the FRIEND equation (81% [SD, 18] vs. 88% [SD, 18]; $p = 0.039$). Peak VO2 (22.5 [SD, 6] vs.

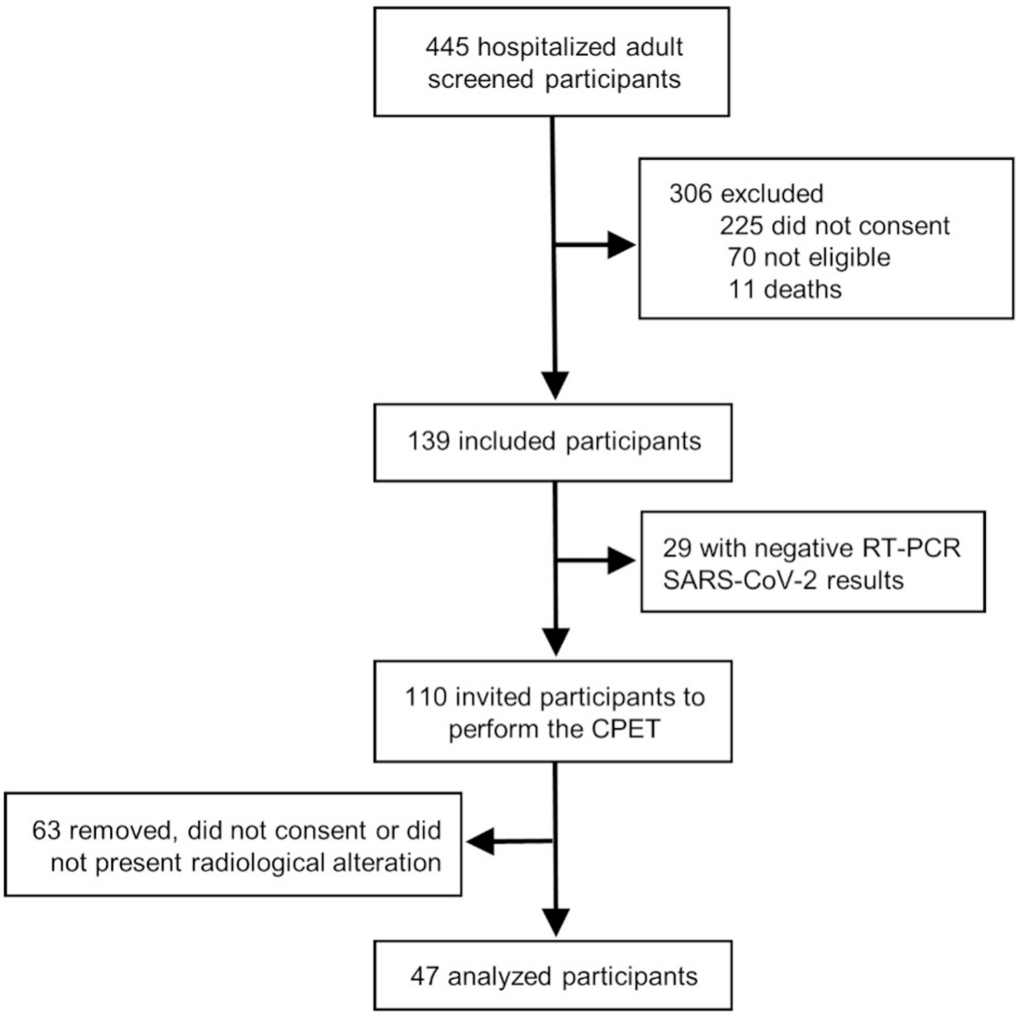

FIGURE 1
Study design. We screened 445 hospitalized patients diagnosed with COVID-19 infection and selected for eligibility when a positive polymerase chain reaction test and signs of lung involvement evaluated by computed tomography chest imaging. Of the 110 eligible patients, 47 accepted the invitation to perform a cardiopulmonary exercise test study 6 months after hospital discharge.

25.0 [SD, 7] mL/kg/min; $p = 0.048$), VO2@AT (14.4 [SD, 4] vs. 12.8 [SD, 3] mL/kg/min; $p = 0.007$), and OUES (2,122 [SD, 611] vs. 2,380 [SD, 860]; $p = 0.02$) were also impaired in COVID-19 patients when compared to healthy controls. The greatest effect size was observed for VO2@AT, ppVO2, peak VO2 and OUES, respectively. Peak VE and percent-predicted VE showed lower values for COVID-19 patients (76 [SD, 23] vs. 84 [SD, 27], $p = 0.08$ and 103 [SD, 40] vs. 93 [SD, 39]; $p = 0.116$, respectively), but without statistical significance. Breathing reserve was normal in all post-COVID patients, with the average peak VE/MVV relation of 0.63 (SD, 0.2).

When considering those participants with ppVO2 less than 80% of predicted, 21 (45%) COVID-19 patients had values below this threshold, in comparison to only 12 (8.5%) of healthy controls ($p = 0.01$). When using ERS algorithm (24) for determining causes of exercise limitation of these 21 COVID-19 patients, 12 (57%) showed findings consistent with cardiocirculatory limitation and nine subjects (43%), findings suggesting peripheral muscle limitation. It is noteworthy that none of the patients showed reduced breathing reserve or signs of pulmonary limitation.

Dysfunctional breathing was prevalent among COVID-19 patients (51%). Persistence of symptoms (dyspnea, fatigue, leg weakness) was associated with the DB ventilatory pattern (OR, 3.8; 95% CI, 1.3–12.1). DB was more common in patients who had lower ppVO2 (78% vs. 89%, $p = 0.012$) and among those with peripheral muscle limitation than cardiocirculatory or normal findings (89% vs. 66% vs.31%, respectively, $p = 0.005$). The relationship between symptoms, DB and reduced ppVO2 is displayed in Figure 3A.

Predictors of decrease predicted peak VO2

We subsequently performed an analysis to evaluate the impact of COVID-19 in the observed ppVO2 (by Wasserman and Hansen algorithm) in comparison to matched controls (Table 3). COVID-19 patients had a reduced ppVO2 with an unadjusted odds ratio (OR) of 0.89 (95%CI, 0.82–0.95; $p = 0.002$) and an adjusted OR of 0.88 (95%CI, 0.82–0.95, $p = 0.002$). We then sought to evaluate which characteristics were associated with the ppVO2 in hospitalized

TABLE 1 Demographic and clinical characteristics of COVID-19 patients and healthy controls.

	Control subjects (*N* = 141)	COVID-19patients (*N* = 47)	*p*
Age, years	54 ± 12	54 ± 14	0.97
Female sex, %	57 (40%)	19 (40%)	1.00
BMI, kg/m^2	31 ± 5	31 ± 6	0.83
Hypertension, %	60 (43%)	24 (51%)	0.36
Diabetes, %	36 (26%)	12 (26%)	1.00
Coronary artery disease, %	–	2 (4%)	
Ventilatory support			
Supplementary oxygen, %		26 (55%)	
High-flow nasal cannula, %		3 (6%)	
Non-invasive mechanical ventilation %		1 (2%)	
Invasive mechanical ventilation, %		2 (4%)	
Vasopressor, %		5 (11%)	
ICU admission, %		5 (11%)	
Hospital LOS, days (median, IQR)		7 (4–10)	
Hemoglobin, g/dl (mean ± SD)		13.7 ± 2	
Hematocrit, % (mean ± SD)		40 ± 4	
Leukocyte count × 10^3 (mean ± SD)		5.4 (3.8–6.9)	
Creatinine, mg/dL (mean ± SD)		0.86 (0.78–1.09)	
D-dimer × 10 2, ng/mL (median, IQR)		635 (391–917)	
US-troponine, (ng/dL) (median, IQR)		0.6 (0.5–0.9)	
WHO COVID-19 severity classification			
-Moderate		33 (70%)	
-Severe/critical		14 (30%)	

BMI, body mass index; CAD, coronary artery disease, CPAP, continuous positive airway pressure; ICU, intensive care unit; LOS, length of stay; US, ultra-sensible; WHO, world health organization.

TABLE 2 Comparison of cardiopulmonary exercise testing between healthy controls and hospitalized COVID-19 patients.

	Control subjects (*N* = 141)	COVID-19patients (*N* = 47)	Effect size	*p*
ppVO2 (%)*	95 ± 35	83 ± 15	0.38 (0.05–0.71)	0.002
ppVO2 (%)**	88 ± 18	81 ± 18	0.39 (0.05–0.72)	0.039
Peak VO2 (mL/kg/min)	25.0 ± 7	22.5 ± 6	0.37 (0.04–0.70)	0.04
OUES	2,380 ± 860	2,122 ± 611	0.32 (0.01–0.65)	0.02
VO2@AT (mL/kg/min)	14.4 ± 4.4	12.8 ± 3.1	0.39 (0.05–0.72)	0.007
Peak oxygen pulse (mL/beat)	13.8 ± 3.9	13.2 ± 3.6		0.15
Peak VO2 (l/min)	2.20 ± 0.8	2.02 ± 0.7		0.19
Peak HR (bpm)	156 ± 22	156 ± 18		0.87
Peak SBP (mmHg)	169 ± 26	164 ± 20		0.23
Peak RER	1.17 ± 0.1	1.18 ± 0.1		0.47
VE/VCO2 slope	31 ± 8	31 ± 7		0.33
Peak VE (l/min)	84 ± 27	76 ± 23		0.08
ppVE (%)	106 ± 40	93 ± 39		0.12

ppVO2, predicted-percentage peak VO2; HR, heart rate; OUES, oxygen uptake efficiency slope; VO2@AT, VO2 at anaerobic threshold; SBP, systolic blood pressure; RER, respiratory exchange ratio; VE, ventilation, ppVE predicted-percentage peak VE. *Wasserman and Hansen algorithm and **FRIEND equation. Continuous data are presented as mean ± standard deviation or median (p25–p75).

COVID-19 patients after discharge (Table 3). The presence of coronary artery disease (OR, 0.83; 95%CI, 0.76–0.89; $p < 0.001$), the use of Bilevel (OR, 0.83; 95%CI, 0.79–0.88; $p < 0.001$), mechanical ventilation (OR, 0.88; 95%CI, 0.79–0.98; $p = 0.02$), and in-hospital length of stay (OR, 0.99; 95%CI, 0.99–0.99; $p = 0.001$) were associated with lower ppVO2.

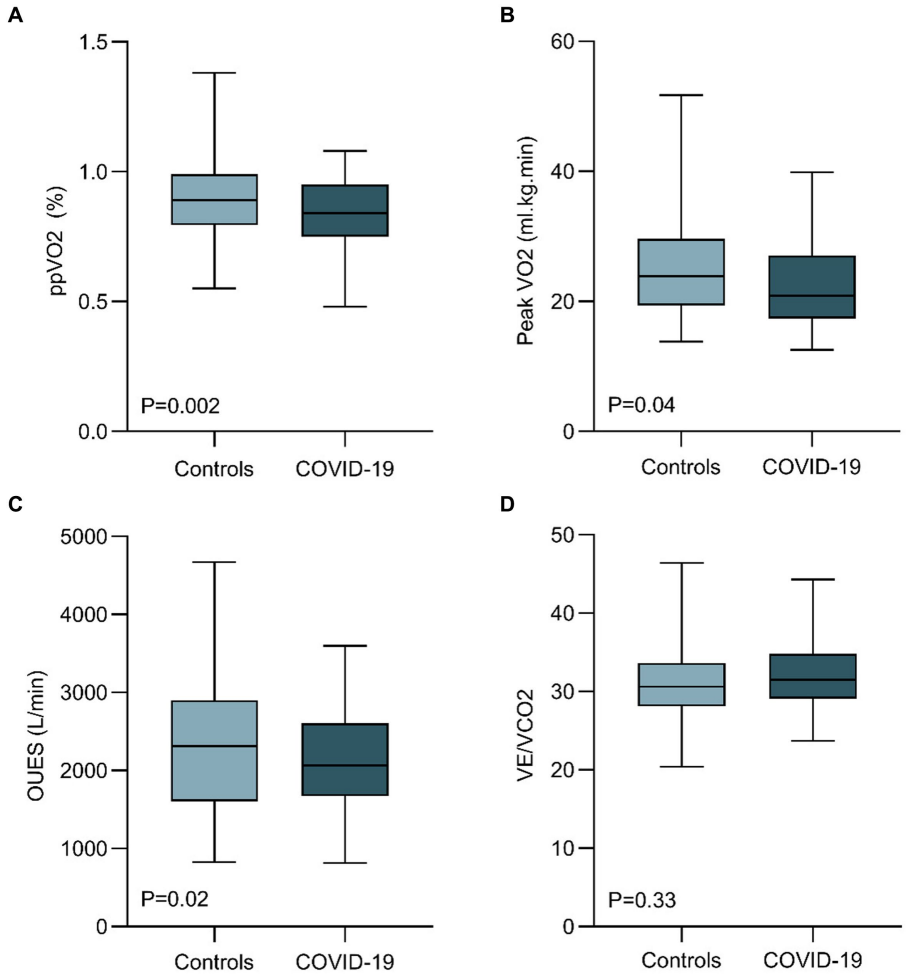

FIGURE 2
Comparison of cardiopulmonary exercise test parameters between healthy controls and hospitalized COVID-19 patients 6 months after discharge. COVID-19 patients 6 months after hospital discharge showed a reduced ppVO2 (calculated by the Wasserman and Hansen Algorithm), peak VO2, and OUES. VE/VCO2 were similar between cohorts. (OUES, oxygen uptake efficiency slope; ppVO2, predicted-percentage peak VO2; VE, ventilation).

Quality of life assessment

Quality of life measurements were compared to national normative data stratified by age and sex. Both physical (45 vs. 49; $p = 0.01$) and mental (47 vs. 51; $p = 0.04$) composite mean scores were significantly reduced in COVID-19 patients. Regarding the domains of physical and mental health, vitality (55 vs. 71; $p < 0.001$), bodily pain (66 vs. 77, $p = 0.004$), role physical (64 vs. 76, $p = 0.04$), role emotional (68 vs. 81, $p = 0.03$) and social functioning (72 vs. 84, $p = 0.006$) were significantly reduced in post COVID-19 subjects. Physical functioning (69 vs. 75, $p = 0.08$) and mental health (69 vs. 74, $p = 0.07$) also were reduced in post-COVID-19 patients, but without statistical significancy. Interestingly, the global health perception of patients was not reduced when compared to controls (68 vs. 69, $p = 0.73$). HRQol results are summarized in Figure 3B.

Physical composite score (Spearman's $\rho = 0.654$; $p < 0.001$), functional capacity ($\rho = 0.649$; $p < 0.001$) and bodily pain ($\rho = 0.637$; $p < 0.001$) showed a significant, moderate correlation with peak VO2 in our sample. The relationship between peak VO2 and PCS was best described as a third-degree polynomial, presenting a moderate coefficient of determination ($R^2 = 0.53$; $p < 0.001$) as shown in Figure 3C.

Discussion

Our study shows that hospitalized COVID-19 patients, even after more than 6 months post-discharge, can still demonstrate reduced functional capacity and HRQoL compared to matched controls. Several CPET prognostic markers, physical and mental aspects of HRQoL were also significantly reduced 6 months after hospital discharge in COVID-19 patients, demonstrating the long-term impact of the disease. Moreover, more than half of the patients has persistent symptoms at 6 months follow-up, increasing the burden of disease.

Our results are consistent with those found in previous studies evaluating patients in the short-term after COVID-19 infection (12, 13). Skjorten and colleagues, using a treadmill, found one-third of patients with a ppVO2 less than 80%, additionally, 15% percent of these patients had shown reduced ventilatory efficiency (12). Clavario et al. reported one-third of patients with a reduced peak VO2 3 months post-discharge

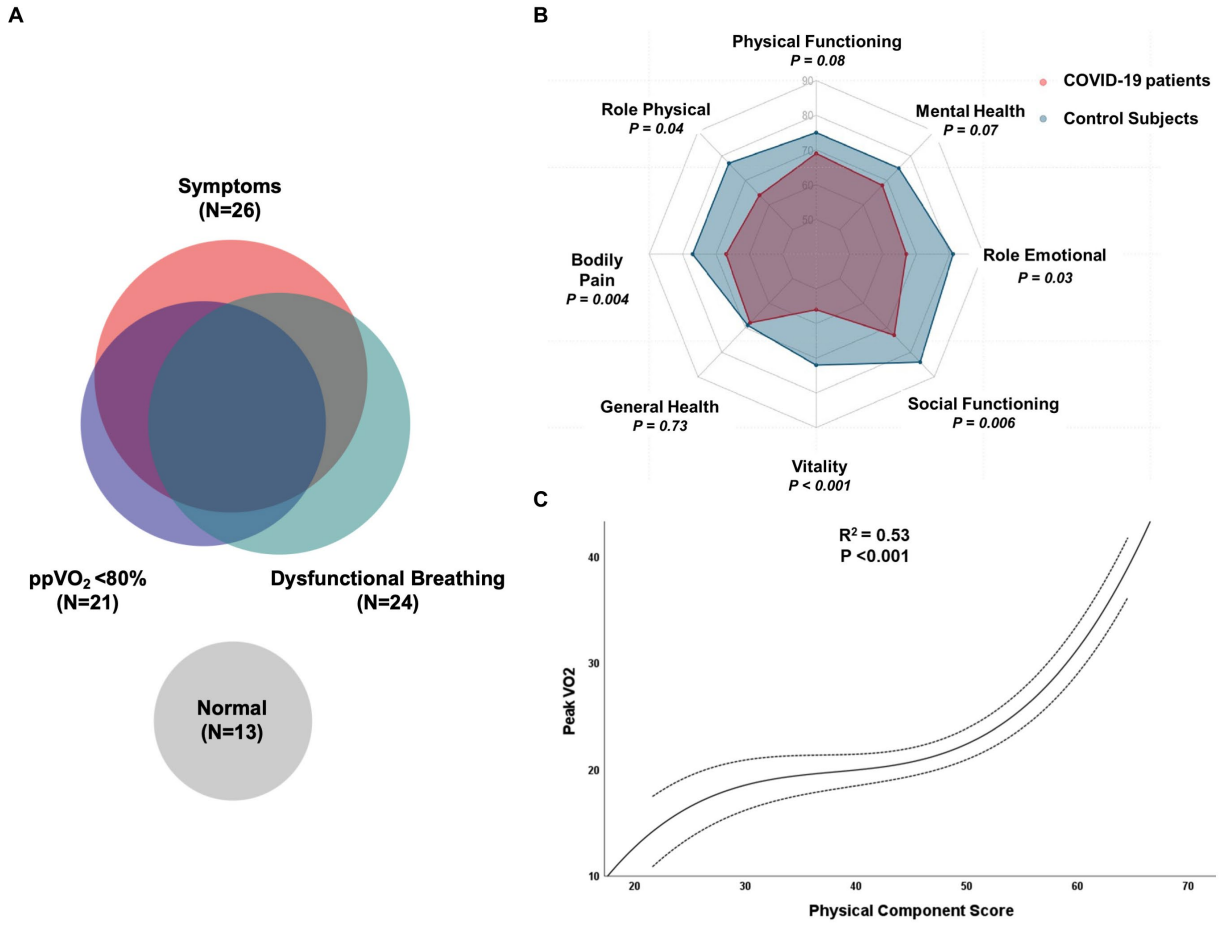

FIGURE 3
(A) Venn diagram illustrating the relationship between symptoms, reduced percent-predicted peak oxygen consumption, dysfunctional breathing and normal evaluation in COVID-19 patients. **(B)** Evaluation of quality-of-life domains of SF-36 between healthy controls and hospitalized COVID-19 patients six months after discharge; **(C)** Cubic regression between peak oxygen consumption during CPET and physical component score of HRQol in COVID-19 patients.

on cycle ergometer CPET, mostly due to muscular impairment (13). Many recent data suggest that peripheral factors are incriminated in persistent functional impairment in post COVID-19 patients. A small study was conducted in 10 patients without cardiopulmonary disease who recovered from COVID-19. Patients were investigated with invasive cardiopulmonary exercise testing (iCPET) and compared to 10 age- and sex-matched controls (25). The reduction in peak VO2 was associated with impaired systemic oxygen extraction, depicting a peripheral rather than a central cardiac limitation.

Functional impairment after COVID-19 infection remains a major concern. We demonstrated that after 6 months of discharge, COVID-19 patients had a reduction in ppVO2 and peak VO2 when compared to matched controls. The observed higher peak VO2 in males was not confirmed by the ppVO2, suggesting an absence of sex-related post-COVID-19 hospitalization functional impairment. Interestingly, we did not find any exercise limitation due to pulmonary gas exchange or ventilatory mechanics. In keeping with previous reports, cardiocirculatory limitation was the predominant deficit encountered in our study. A recent meta-analysis explored the utility of CPET to evaluate long COVID-19 symptoms in adults, showing that exercise capacity was reduced in these patients and that CPET may provide insight into the mechanisms for this impairment (26).

Several patients after COVID-19 had presented a rapid and irregular breathing pattern consistent with DB, which is characterized sometimes by rapid shallow breaths or other erratic ventilatory patterns (20, 21). It was associated with persistent symptoms such as dyspnea and fatigue, and with a reduced ppVO2 as well. We have found a similar prevalence of DB when comparing our data to other studies, also showing a positive correlation of this ventilatory abnormality with symptoms (20, 27). Nevertheless, identification of DB is subjective and requires pattern recognition, without any strict criteria. The development of quantitative methods would help us to diagnose this entity.

Notably, the requirement of Bilevel support, mechanical ventilation, ICU admission, hospital length of stay, and COVID-19 severity were all associated with a reduced ppVO2. The high number of COVID-19 infected patients will certainly impact the demand for dyspnea evaluation and referrals for rehabilitation soon. We should be aware that symptoms persist even 6 months after hospital discharge in COVID-19 patients. A preemptive approach towards rehabilitation could be beneficial, especially in those more likely to be impacted such as in those with severe disease presentations. Physical rehabilitation

TABLE 3 Crude and adjusted analysis of variables related to percent-predicted peak VO2 after COVID-19 hospitalization.

	ppVO2 (%)		
	OR	95% CI	*p* value
COVID-19 vs Controls			
Unadjusted	0.92	0.88–0.97	0.003
Adjusted[a]	0.92	0.87–0.97	0.002
COVID-19			
Age (years)	0.99	0.99–1.00	0.09
Male sex	0.94	0.87–1.02	0.15
BMI (kg/m^2)	1.00	0.99–1.01	0.10
Hypertension	0.95	0.87–1.03	0.25
Diabetes	0.96	0.87–1.06	0.49
CAD	0.83	0.76–0.89	<0.001
Advanced oxygen support	0.91	0.79–1.04	0.20
-High flow cannula	0.94	0.76–1.16	0.57
-Bilevel	0.83	0.78–0.88	<0.001
-Mechanical ventilation	0.88	0.79–0.98	0.02
ICU admission	0.94	0.81–1.09	0.45
Hospital length of stay (days)	0.99	0.99–0.99	0.001
WHO COVID-19 Severe/Critical	0.89	0.80–1.00	0.06

Bilevel, bi-level positive airway pressure; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CPAP, continuous positive airway pressure; CPET, cardiopulmonary exercise testing; ICU, intensive care unit; OR, odds ratio; ppVO2, predicted-percentage peak VO2; WHO, world health organization. Continuous data are presented as mean ± standard deviation or median (p25–p75). [a]Adjusted for age, sex, height, and weight.

after discharge could improve these symptoms, especially in patients with a severe initial COVID-19 presentation, but the efficacy of this intervention is yet to be established in this scenario (27).

Mental and physical aspects of HRQoL were significantly reduced in COVID-19 patients 6 months after discharge. A reduced mental aspect of HRQoL is consistent with the findings of sleep disturbances, depression, anxiety, and cognitive impairment as reported in a systematic review (28). Of note, the comparison of HRQoL scores was adjusted by age and sex according to national normative data, which strengthens the evidence for this impairment when compared to the general population. Both peak VO2 and ppVO2 were positively correlated with several aspects of HRQoL, not only physical, but also social and mental. It provides a better understanding of persistent impairment after moderate to severe COVID-19: there is a pathophysiological basis for these symptoms associated with a documented reduction in exercise capacity.

Our study has several limitations. Although we used a 3:1 control ratio, our study cannot support that the late exercise impairment observed in COVID-19 patients is related exclusively to this etiology. Comparing CPET parameters after hospital discharge with a population affected by another viral pneumonia could better clarify if COVID-19 is responsible for these symptoms or they are merely due to the hospital stay. One of the variables most affected in post COVID subjects is the diffusion capacity, which was not measured in our study. Recruitment to the study is another limitation. The stigma related to COVID-19 infection and the environmental safety for a CPET study were barriers to patient recruitment. Although the selection was not based on the presence of symptoms, patients more likely to present dyspnea or fatigue could be more prone to accept the research invitation. Our inclusion criteria limited the results to hospitalized patients with pulmonary involvement, so caution should be taken in extrapolating these findings to less severe patients.

Conclusion

Hospitalized COVID-19 patients showed decreased exercise capacity after 6 months from discharge related mainly to cardiocirculatory impairment and peripheral muscle limitation. Dysfunctional breathing was common and associated with persistent symptoms. Both physical and mental quality of life domains were reduced in these patients. The requirement of higher level of oxygen support, intensive care admission, longer hospital stay, and COVID-19 severity were the main predictors of reduced peak VO2. Our results highlight the health support required by these patients even after more than 6 months from hospital discharge.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de Ética do Hospital de Clínicas de Porto Alegre. The studies were conducted

in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AS: Writing – original draft, Writing – review & editing. FS: Writing – original draft, Writing – review & editing. MSa: Writing – original draft, Writing – review & editing. DB: Writing – review & editing. MM: Writing – original draft. JM: Writing – review & editing. GJ: Writing – review & editing. IS: Writing – review & editing. GZ: Writing – review & editing. MT: Writing – review & editing. MC: Writing – review & editing. MSc: Writing – original draft. RS: Writing – review & editing. RR: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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PANDEM-Source, a tool to collect or generate surveillance indicators for pandemic management: a use case with COVID-19 data

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Introduction: PANDEM-Source (PS) is a tool to collect and integrate openly available public health-related data from heterogeneous data sources to support the surveillance of infectious diseases for pandemic management. The tool may also be used for pandemic preparedness by generating surveillance data for training purposes. It was developed as part of the EU-funded Horizon 2020 PANDEM-2 project during the COVID-19 pandemic as a result of close collaboration in a consortium of 19 partners, including six European public health agencies, one hospital, and three first responder organizations. This manuscript describes PS's features and design to disseminate its characteristics and capabilities to strengthen pandemic preparedness and response.

Methods: A requirement-gathering process with EU pandemic managers in the consortium was performed to identify and prioritize a list of variables and indicators useful for surveillance and pandemic management. Using the COVID-19 pandemic as a use case, we developed PS with the purpose of feeding all necessary data to be displayed in the PANDEM-2 dashboard.

Results: PS routinely monitors, collects, and standardizes data from open or restricted heterogeneous data sources (users can upload their own data). It supports indicators and health resources related data from traditional data sources reported by national and international agencies, and indicators from non-traditional data sources such as those captured in social and mass media, participatory surveillance, and seroprevalence studies. The tool can also calculate indicators and be used to produce data for training purposes by generating synthetic data from a minimal set of indicators to simulate pandemic scenarios. PS is currently set up for COVID-19 surveillance at the European level but can be adapted to other diseases or threats and regions.

Conclusion: With the lessons learnt during the COVID-19 pandemic, it is important to keep building capacity to monitor potential threats and develop tools that can facilitate training in all the necessary aspects to manage future pandemics. PS is open source and its design provides flexibility to collect heterogeneous data from open data sources or to upload end users's own data

and customize surveillance indicators. PS is easily adaptable to future threats or different training scenarios. All these features make PS a unique and valuable tool for pandemic management.

KEYWORDS

surveillance, pandemic preparedness, public health, COVID-19, open data, data collection, data generation, pandemic management

1 Introduction

PANDEM-2 is a Horizon 2020 EU-funded project aiming to develop and demonstrate innovative solutions to strengthen pandemic preparedness and response at the EU level for public health emergencies at subnational, national, EU, and global levels. The IT tools are accessible through an interactive decision support dashboard that encompasses data for disease surveillance from a variety of domains including data from traditional epidemiological surveillance data sources, non-pharmaceutical interventions, contact tracing, and hospital resources, but also data from non-traditional surveillance data sources such as data from social or mass media analysis, participatory surveillance and flights. An integrated epidemiological and hospital resource capacity modeling is also available to support planning and what-if scenarios.

The PANDEM-2 consortium includes partners that cover key aspects of pandemic preparedness and response including six National Public Health agencies in the EU (RKI in Germany, FOHM in Sweden, THL in Finland, INSA in Portugal, NIPH in Romania, and RIVM in the Netherlands) and three first responders organizations (Austrian Red Cross, Italian Red Cross, INEM Portugal), and the Radboud Medical Center in the Netherlands. All the tools developed were designed and validated in close collaboration with the consortium partners and are distributed using open-source licenses.

PANDEM-Source (PS) is an IT surveillance tool to collect and integrate openly available public health-related data from heterogeneous data sources to better support communicable disease surveillance for pandemic preparedness and response. PS's main objective is to identify, map, and integrate pandemic-related data from multiple sources into a coherent pandemic-management database so it can provide all the necessary data to feed the PANDEM-2 dashboard with, when available, near real-time data. Its data model was developed in close coordination with the consortium partners aiming to address the challenge of monitoring the COVID-19 pandemic response, but it is flexible and can be adapted to other diseases or new threats, variables, and indicators by changing source description files without changes in code.

Effective training of public health professionals is an essential element to strengthen pandemic management (1), which is targeted by the PANDEM-2 project by developing training scenarios and simulation exercises (2). During the simulation exercises, the PANDEM-2 dashboard displays realistic information matching a specific designed scenario for training.

Collecting and producing the required data can be a challenge due to the broad scope of information displayed on the dashboard for pandemic management and training. To ensure quality and facilitate processes, PS includes monitoring systems/visualization of data collection by source and features to detect missing data on an initial set of indicators. The data generation process is based on these "initial" indicators to create a realistic full synthetic dataset covering all necessary variables to perform the simulation exercises. These features were used during the PANDEM-2 simulation exercise, which focused on assessing PANDEM-2 tools applied in Public Health Emergency Operation Centers in Germany and the Netherlands during an influenza pandemic scenario. For this scenario the initial set of indicators was produced using the PANDEM-2 modeling tools and included confirmed cases, deaths, and vaccination status by age group for Germany and the Netherlands. Subsequently, PS generated data for the remaining variables in the dashboard for all EU/EEA countries, including subnational level and distribution by age group, sex, and presence/absence of comorbidities. These generated variables encompassed data on contact tracing, hospital resources, and social media analysis trends (sentiment, emotion, and suggestion). After data generation, PS performed the calculations for those indicators that needed to be computed such as bed occupancy, incidence rates, mortality rates, vaccination rates, etc.

In this paper, we will describe PS's features and design with the aim of disseminating its characteristics and capabilities to strengthen pandemic preparedness and response.

2 Methods

2.1 Identification of relevant variables and indicators for pandemic management

The PANDEM-2 project commenced 12 months after the onset of the COVID-19 pandemic in the EU. The initial work involved a requirement-gathering process with the European public health agencies and first responders on the PANDEM-2 consortium. We conducted a structured process to identify the most important variables and indicators to be included in a dashboard to address current and future needs for pandemic management. This process is described and discussed in (2) and included the following steps: A web and literature search and meetings with experts, which allowed us to identify relevant data sources for the project as well as which ones were openly available. In parallel, all consortium participants were invited to provide a list of data requirements, variables and indicators according to their ideal dashboard to be used for pandemic management. The list of requirements and meeting outputs were analyzed to produce an initial list of variables that were grouped in different data families. A data survey was distributed to end users to score the relevance for pandemic management and to provide details on their data priorities and availability for all the identified

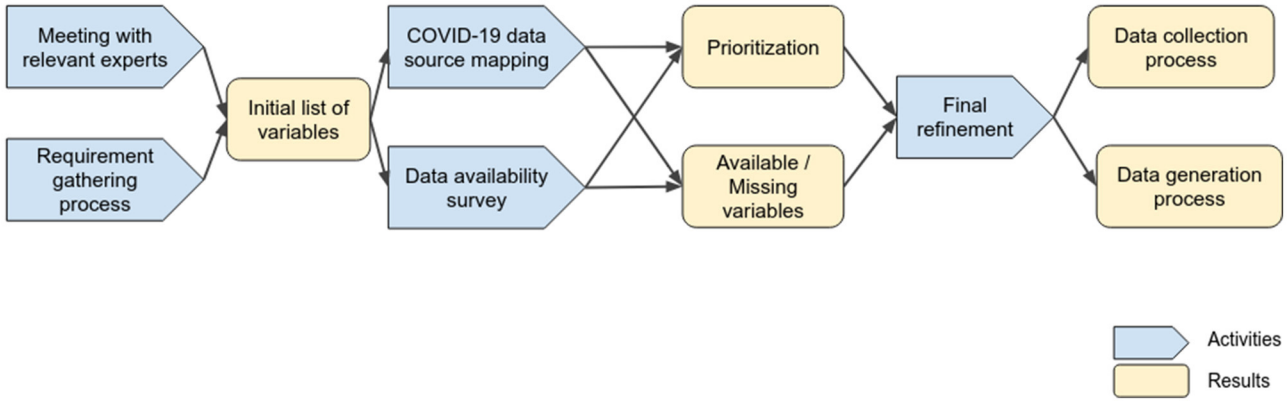


FIGURE 1
Process followed for identifying pandemic management variables and indicators to be collected or generated.

variables focusing on the COVID-19 use case. These outputs were used to accomplish a final refined list of variables taking into consideration PANDEM-2 partners's assessment of importance, priorities, and data availability. We defined an automatic data collection process for variables available in open data sources and data generation for non-available variables. We generated synthetic data for missing relevant variables to showcase the full potential of the PANDEM-2 dashboard and to introduce it as a training resource for pandemic management. Figure 1 schematises this approach by stating activities, results, and dependencies.

2.2 Design goals

PS was designed to achieve the following design goals:

- Adding new sources and variables should be possible without changes in code.
- Keep track of the reporting institution and methodology for collecting and computing data.
- Capability of integrating data from a wide variety of sources and formats.
- Automatic data standardization based on the source description having capacity from transcoding from multiple coding schemas, e.g., the region name in local languages to the region code.
- Integration, type, and standardization errors are informed to the data manager.
- The data integration process should be fault-tolerant. Errors during data importing process should not lead to data loss.
- Generating synthetic data with the purpose of using the PANDEM-2 dashboard as a training resource for pandemic management.

2.3 Assumptions

In order to generate a generic approach for data integration we defined the following assumptions:

- A variable is a label indicating a general concept. Some variables are computed indicators that can be evaluated using data collected directly from data sources, e.g., incidence rate. Names are previously defined and are associated with a particular definition, the type (numeric or text), coding schema, and/or calculation method.
- Limited variable types: integer, numeric, date, datetime, and string.
- Variables can be grouped into observations and attributes. Observations contain mainly epidemiological information such as "number of cases" or "incidence rate." Attributes provide extra information or characteristic details associated with a particular observation, e.g., the age group of the observed cases.
- Variables can be tied together as tuples containing a unique measure, a date, a source, and several attributes:
  - Confirmed cases:13
  - Pathogen: dengue
  - Age group: 10–18
  - Date: 2021-12-13
  - Geo: Brussels
  - Source: ECDC
- Time series are built using observation values in time for tuples with the same attributes, e.g., the evolution of confirmed cases for a given age group and city. Indicators can be calculated using functions at the time series level, e.g., the time series for the effective reproduction number (Rt) is obtained based on the time series of the number of confirmed cases over time for a disease and the given population in that geographical location.
- For a given set of attributes and an observation, there can be only a single unique value.
- Data sources provide stable identifiers that can be used for unequivocally retrieving the associated data.
- Data source resources can be read in a tabular format.

2.4 Data pipeline design

To tackle the issue of data collection and generation we developed the data labeling schema (DLS), a declarative methodology based on text files, for documenting, standardizing,

and integrating surveillance data sources and producing homogeneous and comparable time series. This methodology provides a common approach to address the heterogeneity of formats, sources, and types of data found during the COVID-19 pandemic.

The DLS integration pipeline uses a set of source description files providing information including ownership, how to detect changes to trigger an import, the file format, how to read the files in a tabular format, how to map columns to PS variables, and the applicability of data generation. The list of PS variables contains functions for calculated indicators such as incidence or mortality rate so they can be automatically calculated when the required parameters for its computation are present. Such functions are defined in R language, a widely used language in the domain of epidemiology. Advanced calculations can be performed by integrating third-party algorithms. For instance, social media analysis data are obtained thanks to natural language processing algorithms developed by the University of Galway. A final aggregation step is performed up to country level if not previously provided by the source.

Providing data for training purposes can be a difficult task since not all expected data are available or because the training scenario is completely fictitious. To address this issue, PS includes data generation formulas. When a data source for a training exercise is loaded, PS will automatically detect which variables are missing and will evaluate the synthetic formulas to generate the missing time series. When partitioned data is missing, e.g., deaths by comorbidity, a weighted sample function is applied using probabilities between groups matching the specific scenario. When data is missing for a training exercise, hypothetical estimations are created based on present data. For example, to estimate the number of people traced for contact tracing we used the number of public health workers available and a given capacity to daily contact new confirmed cases, allowing us to simulate system overloading. It should be noted, that here our primary intention was to use these formulas to align with the training scenario previously mentioned, and not to represent accurate epidemiological data estimations. To avoid confusion with real data, time series generated in such a way are tagged in the resulting dataset as "synthetic."

The resulting data are stored as JSON files and available using a REST API (3) allowing to query the integration process and obtain the results. Figure 2 shows the entire PS integration pipeline.

3 Results

3.1 The list of variables

The process of meeting data requirements and defining pandemic management variables produced a list of 29 main variables (Table 1). The complete list of variables is described in (4). Variables are grouped into data families associated with different aspects of pandemic management. Rates and stratification by different attributes are computed for most of the main variables.

3.2 Integrated sources

PS uses a set of source description JSON files containing the necessary information for integrating data and calculating time series. During the PANDEM-2 project, we developed source description files for European Union countries using data from the COVID-19 pandemic. Collected data was limited to the publicly available sources listed here below and excluded any individual case data. We used the data available at the most fine-grained geographical level.

It is important to highlight that PS supports an all-hazard approach (5). Given the emergence of COVID-19 and due to the extensive heterogeneous data required for pandemic management, this proved to be a valuable use-case. However, PS can be easily extended to support other diseases or threats, with their variables and indicators, as well as other geographical scopes.

Sources used to build the PANDEM-2 COVID-19 dataset (4) can be grouped into those used as indicators (or to compute indicators) and those used for standardization. The list of sources implemented are the following:

- Sources used for indicators:
  - ECDC COVID-19 datasets (6): Selection of datasets describing the EU members's surveillance and response to the pandemic published by the European Center for Disease Prevention and Control (ECDC).
  - COVID-19-Datahub (7): A unified dataset collecting global fine-grained case data on the pandemic surveillance and response. This dataset is used for indicators that are not available at a subnational level on ECDC datasets.
  - Our World in Data (8): Our World in Data is a scientific online publication that focuses on global problems. It provides several COVID-19-related datasets. This source was used to obtain excess mortality data since this indicator was missing from previous sources.
  - Influenzanet (9): A Europe-wide network to monitor the activity of influenza-like illness (ILI) with the aid of volunteers via the Internet. It is currently operational in 12 countries. Influenza.net also publishes datasets on participants declaring COVID-19 symptoms and healthcare-seeking behavior as well as provides estimated incidence for the participating countries.
  - Twitter, via the Panacea Lab COVID-19 tweet collection (10): A large-scale COVID-19 Twitter dataset for open science starting in March 2020. This dataset contains COVID-19-related tweet IDs. We obtained the list of IDs from the data-sharing platform Zenodo.org and downloaded the tweet texts using the Twitter API. The tweets were annotated using Natural Language Processing models to produce dedicated time series by country.
  - MediSys (11): The Medical Information System MedISys is an internet monitoring and analysis system developed at the European Commissions Joint Research Center in collaboration with ECs Directorate General for Health and Consumer Protection (DG SANCO) to rapidly identify potential threats to public health using information

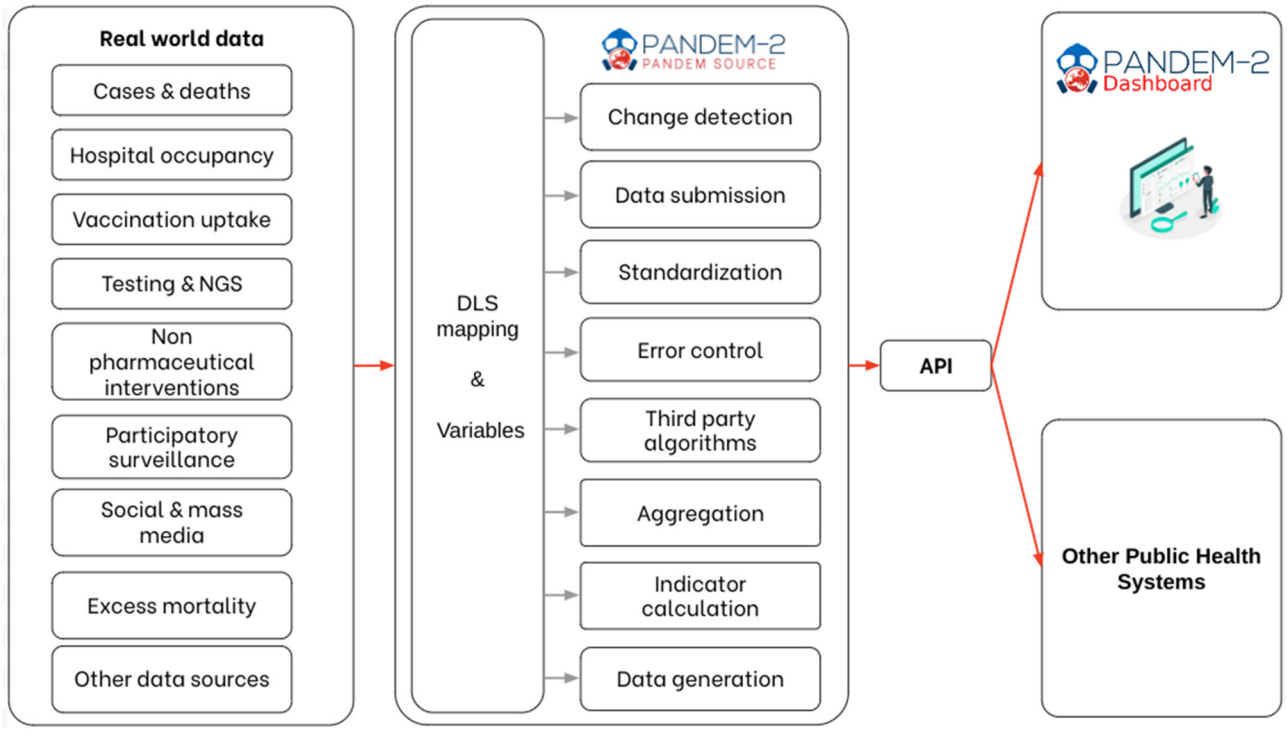


FIGURE 2
PANDEM-Source (PS) integration pipeline.

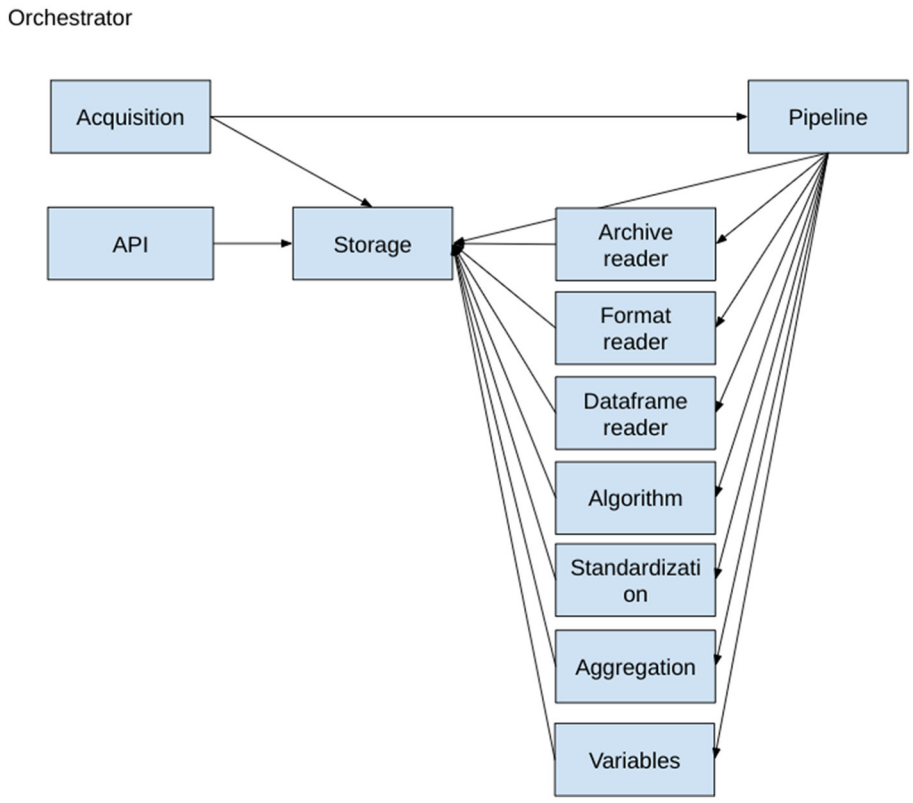


FIGURE 3
PANDEM-Source (PS) actor dependencies.

PANDEM II: Data Surveillance | Integration progress | Data sources | Data dictionary | Time series | About

Data Surveillance

Show 50 entries

	Name	Progress	Step	Status	Last Import Started	Last Import Ended	Next Check	Files	Mb	Issues
1	COVID-19 Datahub	100.00%	ended	success	2023-05-09 21:13:09	2023-05-11 18:47:23	2023-05-11 02:00:00	494	609.8	150
2	ECDC Atlas	100.00%	ended	success	2022-11-15 04:01:06	2022-11-15 06:49:46	2022-11-17 04:00:59	1	10.5	50
3	ECDC COVID-19	100.00%	ended	success	2023-05-30 17:29:29	2023-05-30 17:29:55	2022-11-16 04:00:45	10	64.2	450
4	ECDC COVID-19 Simulated	100.00%	ended	success	2023-05-31 00:17:39	2023-05-31 00:19:49	2022-11-16 04:35:05	81	21.2	100
5	Eurostats NUTS	82.50%	ended	success	2023-05-30 00:52:55	2023-03-30 14:35:08	2023-01-28 01:00:00	4	2.2	102
6	GeoNames	100.00%	ended	success	2022-11-16 01:00:00	2022-11-16 09:56:46	2022-11-17 01:00:00	2	0.1	50
7	ICD-10-CM	100.00%	ended	success	2022-08-20 01:00:07	2022-08-20 01:01:57	2022-11-17 01:00:00	1	21.2	0
8	ISCO-08-ILO	100.00%	ended	success	2022-11-16 00:56:58	2022-11-16 00:57:11	2022-11-18 01:00:00	1	0.3	0
9	Influenza net	100.00%	ended	success	2023-02-06 08:09:56	2023-02-06 08:10:45	2023-02-08 04:00:00	17	0.6	0
10	MediSys	100.00%	ended	success	2022-10-25 21:24:08	2022-11-18 16:01:08	2022-10-25 21:44:07	1	0	0
11	OECD	100.00%	ended	success	2023-01-26 14:56:19	2023-01-26 15:32:20	2023-01-27 14:56:19	1	0	0
12	OpenSky-Network-CovidDataset	100.00%	ended	success	2022-09-11 01:39:22	2022-09-11 02:14:11	2022-11-16 01:00:00	39	16952.5	50
13	Our-World-In-Data	100.00%	ended	success	2022-12-12 02:15:32	2022-12-12 14:53:11	2022-12-14 01:00:00	1	1.8	0
14	OurAirports	100.00%	ended	success	2022-11-16 01:00:01	2022-11-16 09:57:11	2022-11-17 01:00:00	2	20.3	50
15	Pandem-2 2023 FX	98.24%	ended	success	2023-03-13 23:16:02	2023-03-14 06:38:46	2023-02-23 02:03:50	5	15.1	0
16	RIVM COVID-19 manual	100.00%	ended	success	2022-06-02 15:10:02	2022-06-02 15:20:30	2022-11-16 09:52:40	5	15	50
17	RKI COVID-19 manual	100.00%	ended	success	2022-08-15 09:22:34	2022-08-15 09:31:00	2022-11-16 09:52:28	6	11.3	0
18	SeroTracker	100.00%	ended	success	2022-11-16 05:00:04	2022-11-16 09:57:43	2022-11-17 05:00:01	1	20.9	50
19	THL COVID-19 manual	100.00%	ended	success	2022-06-02 15:09:51	2022-06-02 15:20:28	2022-11-16 09:52:41	5	1.7	0
20	Twitter	100.00%	ended	success	2022-11-24 06:14:10	2022-11-24 07:56:13	2022-11-24 08:13:11	1	0.8	0
21	Twitter datasets	100.00%	ended	success	2023-05-23 08:20:13	None	2023-05-24 01:00:00	102	0.1	0

Showing 1 to 21 of 21 entries Previous 1 Next

Jobs

Show 50 entries

	Id	Source	Progress	Step	Status	Started	Ended	Files	Mb	Issues
1	8789	ecdc-covid19-variants-of-interest	100.00%	ended	success	2023-05-30 17:29:29	2023-05-30 17:29:55	1	0	0
2	8788	ecdc-covid19-daily	100.00%	ended	success	2023-05-30 00:58:16	2023-05-30 03:44:20	1	1.6	50
3	8787	ecdc-covid19-age-group	100.00%	ended	success	2023-05-30 00:57:09	2023-05-30 03:00:27	1	2.1	50
4	8786	ecdc-covid19-measures	100.00%	ended	success	2023-05-30 00:54:39	2023-05-30 01:29:38	1	0.1	50
5	8785	ecdc-covid19-vaccination	100.00%	ended	success	2023-05-30 00:54:05	2023-05-30 03:33:31	1	42.6	50
6	8784	ecdc-covid19-weekly	100.00%	ended	success	2023-05-30 00:53:22	2023-05-30 03:23:58	1	1.6	50
7	8782	ecdc-covid19-weekly-hospital-occupancy	100.00%	ended	success	2023-05-30 00:51:43	2023-05-30 13:37:20	1	2.1	50

FIGURE 4
The PANDEM-Source (PS) data integration page.

from the internet. MedISys continuously monitors approximately 900 specialist medical sites plus all the generic EMM news, i.e., over 20,000 RSS feeds and HTML page sites from 7,000 generic news portals and 20 commercial newswires in altogether 70 languages. We generated a connector for Medisys capable of extracting the last 30 days of articles for predefined topics but due to the lack of historic data access, this source could not be included in the COVID-19 dataset.

- OpenSky Network (12): OpenSky Network is a non-profit association that provides open access to flight tracking control data. It was set up as a research project by several universities and government entities with the goal of improving the security, reliability, and efficiency of the airspace. The used dataset is a derived version from the full dataset published on Zenodo covering the period from 2019 to 2022.
- Eurostat (13): Eurostat is the statistical office of the European Union and publishes a wide range of datasets and statistics concerning European countries. We obtained information about available beds and hospital staff resources.
- OECD (14): The OECD (Organization for Economic Co-operation and Development) regularly publishes comparable statistics on numerous subjects. In the case of COVID-19, it was the selected source

TABLE 1 List of PANDEM-Source (PS) variables.

Data family	Main variable	Stratification and rates
Cases	Confirmed cases	By genetic variant, by sex, by presence/absence of comorbidities (presence or absence of any comorbidity), rate in the population (incidence rate)
	Number of notifications	Rate in the population
	Active cases	Rate in the population
	Recovered cases	Rate in the population
	Rt number	
Deaths	Deaths	By bed type (ICU, ward), mortality rate in the population, mortality rate within hospitalized patients
	Excess mortality	
Hospital capacity	Hospitalizations	By bed type, by presence/absence of comorbidities, by presence/absence of comorbidities and bed type, bed occupancy rate, hospitalization rate in the population, hospitalization rate in patitents with/without comorbidities
	Average length of stay	By bed type
	New Hospitalizations (admissions)	By bed type, by presence/absence of comorbidities, new hospitalizations bed occupancy rate, new hospitalizations rate in the population
	Available staff	By staff type (medical doctors, nurses, etc.), rates in the population
	Bed capacity (available beds)	By bed type, bed capacity rate in the population
Syndromic surveillance	Primary care cases	By ILI/ARI and SARI
	Primary care positivity rate	By ILI/ARI and SARI
Testing and lab	Performed tests	By genetic variant, by test type (PCR, antigen test, etc.), positivity rate, testing rate
	Sequenced samples	By mutation, by genetic variant, sequenced rate among tested
Vaccination	Doses injected	By dose number, vaccination rate by dose
	People fully vaccinated	Vaccination rate
Contact tracing	Contact tracing cases	By being already a contact (previously identified as a contact of a case), by reached status (if this person have been contacted), by reached in a day (reached within 24 hours after their test result)
	Contact tracing contacts	By reached status, by reached in a day (reached within 24 hours after contact identification, i.e., same day or day after)
Participatory surveillance	Participants declaring symptoms	
	Number of participants	
	Estimated incidence	
	People seeking health care	By visit type (primary care, emergency, hospital)
Non-pharmaceutical interventions	Implemented_measure	By specific measure (e.g., Contact tracing)
Population studies	Seroprevalence	By study name
	Studied population	By study name
Transport	Number of incoming flights	By country of origin
Social and mass media	Article count	By topic, sentiment, emotion and suggestion
Referential	Population	By subpopulation (age group, sex, etc.)

The complete list of variables is described in (4).

for obtaining an estimation of the evolution of the number of Intensive Care Unit (ICU) operational beds by country.

- SeroTracker (15): SeroTracker is a dashboard and data platform for SARS-CoV-2 serosurveys. They conduct systematic reviews to track serosurveys (antibodies testing-based surveillance) around the world. Seroprevalence studies results were integrated.

- Sources used for standardization:
  - Eurostat (16): The NUTS classification (Nomenclature of territorial units for statistics) is a hierarchical system for dividing up the economic territory of the EU and the UK. Standard region codes and names were obtained.
  - Geonames.org (17): GeoNames is a geographical database distributed under the Creative Commons attribution license. It contains over 27 million geographical names. We

used this source to extract ISO2 and ISO3 code equivalences and to obtain multilingual aliases for countries in the world and regions in Europe.

- ICD-10-CM (18): The ICD-10 Clinical Modification (ICD-10-CM) is a modification of the ICD-10 (International Classification of Diseases) used as a source for diagnosis codes in the United States of America. This source was used to obtain the list of pathogens.
- ISCO-08 (19): ISCO-08 ISCO-08 is a four-level hierarchically structured classification that allows all jobs in the world to be classified into 436 unit groups. We used this codification to store information about staff resources types in hospitals such as doctors or nurses.
- OurAirports (20): OurAirports is a free site where visitors can explore the world's airports, read other people's comments, and leave their own. This site provides freely available files with the list of world airports.

Since PS's sources are currently in the public domain, there are no particular risks in widely sharing the tool or the produced outputs.

3.3 PANDEM-Source pipeline implementation

3.3.1 Source description

The Data Labeling Schema (DLS) is a declarative approach that requires a detailed description of the sources using JSON files in complement with a list of variables, mappings, and indicator formulas. Based on the source description, PS takes care of all transformations to perform the data acquisition, validation, standardization, and, if necessary, the calculation of indicators or data generation. Each data unit goes through the same standardized integration pipeline (Figure 2). This reduces the risk of errors and ensures updated metadata are kept in the final database. Each variable is linked to a unit, a source, and a date of integration, and mapped to a target "pre-defined" PS variable providing a description, a referential (if transcoded was necessary), and associated formulas. If new variables need to be added, the list of variables can be directly modified to include new concepts without changes in code. A CSV file can be easily modified by a data manager allowing complete autonomy on variable definitions, which is a key feature to allow adaptation to unknown or novel threats. The file is publicly available on GitHub.[1]

3.3.2 Data acquisition

The source descriptor file of each source must also define all necessary information to monitor each source, trigger automatic updates when changes are performed on the source, and how to interpret file format to acquire data. Multiple acquisition channels were implemented including git repositories, URLs, and predefined Application Programming Interfaces (APIs). If a new channel is required, the user can provide custom R or Python scripts to perform the data acquisition. PS checks for updates on a regular predefined basis using when-available versioning methods to avoid downloading data to detect changes.

The source descriptor files also define the format of target files, including Excel, CSV, JSON, and XML. Each format has its own formatting properties to interpret the provided data. If the source files are too complex or need to be cleaned before integration, PS supports the usage of dedicated Python scripts to pre-process datasets.

3.3.3 Standardization

A number of well-defined standards (21, 22) are included in PS and the tool automatically monitors and updates these references from public data sources to compute specific indicators, from NUTS, ISO country codes, ICD-10 diseases, or geonames. When input data do not match the expected format or referential data, PS provides a list of integration issues allowing the data manager to visualize and fix them. For instance, if a source provides the number of confirmed cases for an unknown country, the data are ignored and details of integration issues are reported. The user can define mappings using JSON files to support transcoding between different codification systems such as ISO3 country codes or region names to NUTS.

3.3.4 Calculated metrics and indicators

Calculated indicators such as incidence rates and effective reproduction number (Rt) are produced by R scripts included in PS, which can be also modified by any user with basic knowledge of R language. PS proceeds automatically to indicator calculation whenever all necessary parameters are provided by a source. The indicator can also be collected if already computed on the source. Computing indicators is preferred to directly collecting them from data sources to ensure the same methodology is used, thus supporting comparability. Aggregation from the subnational to the national level is also performed automatically.

3.3.5 Data generation

In the list of variable definitions, PS also includes formulas for data generation allowing creating the entire PS datasets from a minimal set of input variables. This data generation feature was designed to generate training datasets that can be used during simulation exercises. This feature was used in the PANDEM-2 Functional Exercise which simulated pandemic Influenza and included two National Public Health agencies (Germany, the Netherlands) supported by all other end user organizations within the PANDEM-2 consortium. The PANDEM-2 modeling tools (23) were used to produce the time series for the number of cases, deaths, hospitalisations, and vaccinations, and PS used its data generation functions for generating plausible data about social media posts, participatory surveillance, contact tracing, public health staff variations, syndromic surveillance, and stratifications by comorbidities and age groups. This feature reduced the amount of effort needed to prepare the data for the simulation exercise.

1 https://github.com/pandem2/pandem-source/blob/main/pandemsource/data/list-of-variables.csv

3.4 PANDEM-Source architecture

PS is a Python package that implements the DLS with out-of-the-box definitions for integrating a wide range of indicators from heterogeneous surveillance data sources. It has been published on Pypi[2], its code is open under the EUPL[3] license and it is available on GitHub[4].

PS has been implemented following a microservices architecture using the Actor Model and using the package with pykka.[5] The actor architecture diagram is shown on Figure 3. Each actor receives messages, processes them one by one, and can send messages to other actors. Messages can be any Python object. This programming pattern allows to achieve a good level of parallelization of tasks while keeping a simple programming model and file access. For external algorithm integration, we have used docker containers and REST APIs. The following classes of actors have been defined:

- **Orchestrator:** Launch actors, manage docker encapsulation, and close actors.
- **Storage**: Keep persistent information of the integration process and process all data storage operations.
- **Acquisition**: Triggers data integration of known data source files.
- **Data pipeline**: Ensures that integration is performed and ensures that the process will run until an end (error, warning, or success).
- **Algorithms:** Execute a particular algorithm during the pipeline.
- **Format readers:** Transform input files into data frames.
- **Dataframe reader:** Transform data frames into a list of non-standard tuples.
- **Standardization:** Transform a list of non-standard tuples into a list of standard tuples.
- **API:** Provides a REST API for accessing public endpoints.
- **Variables:** Reads and writes standardized variable values. Provides necessary mapping information to standardization actor in order to standardize variable values e.g., Country Name => ISO code.

3.5 Integrating social media analysis components

The integration of social media components necessary to classify tweets required the execution of Social Media Analysis (SMA) components developed as part of PANDEM-2. These components were packaged and exposed as an API and utilized a TensorFlow Serving Docker to facilitate its integration. PS includes all necessary parameters to automatically launch the right docker tensor flow server locally if not already running on the configured URL; the only information that is required to run the algorithms is the folder where the models are saved. The models are launched using configuration files, so adding new models does not require changes to its code.

Once the models are running, PS will evaluate any source including the variable *article text*, and add the resulting model outputs as new attributes of the related tuple.

After annotation, the article text is removed for data protection reasons, and PS will calculate the aggregations for each used algorithm and produce the related time series.

3.6 Integrating the next generation sequencing simulator

Another external algorithm utilized is the Multiparametric Next Generation Sequencing (NGS) simulator (24). This tool is used to generate realistic time series by variant and mutation not being publicly available. The simulator combines real data from different sources to produce non-available time series such as cases by variants or the number of hospitalizations by age group and vaccination status. The resulting datasets are built using machine learning approaches to find a realistic combination of these variables. This simulator is written in R.

PS uses the simulator, which needs to be installed as an R package. It uses git to locally check if there have been changes on the input files before launching the simulator.

3.7 PANDEM-Source python package

PS includes a Shiny[6] app for validating the integration and visualizing the integrated time series. The 'data integration dashboard' is structured as follows:

3.7.1 Data integration page

List of integrated sources showing current integration status, next expected check for changes, the history of data sets collection executed, and issues found (see Figure 4). This page refreshes automatically.

3.7.2 Data sources page

List of defined data sources including information about the source descriptor files such as acquisition channel and variable mappings (see Figure 5).

3.7.3 Data dictionary page

The entire list of variables defined on PS including all metadata and formula definitions (see Figure 6).

3.7.4 Time series page

Displays all the integrated time series. A dynamic filter system and the count of matching time series help the user explore and

2 https://pypi.org/project/pandem-source/

3 https://ec.europa.eu/info/european-union-public-licence_en

4 https://github.com/pandem2/pandem-source

5 https://pykka.org/en/latest/

6 https://shiny.rstudio.com/

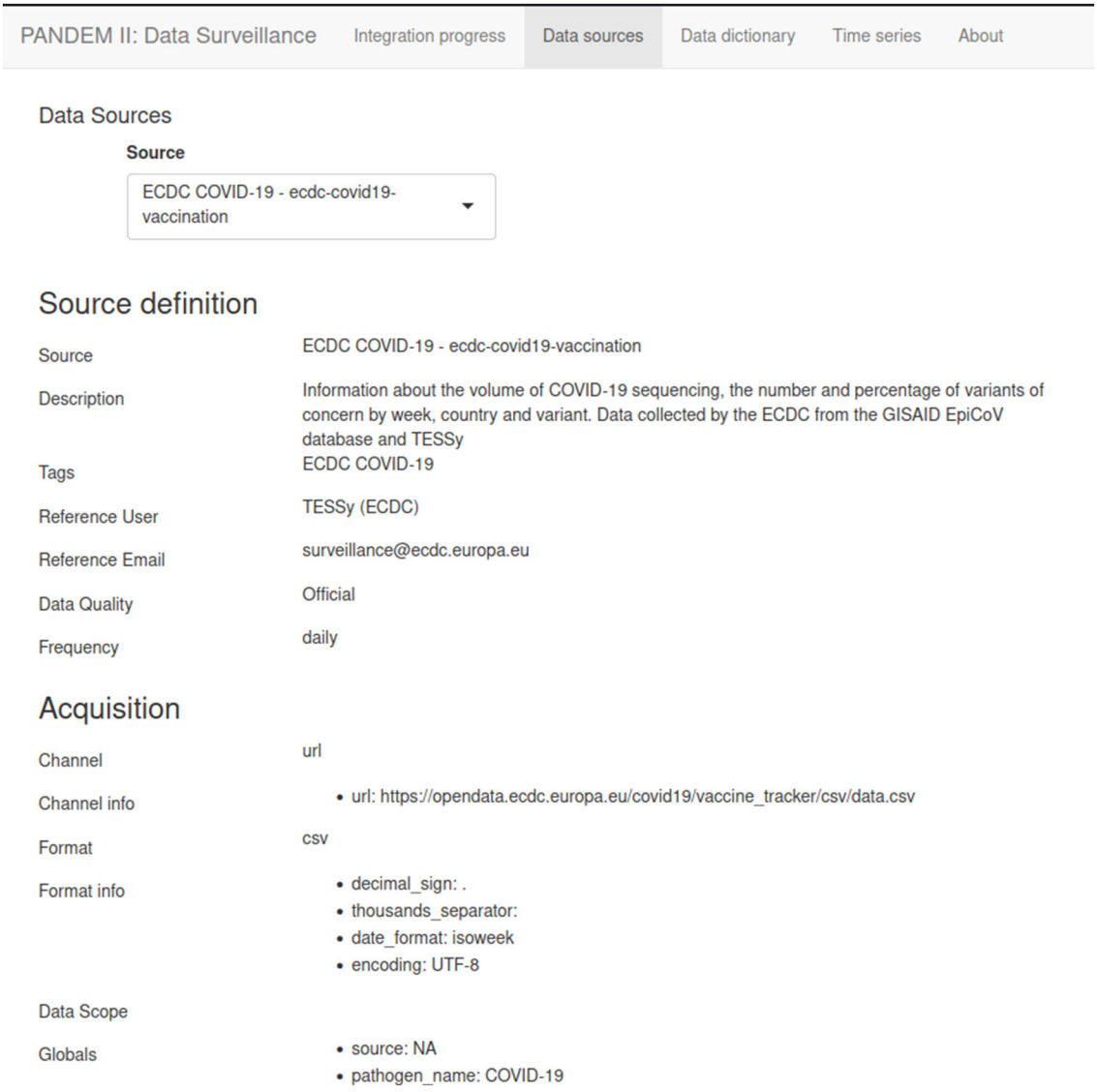


FIGURE 5
The PANDEM-Source (PS) data source page.

understand the underlying data (see Figure 7). Time series from different sources can be easily compared.

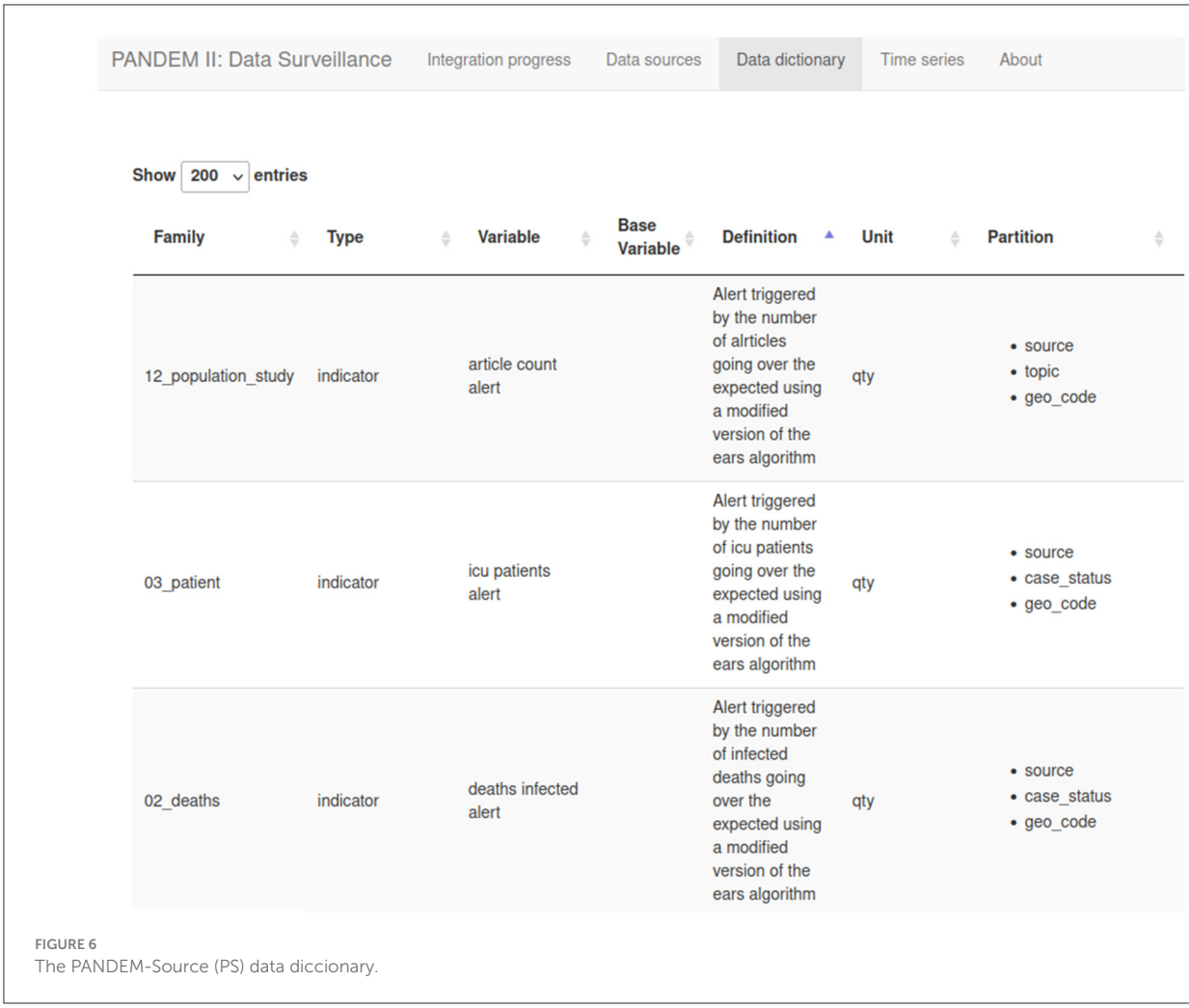
3.7.5 Exporting data

Data processed by PS is available via a REST API. Which can be regularly called to get the most current data.

The REST API is also the way of acquiring data for the Shiny[6] 'data integration dashboard' so any data on the integration dashboard can be replicated on the PANDEM-2 database. Figure 8 displays the implemented endpoints of the REST API.

4 Conclusions

In the context of the COVID-19 pandemic and within the umbrella of the PANDEM-2 project, PS has been developed in collaboration with large variety of health and public health experts to include within the PANDEM-2 dashboard relevant indicators for infectious disease surveillance and to monitor the health response. During the PANDEM-2 simulation exercises, PS and the PANDEM-2 dashboard have proven useful to facilitate training for pandemic management. The design provides flexibility to collect data from open data sources or to upload end users's own data and customize indicators. PS can support public health agencies and first responders in developing their own data collection tools according to their specific training and response needs and reduce the development effort of building them from scratch. The flexibility and easy-to-customize are the main features of PS which are supplemented by the capacity to generate realistic epidemiological synthetic datasets that can be used for training purposes. All these characteristics make PS a unique and valuable tool for pandemic management. To the best of our knowledge, although some data collection tools have been developed during the COVID-19 pandemic (7, 25, 26), PS is unique in terms of flexibility and customization to be adapted to different data



Family	Type	Variable	Base Variable	Definition	Unit	Partition
12_population_study	indicator	article count alert		Alert triggered by the number of alrticles going over the expected using a modified version of the ears algorithm	qty	• source • topic • geo_code
03_patient	indicator	icu patients alert		Alert triggered by the number of icu patients going over the expected using a modified version of the ears algorithm	qty	• source • case_status • geo_code
02_deaths	indicator	deaths infected alert		Alert triggered by the number of infected deaths going over the expected using a modified version of the ears algorithm	qty	• source • case_status • geo_code

FIGURE 6
The PANDEM-Source (PS) data diccionary.

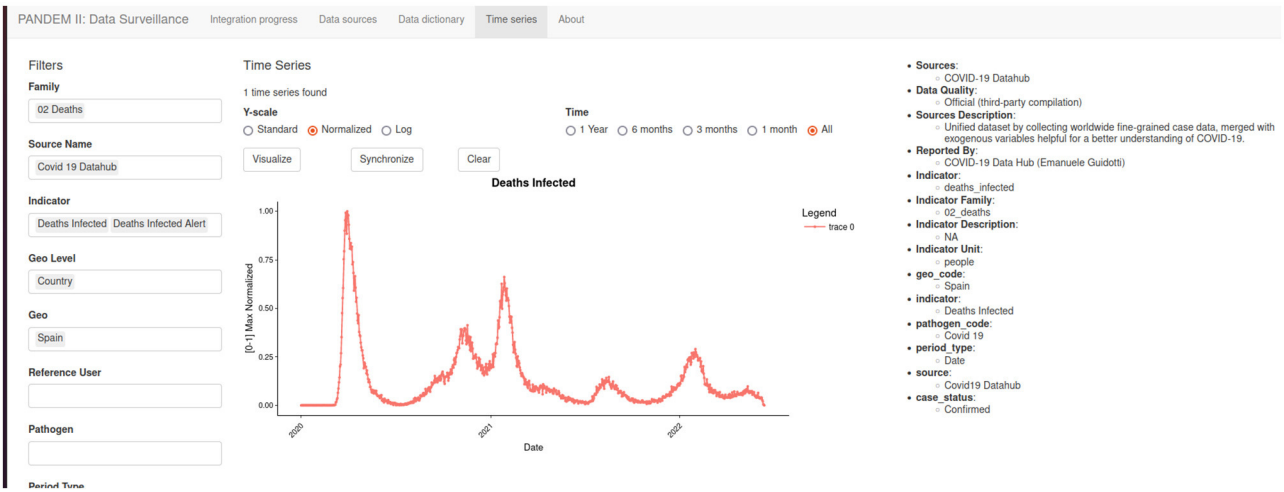


FIGURE 7
The PANDEM-Source (PS) time series page.

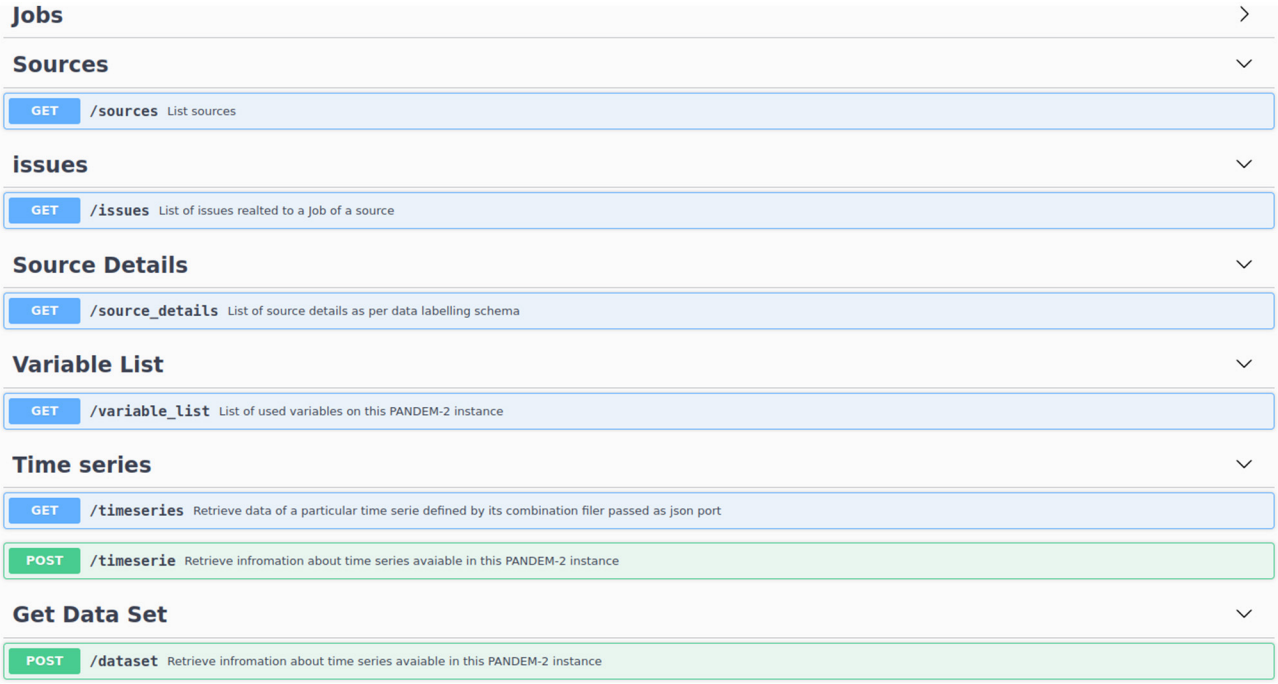


FIGURE 8
Implemented endpoints of the PANDEM-Source (PS) REST API.

sources or diseases or to generate data for training. By its broad approach, it also differs from other initiatives by the heterogeneity of the data sources and collected data. Furthermore, its flexibility allows to quickly adapt to emerging threats which impose new data needs. We believe these characteristics make the tool useful not only for training purposes but also, with further development and adaptation according to the context, to be deployed to support monitoring and managing an emergent epidemic or pandemic.

At the end of the data integration process, PS also allows users to visualize the uploaded data as time series by geographical level or other shared attributes, such as variant or age group, which may facilitate monitoring and validate the surveillance results before being captured in the dashboard (or just to visualize some results from some variables not incorporated in the dashboard). This approach leverages visualization and comparison of any available indicator. For instance, it allows the visualization of social media emotion trends together with other variables such as the evolution of the seroprevalence in a specific population or the evolution of people's opinions to specific public health-related topics or measures which is also based on social media analysis.

PS is a ready-to-use open-source tool allowing pandemic managers to collect and harmonize multiple surveillance data on specific pathogens from traditional and non-traditional publicly available or restricted data sources. It currently collects data for COVID-19 surveillance and response from different domains (cases, deaths, ICU beds occupancy, social media analysis, Lab and NGS data, and non-pharmaceutical interventions) and different data sources such as ECDC or other public health agencies' websites—via the COVID-19 Datahub scripts, Influenzanet, Twitter, MediSYS, etc.

In summary, PS contributes to the pandemic management community through:

- Out-of-the-box data collection for pandemic preparedness and response:
    - Flexibility and customization of data collection.
    - Data can be visualized in the tool.
    - Exploited directly through the PS API.
    - Visualized through the PANDEM-2 dashboard.
- Simplifying cross-domain data collection for epidemiological surveillance.
- Allowing foundation for a multi-source multi-threat early warning system.
- Proposing a standard methodology for collecting surveillance data and computing indicators that could support standardization and data sharing among countries.
- Generating data to be used for training purposes.

It is relevant to highlight some potential limitations when using the tool. Firstly, data availability may be a limiting factor. It is possible, as may happen at the beginning of an epidemic or pandemic, that data are scarce. Secondly, we found that, although some data may be potentially available, there are data sharing limitations in different scenarios, such as sharing sensitive data with the general public or with other countries. There may also be restrictions to share personal data for public health surveillance purposes without patient consent. Related to these previous points it is worth mentioning that often the most useful data to respond at the local level is not available or, if available, the data are sensitive due to data protection issues (possibility to identify individuals).

Thirdly, the list of data sources required (open or restricted) may substantially change over time which can be explained, among other reasons, because of changes in data providers, data sharing procedures or permissions but also due to shifts of threat or pathogen. Finally, some users may need some training to install and use the tool (it is not always possible to have qualified assistance). Despite these limitations, we consider that PS is a useful tool for pandemic preparedness and response-related activities due to its flexibility and easy-to-customize nature, features which also facilitate its use. IT solutions to facilitate and strengthen disease prevention and control are needed and will be developed in the coming years, and PS, as well as other tools developed under the PANDEM-2 project, can be useful prototypes to be further developed according to future needs and threats.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://github.com/pandem2/pandem-source.

Author contributions

FO: Conceptualization, Methodology, Software, Supervision, Writing—original draft. CC: Software, Writing—review & editing. WM: Software, Writing—review & editing. JH: Supervision, Writing—review & editing. MC: Funding acquisition, Supervision, Writing—review & editing. ES: Software, Supervision, Writing—review & editing. AS: Methodology, Writing—review & editing.

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Conflict of interest

FO, CC, WM, ES, and AS were employed by Epiconcept.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Translating the COVID-19 epidemiological situation into policies and measures: the Belgian experience

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The COVID-19 pandemic led to sustained surveillance efforts, which made unprecedented volumes and types of data available. In Belgium, these data were used to conduct a targeted and regular assessment of the epidemiological situation. In addition, management tools were developed, incorporating key indicators and thresholds, to define risk levels and offer guidance to policy makers. Categorizing risk into various levels provided a stable framework to monitor the COVID-19 epidemiological situation and allowed for clear communication to authorities. Although translating risk levels into specific public health measures has remained challenging, this experience was foundational for future evaluation of the situation for respiratory infections in general, which, in Belgium, is now based on a management tool combining different data sources.

KEYWORDS

data, policies, barometer, risk management, COVID-19, management tool

Introduction

Following the WHO International Health Regulations from 2005 "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks," Belgian authorities established the Risk Assessment Group (RAG) and the Risk Management group (RMG) in 2007 (1, 2). The importance of these structures was confirmed in 2013 by the Decision No 1082/2013/EU of the European Parliament and European Council on serious cross-border threats to health.

Identification of potential threats to public health in Belgium is performed by the Belgian Health Institute, Sciensano, and is based on epidemic intelligence and systematic decoding of signals identified through epidemiological surveillance. These public health threats can be of microbiological, chemical or environmental origin. The RAG has the responsibility, upon

identification of a possible threat to public health, to (i) evaluate the threat, (ii) assess the risk posed to public health for the Belgian population, (iii) propose measures to limit or control the threat (within the public health domain) and (iv) follow-up risks and interventions. The RAG is coordinated by Sciensano and is composed of representatives of the health authorities (infection prevention and control departments), the Belgian Superior Health Council and professionals invited based on their expertise (epidemiologists, clinicians, microbiologists, hygienists, environmental specialists, biostatisticians, etc).

Recommendations proposed by the RAG are presented to the RMG, which is composed of representatives of health authorities (administration and ministries), and which is in charge of taking decisions on measures to limit the impact or control the threat, implement these measures and communicate them (Figure 1).

During the COVID-19 pandemic, a substantial number of advice requests were issued to the RAG on a wide range of topics, including testing strategy and measures for cases and contacts (3). In addition, since August 2020, the RAG has made a weekly evaluation of the COVID-19 epidemiological situation, based on data collected through different surveillance systems.

The magnitude and intensity of the COVID-19 crisis led to increased possibilities in terms of data collection and analyses or linkage between databases. Existing routine surveillance systems were enhanced, with automation of data extraction, leading to an exhaustive, nearly real time national laboratory-based surveillance for cases (4). Novel surveillance systems were also developed, including registration of all hospitalizations for COVID-19 (5), a performant system for an accurate estimation of COVID-19 mortality in health care settings (including nursing homes) (6), surveillance of SARS-CoV-2 in waste water (7), genomic surveillance (8) and data collection on COVID-19 cases in schools and in nursing homes (9). Links with academic partners were reinforced, for instance for scenarios analysis and modeling (10). In addition, other sources of data, *a priori* not directly linked to public health, also provided information: mobile phone network provider or Google data informed on population mobility which was used to assess behavior and contacts among individuals (11); and passenger locator forms, which were mandatory in Europe over an extended period, allowed for monitoring travelers.

All data were collected independently from each other and following different flows. When possible, data were gradually integrated into the Healthdata.be platform, a system for standardizing the flow of health-related scientific data (12). All data, coming from the Heatlhdata.be platform or not, were collated by epidemiologists from Sciensano, analyzed and presented in a comprehensive weekly epidemiological report (13). These reports were publicly available to health authorities and to the general public, but because of the diverse sources of data, the interpretation of the epidemiological situation was complex. A simple way to communicate on the epidemiological situation and the risk for public health, as well as a link of a given risk level with specific control measures were requested by the authorities. For this purpose, different attempts were made to set up a dynamic management tool acting as a "COVID-19 barometer." Starting from May 2020, different expert groups or authorities proposed different systems, that were not fully implemented in practice. From December 2020 onwards, it has been the responsibility of the RAG to coordinate the management tool.

Here, we describe the successive tools that were implemented and how they were used by the RAG in the COVID-19 context. We discuss lessons learned from these tools and what they can bring to future surveillance and policy making.

Policy options and implications: use of management tools

Successive management tools used in Belgium during the COVID-19 pandemic by the RAG, selection of indicators and thresholds

Once a week, the COVID-19 epidemiological situation was discussed with a core group of experts from the RAG. Between August 2020 and December 2022, a total of 122 evaluations were performed. The epidemiological evaluation was based on a wide range of

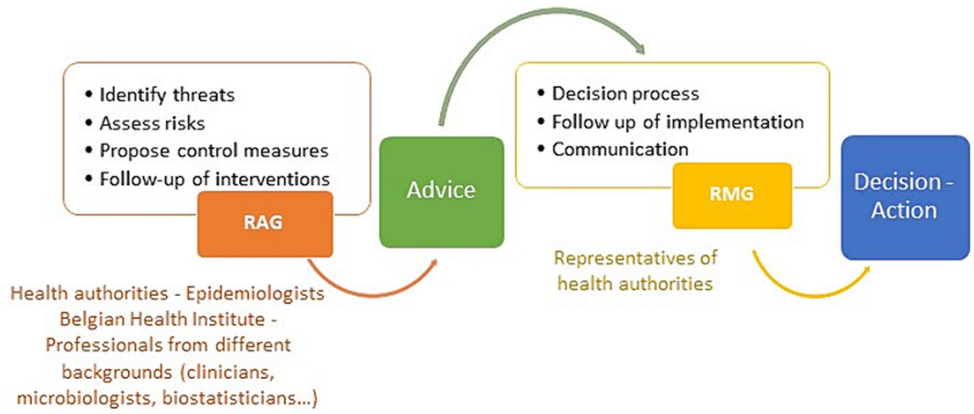

FIGURE 1
Description of the risk assessment and decision making process in Belgium. Note that during the COVID-19 crisis additional bodies were involved such as the GEMS or the Commissariat.

TABLE 1 Indicators used for the weekly evaluation of the epidemiological situation.

Indicators	Period used	Data sources and references
Number of new COVID-19 cases and Rt of cases	August 2020–present	COVID-19 test database (4)
Number of COVID-19 positive tests and positivity rate	August 2020–present	COVID-19 test database (4)
Number of self-tests sold in pharmacies and positivity rate of self-tests	April 2021–July 2023	COVID-19 test database and APB (Belgian Association of Pharmacies)
Number of admissions in hospitals for COVID-19 and number of beds occupied (total and ICU)	August 2020–July 2023	COVID-19 hospital database (5)
Doubling time of number of hospitalizations for COVID-19	August 2020–July 2023	COVID-19 hospital database (5)
Number of deaths due to COVID-19	August 2020–July 2023	COVID-19 mortality database (6)
Circulating SARS-CoV-2 variants	December 2020–present	Molecular surveillance (8)
SARS-CoV2 viral load in waste water	September 2021–present	Wastewater surveillance (7)
Number of consultations for COVID-19 (suspicion) in GP practices	October 2020–present	Sentinel GP network and GP barometer (24, 25)
Number of cases, hospitalizations and death due to COVID-19 in nursing homes	October 2020–July 2023	Surveillance in nursing homes (9)
Number of children absent in schools	December 2020–May 2022	Surveillance in schools (26)
Number of arriving travelers, by country of departure	January 2021–February 2022	Passenger Locator Forms (PLF)
Place and source of infections	December 2020–November 2021	Contact tracing database (27)
Mobility of Belgian citizens	August 2020–March 2022	Mobile operator Proximus and Google databases
Vaccination coverage	March 2021–present, when relevant	LinkVacc database (28)
International situation	August 2020–present, when relevant	ECDC, WHO

indicators, which resulted from the enhanced surveillance efforts (Table 1).

From December 2020 onwards, the outcome of the epidemiological assessment was translated into a risk level. Three successive management tools were implemented by the RAG over time to define such risk levels (Table 2). These tools were mainly based on indicators reflecting viral circulation and pressure on health care (both first line and second line care). For each tool, indicators were chosen based on (i) their relevance depending on the phases of the epidemic and the objective of measures taken (reduction of the impact of infection at individual level and/or prevention of healthcare system overload), (ii) the testing strategy at a given time, (iii) the evolving population immunity and (iv) the evolving knowledge of the RAG members. For each indicator, thresholds were defined upon discussion with the group of experts, built on acquired experience as well as from quantitative evidence based on earlier waves and model-based relationship between earlier (e.g., infections) and later indicators (e.g., hospitalization and ICU admission). Additional indicators, such as the results of the waste water surveillance, the genomic surveillance, the (excess) mortality or the international situation, were not part of the tool *per se*, but were included in the global evaluation when relevant.

The first epidemic management tool, which was used by the RAG from December 2020 to July 2021, was initially proposed by the "*Corona Commissariat,*" a multidisciplinary coordination committee put in place in Belgium between October 2020 and April 2022 in order to, among others, coordinate communication between the different political authorities at the federal and federated levels, provide support to policy decisions and their implementation, and monitor the social and economic impact of the measures taken (14, 15). The tool consisted of two phases: a control phase and a lock-down phase. The thresholds to move from one phase to another were based on the 14-day incidence in cases, the positivity rate and the Rt calculated based on the number of cases, as these were the indicators relevant at the time. In the control phase, case management was done at a local level (analysis of clusters in collectivities, whereabouts, analysis of local increases of number of cases at municipality level up to the smallest administrative unit). The lock-down phase was reached when viral circulation exceeded the threshold of a national 14-day incidence of 100 new cases per 100,000 inhabitants. In that situation measures were expected to be applied in order to reduce viral circulation and return to the control phase. In addition, the lock-down phase was further subdivided into 3 plans (A, B and C) since, within this phase, the situation could stabilize/improve or on the contrary evolve unfavorably and require additional measures. The measures to be applied for each phase or plan were defined by a multidisciplinary group of experts (GEMS, Group of Experts for the Management Strategy for COVID-19, reporting to the Corona Commissariat), advising the Belgian authorities, complementary to the RAG.

The second epidemic management tool was in use from July 2021 to January 2022. This tool evolved from the first and consisted of five alarm levels, the first two constituting the "risk management phase" and the later three the "crisis management phase." Similar to the control phase of the first epidemic management tool, the objective of the risk management phase was to limit, as much as possible, large-scale national measures and to contain localized outbreaks with appropriate measures taken at local level (administrative unit of

TABLE 2 Indicators and thresholds defined for the successive epidemic management tools.

			Indicators							Communication
Name	Date	Levels	14-day incidence cases	Positivity Rate	Rt	Consultations at GP practices	7-day incidence hospitalizations	ICU occupancy	Doubling time	
Epidemic management tool 1	Dec 2020 – July 2021	Control phase	<100/100000	<3%	<1					Weekly COVID-19 bulletin
		Lock-down phase plan A	100–300/100000	>3%			>4,5/100000			
		Lock-down phase plan B	>300/100000	increasing trend			>4,5/100000 and increasing trend			
		Lock-down phase plan C				GP capacity overloaded	>9/100000			
Epidemic management tool 2	July 2021 – Jan 2022	Level 1: Risk management	<20/100000	0–3%	<1,000	<25/100000	<2/100000	<15%	>100 d	RAG epidemiology report and weekly COVID-19 bulletin
		Level 2: Risk management	20–99/100000	0–3%	<1,000	25–49/100000	2–4,5/100000	15–24%	21–100 d	
		Level 3: crisis management	100–299/100000	3,1–6%	1,000-1,299	50–99/100000	4,6–6/100000	25–49%	16-20d	
		Level 4: crisis management	300–399/100000	6,1–10%	1,300-1,500	100–125/100000	6,1–9/100000	50–59%	5–15 d	
		Level 5: crisis management	>400/100000	>10%	>1,500	100–125/100000 + increasing trend	>9/100000	>60%	< 5d	
Epidemic management tool 3	Jan 2022 - present	Level 1	<200/100000		<1,000	<50/100000	<4/100 00	<15%		RAG epidemiology report and weekly COVID-19 bulletin
		Level 2	200–499/100000		1,000-1,299	50–99/100000	4–9,9/100000	15–24%		
		Level 3	≥500/100000		≥1,300	≥100/100000	≥10/100000	≥25%		

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municipality). The three levels of the crisis management phase were linked to the same measures as defined in plans A, B and C of the lock-down phase of the first epidemic management tool (3). The five levels of this tool were defined based on early indicators (14-day incidence of cases, positivity rate, Rt calculated based on the number of cases, number of consultations for suspicion of COVID-19 at General Practioner (GP) practices) as well as late indicators (7-day incidence of hospital admissions, occupancy of ICU beds and doubling time of hospital admissions). Compared to the first epidemic management tool, late indicators were included in the second version of the management tool because, as the epidemic evolved with increasing immunity in the population through vaccination or past infections, the impact of infections on individuals and society was reduced, and more importance was given to the severe infections with burden on hospitals.

The third epidemic management tool was in place from January 2022 to August 2023. This tool was developed upon request from the authorities who wished for a simplified management strategy that would indicate, on the basis of progressive, balanced and conditioned measures, how an epidemiological baseline situation could be achieved. The objective of this tool was also to provide clear communication toward the general public regarding public health measures. For this reason, the number of levels was reduced to three. Management level 1 was defined as an epidemiological situation under control, with virus circulation remaining at low level and without impact on the health care system. Management level 2 was reached when the viral circulation increased and pressure on the health care system was reported; measures were then needed to reverse the trend. Management level 3 reflected a situation of high virus circulation with an important risk of health care system overload (3). Because of the increasing use of self-tests instead of tests in laboratories, for which results were not systematically reported, the incidence in the number of new cases became less reliable (16). The three levels of this tool were therefore primarily defined based on hospital indicators (7-day incidence of hospital admissions and occupancy of ICU beds) as well as the number of consultations at GP practices for suspected COVID-19 (as an earlier indicator). Supporting indicators included the positivity rate for symptomatic patients, the Rt and the 14-day incidence of the number of cases.

As shown in Figure 2, since December 2020, a risk level was thus applied to the epidemiological situation on a weekly basis, based on the management tools described above. Figure 2 also indicates the measures that were taken or relaxed over time. A discrepancy between the management level proposed by the RAG and the measures taken by authorities was often, but not always, observed. For instance, in October–December 2021, when Belgium faced a wave of COVID-19 cases and hospitalizations linked to the Delta variant, the RAG recommendations and the authorities decisions were aligned and recommended measures were applied. On the other hand, in January 2022, all indicators were on the rise due to the Omicron variant and the epidemiological situation was evaluated by the RAG as "alarm level 5" (highest level). At the same time, at authorities' level, it was decided to stop testing of asymptomatic high-risk contacts (to prioritize testing for symptomatic patients) and stop quarantine for fully vaccinated high-risk contacts. In February and March 2022, measures were progressively relaxed for events, restaurants, night clubs, etc. while the management level was, respectively, set by the RAG at level 3 in February (highest level) and at level 2 in March.

Strengths and weaknesses of the Belgian system: regular evaluation combined to management tools

The establishment of an independent group of experts, within an existing structure for risk assessments (the RAG), allowed for a comprehensive interpretation of the epidemiological situation based on all available data and on a regular basis. In addition, within the management tools, the results of surveillance data were compiled in a clear manner and translated, weekly, into one risk level. The opinion of the experts participating to the RAG was important to reach a conclusion; in addition to the indicators, they took into account the expected future evolution of the epidemic and the link between the management level and the measures needed. Altogether, the system provided the authorities with scientific-based information translated into a risk-level, enabling them to take decisions which ultimately could control the evolution of the epidemic (reduction in cases, hospitalizations and deaths).

The strengths of this system were to (i) provide a simple and clear way of communication between experts and health authorities integrating various types and sources of data, and (ii) maintain a continuous and structured analysis, based primarily on objective indicators and thresholds. Although several management tools followed one another, the indicators and thresholds remained comparable, offering a stable framework for the evaluation and understanding of the epidemiological situation. This was exemplified when the Omicron variant replaced the Delta variant, the relationship between the indicators linked to cases and those linked to hospitalizations changed, highlighting the lower severity of the disease caused by the Omicron variant.

The system also showed some limitations. First, although one of the objectives of the management tools was to inform decision making, and despite the fact that in Belgium authorities heed the scientific evidence produced, a simple linkage of a risk level to a defined set of measures could in practice rarely be applied. This could be explained by the fact that the evaluation and the management tool focused on the epidemiological situation, while the decision process also had to take into account other factors such as the socio-economic situation and the mental health of the population (17). Second, the expectations from the authorities and the experts of the RAG regarding the management tool sometimes differed. Even though there was a clear will from authorities to base decision making on scientific evidence, they wished for a quantitative system resulting in a simple two level switch (on/off), whereas the RAG experts considered the situation as more complex, hence requiring a qualitative global interpretation in addition to the quantitative evaluation. Third, since the management tool was based on a series of indicators as well as a qualitative interpretation, and because several different management tools were successively set up, understanding the process was not always easy for the general population. Thus, the communication benefit offered by the management tool was of interest for the authorities but less so to the general population.

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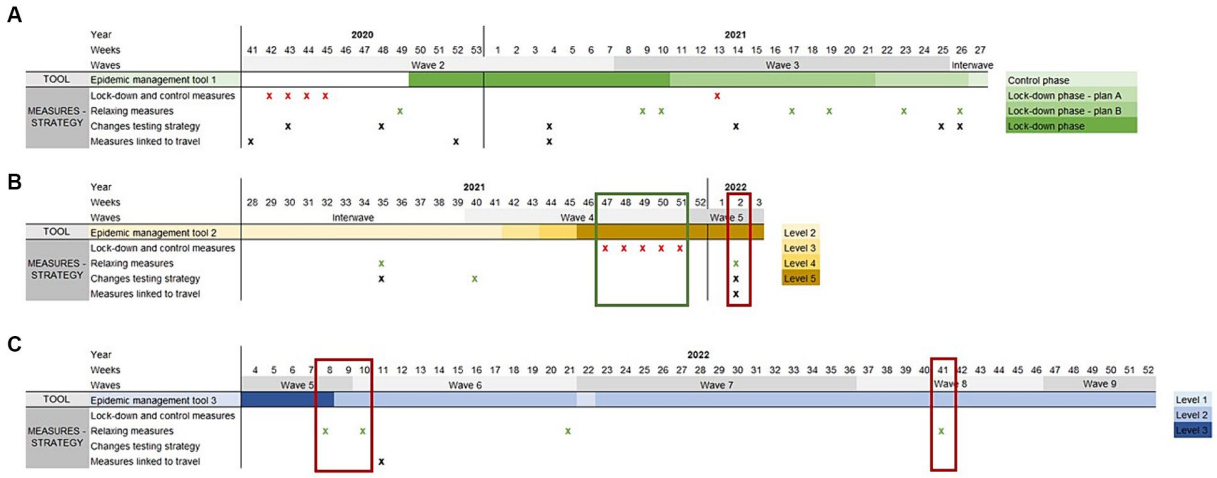

FIGURE 2
Parallel evolution of tools set up by the RAG for epidemic management and measures taken, between week week 41 of 2020 and week 52 of 2022. For each week, the level, as defined by the epidemic management tools, is indicated (panel **A**: Epidemic management tool 1: control phase and lock-down phase, later divided in 3 plans (plan A, B and C); Panel **B**: Epidemic management tool 2: levels 1 to 5; Panel **C**: Epidemic management tool 3: levels 1 to 3). The time when a measure was taken or a change in strategy applied is indicated by a cross (red cross: control measures; green cross: relaxing measures; black cross: changes in testing strategy or measures linked to travel). The red boxes provide examples of discrepancies between the management level decided by the RAG and the measures taken, the green box shows an example of management level and measures taken aligned.

Development of management tools in other European countries during the COVID-19 pandemic

In order to feed the discussion within the RAG in Belgium on the usefulness of a management tool during epidemics, a consultation of practices regarding the use of a tool for the management of the COVID-19 pandemic in other European countries was performed in May 2023, through the Population Health Information Research Infrastructure portal (PHIRI) (18). Eleven of the 14 EU countries who replied mentioned using or having used a management tool to monitor the COVID-19 epidemiological situation. All countries using a management tool based it on similar indicators as Belgium, namely the incidence of new cases, the incidence of new hospitalizations and the ICU occupancy. Ten countries mentioned associating a risk level to specific public health measures. However, it remains unclear how/if, in practice, these measures were implemented according to the defined risk level.

Recommendations for further use of a management tool

Progressively, surveillance of COVID-19 in Belgium has been integrated into a broader monitoring, including influenza and other respiratory infections (19). The experience gathered during the COVID-19 crisis in terms of data management and data use for risk assessment founded the scheme for the current assessment of the epidemiological situation of these infections.

- It is important to invest in automated near real time data collection systems and performant data flows. Although an enhanced data collection, as done during COVID-19 pandemic, is not sustainable in the longer term, an easy reactivation when needed must be assured. In addition, some systems that were set up for COVID-19, such as automated data extraction from laboratory-based surveillance, should be continued and generalized to other pathogens in order to ensure timeliness, completeness and quality of data.
- Artificial intelligence approaches could be implemented to improve the analysis of large volumes or different data types (20, 21)
- Developing a management tool with risk levels can be considered to assess the severity of the epidemiological situation of respiratory infections and to inform public health preparedness and response.
- The risk levels should be defined by various indicators, combining different data sources, to gather early signals as well as to assess the severity of the situation.
- A set of measures and actions can be associated to each level, including public health mitigation measures and actions linked to surveillance intensity. Dialog between policy makers and surveillance / public health professionals is essential to ensure the applicability of such measures.
- Maintaining a stability of levels is important for clarity and endorsement by the general public.
- An evaluation of the management systems developed by each individual country during the COVID-19 pandemic should be carried out to define the most efficient system for risk assessment and risk management of epidemics.

These recommendations are in line with several initiatives put in place at international level, in the aftermath of the COVID-19 crisis, to support preparedness plans for pandemic and epidemic threats. The WHO has for instance developed an approach for the surveillance of epidemic threats called the WHO Hub for Pandemic and Epidemic

Intelligence. It combines information from traditional surveillance, event-based surveillance, participatory or community surveillance, and on-the-ground investigations with contextual information, to generate an assessment of public health risk (21). WHO also issued a framework for resilient surveillance for respiratory viruses of epidemic and pandemic potential ("Crafting the mosaic") where it is stressed that multiple approaches (different systems, investigations or studies) are needed together to provide essential information to policy makers (22). Taken together, these initiatives highlight the importance of collaboration between different instances (government institutions, non-governmental organizations, academia, private sector, civil society) and integration of the different surveillance systems (23).

Conclusion

The important changes developed for the surveillance of COVID-19 serve current data collection and risk assessments for respiratory infections. In Belgium, enhanced data collection has not been maintained in a continuous way but could be reactivated if needed. An integrated surveillance for respiratory infections has been implemented, based on sentinel surveillance at the level of general practices (number of consultations, sentinel sampling) and hospitals (number of hospitalizations, severity of disease, sentinel sampling). Based on the COVID-19 experience, an adapted management tool for respiratory pathogens has been developed to facilitate risk assessment, communication toward authorities and propose recommendations for mitigation measures depending on a risk level in the current winter season (24). An evaluation of this tool is foreseen.

Author contributions

GM: Conceptualization, Formal analysis, Writing – original draft, Supervision. VL: Conceptualization, Formal analysis, Writing – review & editing. GS: Conceptualization, Formal analysis, Writing – review & editing, Supervision. CB: Formal analysis, Writing – review & editing. CF: Methodology, Writing – review & editing. NH: Formal analysis, Writing – review & editing. PH: Methodology, Writing – review & editing. GM: Formal analysis, Methodology, Writing – review & editing. JaS: Formal analysis, Writing – review & editing. CK: Formal analysis, Writing – review & editing. SB: Formal analysis, Writing – review & editing. RB: Data curation, Writing – review & editing. JoS: Formal analysis, Writing – review & editing, Supervision TL: Conceptualization, Formal analysis, Writing – original draft, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Exploring depressive symptom trajectories in COVID-19 patients with clinically mild condition in South Korea using remote patient monitoring: longitudinal data analysis

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Background: During the height of the COVID-19 pandemic, the Korean government temporarily allowed full scale telehealth care for safety and usability. However, limited studies have evaluated the impact of telehealth by analyzing the physical and/or mental health data of patients with COVID-19 diagnosis collected through telehealth targeting Korean population.

Objective: This study aimed to identify subgroup of depressive symptom trajectories in patients with clinically mild COVID-19 using collected longitudinal data from a telehealth-based contactless clinical trial.

Methods: A total of 199 patients with COVID-19 were accrued for contactless clinical trial using telehealth from March 23 to July 20, 2022. Depressive symptoms were measured using the patient health questionnaire-9 on the start day of quarantine, on the final day of quarantine, and 1 month after release from quarantine. Additionally, acute COVID-19 symptoms were assessed every day during quarantine. This study used a latent class mixed model to differentiate subgroups of depressive symptom trajectories and a logistic regression model with Firth's correction to identify associations between acute COVID-19 symptoms and the subgroups.

Results: Two latent classes were identified: class 1 with declining linearity at a slow rate and class 2 with increasing linearity. Among COVID-19 symptoms, fever, chest pain, and brain fog 1 month after release from quarantine showed strong associations with class 2 (fever: OR, 19.43, 95% CI, 2.30–165.42; chest pain: OR, 6.55, 95% CI, 1.15–34.61; brain fog: OR, 7.03, 95% CI 2.57–20.95). Sleeping difficulty and gastrointestinal symptoms were also associated with class 2 (gastrointestinal symptoms: OR, 4.76, 95% CI, 1.71–14.21; sleeping difficulty: OR, 3.12, 95% CI, 1.71–14.21).

Conclusion: These findings emphasize the need for the early detection of depressive symptoms in patients in the acute phase of COVID-19 using

telemedicine. Active intervention, including digital therapeutics, may help patients with aggravated depressive symptoms.

KEYWORDS

telehealth, telemedicine, depression, COVID-19, LCMM

1 Introduction

As the COVID-19 outbreak transition into a pandemic, the role and the use of telehealth is expanding and gaining significant background. Many countries have introduced remote patient monitoring systems that use telehealth to manage patients at remote locations (1–3). Telehealth has been shown to be an excellent method for delivering care as it allows not only patients but also health care providers to protect themselves from the risk of infection (1, 4). Since the outbreak of the COVID-19 pandemic, telemedicine, which had been under limited pilot phase in Korea, was temporarily allowed in full scale for patients diagnosed with COVID-19. Until May 2023, all patients with COVID-19 were obligated to quarantine at home for 5–7 days during the acute clinical phase. Patients with COVID-19 received prescriptions for related acute respiratory symptoms via contactless consultations during the quarantine period.

Meanwhile, the impact of COVID-19 on mental health has been continuously reported. The prevalence of depression symptoms in adults in the US during the COVID-19 pandemic was more than three times that of pre-pandemic era (5). In the UK, the prevalence of depression increased to 32% from 4.12% in the pre-pandemic period (6). In China, the prevalence of depression has been moderately high (7). South Korea likewise saw an increase in manifestation of depression. During the COVID-19 pandemic, 30.7% of 2,288 adult residents reported a Patient Health Questionnaire-2 score of 3, indicating a high prevalence of depression (8).

With the transition to the long-COVID era, many studies have explored mental health trajectories, including low, moderate, severe, and worsening mental health, using longitudinal data (9–11). Contributing social and psychological factors have also been identified. The unpredictable disease course of COVID-19 and COVID-19-related financial and social impairments have been reported to be related to the initial elevation in the level of depressive or anxiety symptoms (11–13). Moreover, the exacerbation of COVID-19 symptoms may also contribute to the development of mental health symptoms (14, 15).

Depression is strongly associated with somatic symptoms (16). Meanwhile, acute COVID-19-related somatic symptoms are associated with the exacerbation of depression and anxiety (15). In Korea, depression has been identified as the main symptom among COVID-19-related persistent symptoms (17). However, no study has explored the association between the trajectories of depression in the acute phase and acute COVID-19-related symptoms for these patients to provide a Korean perspective.

Against this background, the SMILE (Smart Monitoring solution for Infectious disease management through Lifestyle Evaluation) research team at Seoul National University Hospital established a remote patient monitoring system to effectively respond to the infectious disease. A contactless clinical trial protocol using telehealth was developed (18). Longitudinal data, including physical and mental health-related data, were prospectively collected from patients with COVID-19. Obvious next step was to demonstrate the impact of telehealth by analyzing the collected data. Thus, goal of current study was to identify subgroups of depressive symptom trajectories in patients with clinically mild COVID-19 in Korea and explore the contributing COVID-19-related symptoms to those groups using collected longitudinal data from a contactless clinical trial using telehealth.

2 Methods

2.1 Study design

This is a prospective observational study.

2.2 Participants and procedures

After institutional review board approval (IRB number: H-2107-049-1233), 199 adult patients with confirmed COVID-19 diagnosis quarantined at home were enrolled in this prospective trial from March 23 to July 20, 2022. The inclusion criteria were as follows: (1) 19 years or older; (2) confirmed COVID-19 diagnosis; (3) understand the study purpose, and (4) agree to participate in the trial.

This study was based on a published protocol developed for patients quarantined at residential treatment centers (18) with modification for home use. The study participants were recruited using convenience sampling. The research team displayed a poster that provided information on the research purpose and methods on the staff portal site and notice board at the study hospital. Patients who were hospital employees or acquaintances voluntarily contacted the research assistants and filled out an application form online through a URL or QR code in the poster.

Research assistants explained the purpose of the study to the prospective participants and oral informed consent was obtained over a phone call. Data were collected using Google Forms (Google, CA, USA). Through a mobile messenger, the study team sent the URL of the Google form containing an online questionnaire on mental health status. The participants completed online questionnaires on every quarantine day and 1 month after the release from quarantine.

2.3 Measures

Depression symptoms were measured using the patient health questionnaire-9 (PHQ-9) (19) at three time points: on the start day of quarantine (Time 1), on the final day of quarantine (Time 3), and

1 month after release from quarantine (Time 4). Participants were asked on the frequency of the nine potentially bothering symptoms. Each item was scored using the following four-point Likert scale: not at all = 0, several days a week = 1, more than half the week = 2, nearly every day = 3. Severity of depression was divided into five tiers, a score of 1–4 as none, 5–9 as mild, 10–14 as moderate, 15–19 as moderately severe, and 20–27 as severe.

General characteristics of the participants, including gender, age, past medical history, smoking status, and initial neuropsychiatric symptoms, were assessed at Time 1. Past medical history included history of diabetes mellitus, hypertension, cardiovascular disease, and respiratory disease. Initial neuropsychiatric symptoms included depression, lethargy, anxiety, sensitivity, insomnia, panic attack, and suicide attempts. Self-reported acute COVID-19 symptoms were assessed at every quarantine day (Time 2) and at Time 4. Self-reported acute COVID-19 symptoms at Time 2 included cough, sputum, fever, rhinorrhea, sore throat, dyspnea, chest pain, pain, sleeping difficulty, loss of smell, loss of taste, and various gastrointestinal symptoms, which includes nausea, vomiting, abdominal discomfort, constipation, and diarrhea.

2.4 Statistical analysis

All analyses were conducted using R version 4.2 (R Project for Statistical Computing). To identify the subgroups of depressive symptom trajectories over time, we used the latent class mixed model (LCMM), also called growth mixture modeling (20–23), subsequently selecting the models that provided the best fit for the data. To assess the clinical characteristics of the subgroups identified at Time 1, we conducted a logistic regression with subgroups identified as dependent variables and sociodemographic features, past medical history, initial psychological symptoms, and acute COVID-19 symptoms measured at Time 1 as independent variables. To support the sample size considerations for binary logistic regression analysis, we fitted the logistic regression model using a modified estimation procedure known as Firth's correction (24). We then selected variables at Time 1 that were significantly associated with subgroup identification. Next, after selecting the clinical characteristics from Times 1, 2, and 4 associated with the subgroups of trajectories, we conducted additional logistic regression using a stepwise approach with subgroups identified as dependent variables and those variables measured at Times 2 and 4 as independent variables. In this analysis, we added previously selected significant variables at Time 1 to the logistic regression model as fixed variables. The model was also fitted using Firth's correction (24), and statistical significance was tested at the $\alpha = 0.05$ level.

3 Results

Table 1 presents the clinical characteristics of the 199 participants.

TABLE 1 Clinical characteristics of the participants.

Characteristics, *n* (%)		Time 1	Time 2	Time 4
Gender				
Male	63 (31.7)			
Female	136 (68.3)			
Age (years), mean (SD)	36.7 (9.4)			
Age group (years)				
Under 30	47 (23.6)			
30–39	89 (44.7)			
Over 40	63 (31.7)			
Past medical history				
Non-psychiatric	19 (9.5)			
Sleep disorder	20 (10.1)			
Neuropsychiatric treatment	22 (11.1)			
Smoking status				
Never-smoker	158 (79.4)			
Ex-smoker	25 (12.6)			
Smoker	16 (8.0)			
Initial neuropsychiatric symptoms				
Yes		135 (67.8)		
No		64 (32.2)		
COVID-19 related symptoms				
Cough		158 (79.4)	185 (93.0)	120 (60.3)
Sputum		148 (74.4)	189 (95.0)	96 (48.2)
Fever		80 (40.2)	87 (43.7)	9 (4.5)
Rhinorrhea		94 (47.2)	154 (77.4)	39 (19.6)
Sore throat		163 (81.9)	169 (84.9)	31 (15.6)
Dyspnea		5 (2.5)	14 (7.0)	20 (10.1)
Chest pain		16 (8.0)	26 (13.1)	9 (4.5)
Gastrointestinal symptoms		68 (34.2)	103 (51.8)	49 (24.6)
Pain		107 (53.8)	142 (71.4)	21 (10.6)
Sleeping difficulty		50 (25.1)	64 (32.2)	38 (19.1)
Loss of smell			46 (23.1)	39 (19.6)
Loss of taste			44 (22.1)	36 (18.1)
Post-COVID-19-related symptoms				
Headache				32 (16.1)
Brain fog				52 (26.1)
Fatigue				135 (67.8)

The LCMM identified two latent classes as the best fit for the data. The estimated mean trajectories of the two classes are shown in Figure 1. In class 1 ($n = 163$; 81.9%), the mean trajectory declined linearly at a slow rate. The PHQ-9 mean scores of class 1 at each time point were 1.64 (SD 1.89) at time 1, 2.33 (SD 2.15) at time 3, and 1.62 (SD 1.68) at time 4. In class 2 ($n = 36$, 18.1%), patients had a higher level of depression symptoms than those in class 1 at time 1 and showed increased linearity with the progress of the quarantine period. The PHQ-9 mean scores of class 2 at each time point were 5.0 (SD 3.58) at time 1, 5.03 (SD 2.95) at time 3, and 7.89 (SD 2.57) at time 4.

Table 2 presents the clinical characteristics of the participants in the subgroups identified by the LCMM at time 1. Initial neuropsychiatric symptoms were observed in 80.6% of patients in

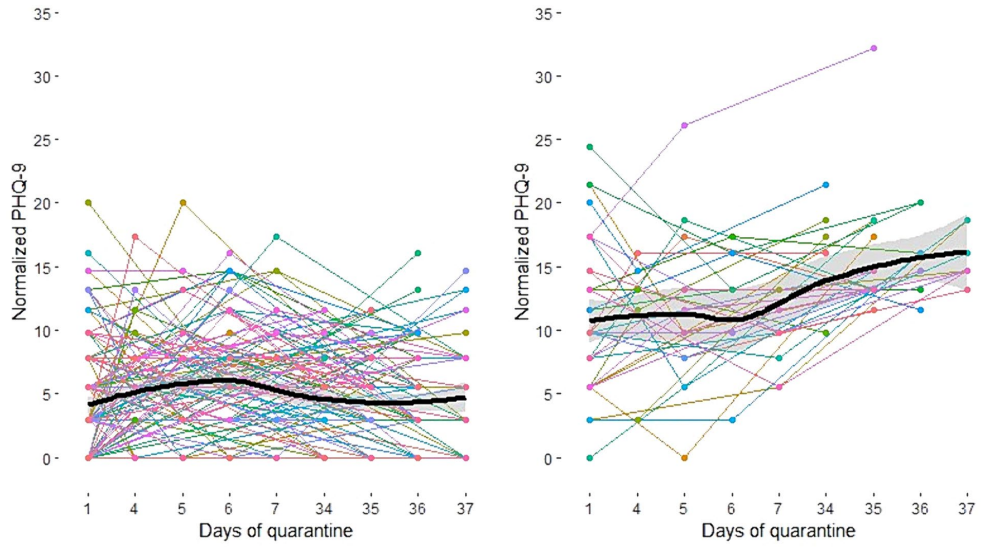

FIGURE 1
Estimated mean trajectories of depression symptoms in patients with COVID-19 (**Left**: Class 1, **Right**: Class 2).

class 2 and in 65% of patients in class 1, which showed statistically significant difference ($p < 0.001$). More than 70% of the patients in both classes experienced cough, sputum, and sore throat, among the COVID-19-related symptoms. Of note, there was statistically significant difference in incidence of chest pain (5.5 and 19.4% of patients in classes 1 and 2, respectively).

Table 3 presents the results of the logistic regression model for COVID-19-related symptoms at time 1. Among COVID-19 symptoms, rhinorrhea and chest pain showed positive associations with increased odds of exacerbation of depression. Although extent was not statistically significant (rhinorrhea: odds ratio [OR], 2.06, 95% CI, 0.96–4.57; chest pain: OR, 3.07, 95% CI, 0.92–10.31), these two variables were chosen as fixed variables for the final model.

Table 4 presents the association between COVID-19 symptoms and the class 2. The final model included rhinorrhea and chest pain at time 1; cough at time 2; and fever, rhinorrhea, chest pain, gastrointestinal symptoms, sleeping difficulty, headache, and brain fog at time 4. Among these symptoms, fever at time 4 showed a strong association with class 2, indicating the exacerbation of depression during quarantine (OR, 19.43; 95% CI, 2.30–165.42). Patients with chest pain or brain fog at time 4 were more likely to have exacerbated depression during quarantine (chest pain: OR, 6.55, 95% CI, 1.15–34.61; brain fog: OR, 7.03, 95% CI, 2.57–20.95). In addition, patients who experienced gastrointestinal symptoms or sleeping difficulty at time 4 were more likely to have exacerbated depression during quarantine (gastrointestinal symptoms: OR, 4.76, 95% CI, 1.71–14.21; sleeping difficulty: OR, 3.12, 95% CI, 1.71–14.21).

4 Discussion

Longitudinal data related to depressive symptoms and COVID-19-related symptoms was collected through a contactless clinical trial using telehealth targeting patients with clinically mild symptoms at the acute phase of COVID-19 in South Korea. The results showed two subgroups of depressive symptom trajectories from COVID-19 infection to 1 month after quarantine: the stable group (class 1) and the exacerbated group (class 2).

LCMM was used to identify the two subgroups of patients with COVID-19 based on the trajectory of their PHQ-9 scores across multiple time points. Studies have used LCMM to successfully identify meaningful latent subgroups using longitudinal data (25). For example, it has been used to categorize trajectories of depression and anxiety symptom changes (26) and shown to perform as accurately as the traditional cutoff score approach in identifying heterogeneous subgroups in a longitudinal study on perinatal depression (27). The LCMM provided strong robustness in current analysis given the lack of a traditional or standard method for categorizing longitudinal post-COVID-19 depression changes.

Among the acute COVID-19-related symptoms at time 4, chest pain, gastrointestinal symptoms, sleeping difficulty, and brain fog, which are commonly observed in patients with depression (16), were significantly associated with class 2. The Patient Health Questionnaire 15, which is one of the most useful tools for measuring somatization in psychiatric patients, also includes the following symptoms: trouble sleeping, chest pain, and gastrointestinal symptoms, such as constipation, loose bowels, diarrhea, nausea, and indigestion (28). Indeed, 69% of patients with major depressive disorder who visited primary care facilities reported that physical symptoms were the main reason for their hospital visit (16). Ran et al. (29) found a significant correlation between depression and somatization in patients with COVID-19, which is consistent with the findings of the current study.

In addition, patients from Eastern cultures, compared to Western counterparts, tend to deny psychological symptoms and complain more about physical symptoms (16, 30–32). Therefore, early detection of depression is important for patients with persistent non-specific somatic symptoms, even after recovery from COVID-19. In Eastern

TABLE 2 Clinical characteristics of the participants at Time 1 in subgroups.

Characteristics	Class 1 (n = 163)	Class 2 (n = 36)	Total (n = 199)	χ^2/t	p
Gender, *n* (%)					
Male	53 (32.5)	10 (27.8)	63 (31.7)	0.13	0.72
Female	110 (67.5)	26 (72.2)	136 (68.3)		
Age (years), mean (SD)	37.2 (9.1)	34.4 (10.3)	36.7 (9.4)	−1.65	0.10
Age group (years), *n* (%)					
Under 30	33 (20.2)	14 (38.9)	47 (23.6)	5.68	0.06
30–39	76 (46.6)	13 (36.1)	89 (44.7)		
Over 40	54 (33.1)	9 (25.0)	63 (31.7)		
Past medical history, *n* (%)					
Non-psychiatric	17 (10.4)	2 (5.6)	19 (9.5)	0.34	0.56
Sleep disorder	13 (8.0)	7 (19.4)	20 (10.1)	3.12	0.08
Neuropsychiatric treatment	15 (9.2)	7 (19.4)	22 (11.1)	2.19	0.14
Smoking status, *n* (%)					
Never-smoker	131 (80.4)	27 (75.0)	158 (79.4)	0.68	0.71
Ex-smoker	20 (12.3)	5 (13.9)	25 (12.6)		
Smoker	12 (7.4)	4 (11.1)	16 (8.0)		
Initial neuropsychiatric symptoms					
Yes	106 (65.0)	29 (80.6)	135 (67.8)	20.41	<0.001
No	57 (35.0)	7 (19.4)	64 (32.2)		
COVID-19-related symptoms					
Cough	130 (79.8)	28 (77.8)	158 (79.4)	<0.001	0.97
Sputum	119 (73.0)	29 (80.6)	148 (74.4)	0.53	0.47
Fever	63 (38.7)	17 (47.2)	80 (40.2)	0.58	0.45
Rhinorrhea	72 (44.2)	22 (61.1)	94 (47.2)	2.75	0.10
Sore throat	135 (82.8)	28 (77.8)	163 (81.9)	0.22	0.64
Dyspnea	4 (2.5)	1 (2.8)	5 (2.5)	<0.001	1.0
Chest pain	9 (5.5)	7 (19.4)	16 (8.0)	5.96	0.02
Gastrointestinal symptoms	52 (31.9)	16 (44.4)	68 (34.2)	1.54	0.21
Pain	89 (54.6)	18 (50.0)	107 (53.8)	0.10	0.75
Sleeping difficulty	37 (22.7)	13 (36.1)	50 (25.1)	2.15	0.14

cultures such as Korea, health authorities should prepare public health measures to monitor not only the progress of infectious diseases, but also the mental health.

The current study attempted to monitor and analyze acute COVID-19 somatic and depressive symptoms simultaneously using telehealth services for patients in remote locations. Results suggest that early detection of patients with depressive symptoms in the acute phase of COVID-19 using telemedicine is feasible. Digital therapeutics have been reported to be effective for patients with mental illnesses (33, 34). During the COVID-19 pandemic, even the general population without a history of mental illness preferred digital therapeutics to visiting psychiatric clinics (35). Thus, worsening of depressive symptoms may be prevented by offering digital therapeutics intervention to those with early detection during quarantine, when visit to the clinic in person can be limited (36).

4.1 Limitations

First, patient accrual done using convenience sampling may have led to the snowball sampling. Thus, the generalizability of the study results cannot be ensured. Second, the data were assessed using patient self-reports, which may be led to inaccurate estimates of symptom changes. Third, the patients could have undergone interventions, such as drug therapy for COVID-19 symptoms, that were not considered in the statistical analyses. Fourth, the PHQ-9 measures depressive symptoms over the past 2 weeks, resulting in timeline issues for Times 1 and 3 that must be considered with respect to the quarantine duration of approximately 7 days. Further study may be conducted using more specific tools such as the Hamilton depression rating scale (37) rather than PHQ-9. Fifth, current study did not collect social determinants and socio-economic status of the participants, which

TABLE 3 Association between COVID-19 symptoms at Time 1 and depression Class 2.

Characteristics	Odds ratio	95% Confidence interval	*p*
Gender			
Male			
Female	1.46	0.59–3.91	0.42
Age group (years)			
Under 30			
30–39	0.53	0.22–1.30	0.16
Over 40	0.43	0.15–1.16	0.097
Past medical history			
Non-psychiatric	0.70	0.11–3.22	0.66
Sleep disorder	1.85	0.59–5.45	0.28
Neuropsychiatric treatment	1.54	0.51–4.30	0.43
Initial neuropsychiatric symptoms			
Yes			
No	1.37	0.56–3.63	0.50
Smoking status			
Never-smoker			
Ex-smoker	1.26	0.37–3.83	0.70
Smoker	2.24	0.50–8.95	0.28
COVID-19-related symptoms at Time 1			
Cough	0.67	0.27–1.77	0.40
Sputum	1.22	0.51–3.20	0.67
Fever	1.12	0.50–2.47	0.79
Rhinorrhea	2.06	0.96–4.57	0.064
Sore throat	0.67	0.24–2.06	0.47
Dyspnea	0.55	0.04–4.42	0.59
Chest pain	3.07	0.92–10.31	0.068
Gastrointestinal symptoms	1.45	0.66–3.16	0.65
Pain	1.14	0.49–2.68	0.76
Sleeping difficulty	1.19	0.48–2.77	0.70

TABLE 4 Association between COVID-19 symptoms and depression Class 2.

Characteristics	Odds ratio	95% Confidence interval	*p*
Gender			
Male			
Female	0.67	0.21–2.13	0.49
Age group (years)			
Under 30			
30 to 39	0.64	0.18–2.28	0.48
Over 40	0.56	0.15–2.10	0.39
COVID-19-related symptoms at Time 1			
Rhinorrhea	1.30	0.48–3.51	0.61
Chest pain	3.81	0.81–17.36	0.09
COVID-19-related symptoms at Time 2			
Cough	0.29	0.07–1.24	0.09
COVID-19-related symptoms at Time 4			
Fever	19.43	2.30–165.42	0.007
Rhinorrhea	2.97	1.05–8.46	0.039
Chest pain	6.55	1.15–34.61	0.035
Gastrointestinal symptoms	4.76	1.71–14.21	0.002
Sleeping difficulty	3.12	1.05–9.69	0.041
Headache	2.39	0.74–7.75	0.14
Brain fog	7.03	2.57–20.95	<0.001

play an important role in mental health, but was not considered in the current analysis.

5 Conclusion

Results from current study demonstrated the potential impact of telehealth through the use of longitudinal data collected from a contactless clinical trial. We identified two subgroups of depressive symptom trajectories in Korean patients with clinically mild COVID-19: the stable group (class 1) and the worsening group (class 2). The COVID-19-related symptoms associated with these groups were fever, chest pain, brain fog, sleeping difficulty, and gastrointestinal symptoms 1 month after release from quarantine. Findings from current analysis suggested that early detection of patients with high risk may provide a chance for more effective intervention, such as digital therapeutics, prior to deterioration of mental health. In addition, further study may help to elucidate how post-COVID-19 syndrome impacts mental health of patients with COVID-19, and which of social determinants of health, such as socioeconomic status, education level, and ethnicity of these patients impact mental health to be nominated as potential risk factor.

Data availability statement

The datasets presented in this article are not readily available because hospital regulation restrictions and patient privacy concerns. Requests to access the datasets should be directed to EC, ekchie93@snu.ac.kr.

Ethics statement

The studies involving humans were approved by Institutional Review Board at Seoul National University Hospital (IRB number: H-2107-049-1233). The studies were conducted in accordance with

the local legislation and institutional requirements. Written informed consent from the patients/participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

SS: Conceptualization, Writing – review & editing, Formal analysis, Methodology, Writing – original draft. SK: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. YK: Formal analysis, Writing – review & editing. YB: Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization, Methodology. EC: Conceptualization, Writing – review & editing, Funding acquisition, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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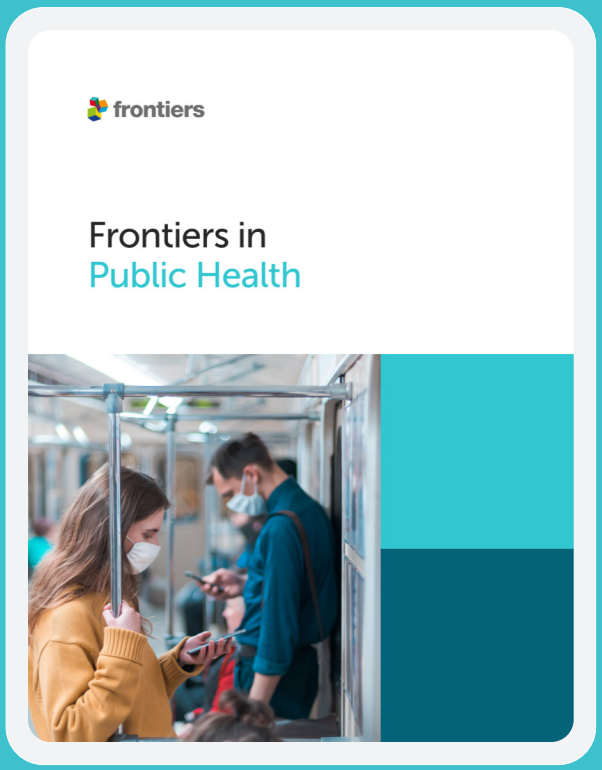

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