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COVID-19: Epidemiologic trends, public health challenges, and evidence-based control interventions

Edited by
Roger Nlandu Ngatu, Jean Marie Kayembe Ntumba,
Benjamin Longo - Mbenza and Xu-sheng Zhang

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COVID-19: Epidemiologic trends, public health challenges, and evidence-based control interventions

Topic editors
Roger Nlandu Ngatu — Kagawa University, Japan
Jean Marie Kayembe Ntumba — Université de Kinshasa, Democratic Republic of Congo
Benjamin Longo - Mbenza — Walter Sisulu University, South Africa
Xu-sheng Zhang — Public Health England, United Kingdom

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A Call to Use the Multicomponent Exercise Tai Chi to Improve Recovery From COVID-19 and Long COVID

Juan Pablo Castro[1], *Marie Kierkegaard*[2] *and Manuel Zeitelhofer*[3]*

[1] *Fundación Neumológica Colombiana, Bogotá, Colombia,* [2] *Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden,* [3] *Division of Vascular Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden*

Approximately 10% of all COVID patients develop long COVID symptoms, which may persist from 1 month up to longer than 1 year. Long COVID may affect any organ/system and manifest in a broad range of symptoms such as shortness of breath, post-exercise malaise, cognitive decline, chronic fatigue, gastrointestinal disorders, musculoskeletal pain and deterioration of mental health. In this context, health institutions struggle with resources to keep up with the prolonged rehabilitation for the increasing number of individuals affected by long COVID. Tai Chi is a multicomponent rehabilitation approach comprising correct breathing technique, balance and neuromuscular training as well as stress- and emotional management. In addition, practicing Tai Chi elicits the relaxation response and balances the autonomic nervous system thus regulating respiration, heart rate, blood pressure and vitality in general. Moreover, Tai Chi has been shown to increase lung capacity, improve cognitive status and mental health, and thereby even the quality of life in diseases such as chronic obstructive pulmonary disease (COPD). Hence, we advocate Tai Chi as potent and suitable rehabilitation tool for post-COVID-19-affected individuals.

Keywords: COVID-19, Tai Chi, multicomponent rehabilitation, quality of life, chronic fatigue, mental health, relaxation response

Edited by:
Roger Nlandu Ngatu,
Kagawa University, Japan

Reviewed by:
Marian S. Boshra,
Beni Suef University, Egypt

Correspondence:
Manuel Zeitelhofer
manuel.zeitelhofer@ki.se

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- Tai Chi is a multicomponent exercise that promotes self-efficacy and empowers affected individuals to actively contribute to their own disease management.
- Tai Chi has been shown to improve life quality and clinical parameters of chronic obstructive pulmonary disease (COPD) and other complex diseases.
- Tai Chi builds strength, improves mobility and balance, and elicits activation of the relaxation response.

WHAT ARE THE NEW FINDINGS?

- Tai Chi is suited for rehabilitation after COVID-19 and treatment of long COVID symptoms.
- Tai Chi potentially improves lung function by counteracting the fibrotic scar formation and may decrease chronic fatigue syndrome by balancing the autonomous nervous system and thereby the risk for development of mental disorders.
- Tai Chi may reduce the economic burden associated with COVID-19 rehabilitation.

WHAT ARE THE RECOMMENDATIONS FOR POLICY AND PRACTICE?

- We recommend to implement Tai Chi for acute COVID-19 rehabilitation directly after discharge from the hospital and for long COVID.
- The Tai Chi rehabilitation program should last for a minimum of 3 months with twice training for 1 h per week.
- Training by oneself in between the weekly classes should be encouraged.

INTRODUCTION

Physical inactivity increases the risk for modern society diseases such as diabetes and cardiovascular diseases, and likely even susceptibility for infectious diseases such as COVID-19. Recent data have shown that the risk for hospitalization and death due to COVID-19 increases more than 2-fold in physically inactive persons compared to persons performing at least 150 min/week moderate to vigorous physical activity (1). Moreover, one-third of patients suffering from long COVID are still experiencing symptoms such as fatigue, post-exertional malaise, cognitive dysfunction, breathlessness and muscle and joint pain even after 1-year, which results in reduced quality of life (2). Of note, long COVID is very common in young to middle aged persons, a population group engaged in work and family life, potentiating both the social and economic burden associated with the current pandemic. Thus, it is of utmost importance to establish an efficient rehabilitation program to counteract debilitating post COVID symptoms.

TAI CHI AS A MULTICOMPONENT EXERCISE

Tai Chi is a moderate intensity, multicomponent mind-body practice that provides tools for management of chronic diseases, as illustrated by promoting of self-efficacy in patients with chronic obstructive pulmonary disease (COPD) (3). Moreover, it has been shown that Tai Chi has beneficial effects on functional outcomes and quality of life in complex diseases such as cardiovascular, multiple sclerosis (MS), chronic pain and fibromyalgia (4). Tai Chi comprises diaphragmatic breathing technique, balance- and neuromuscular training, postural alignment, stress management and mindfulness. In addition, Tai Chi training teaches the connection of breath and movement and thereby fosters the elicitation of the relaxation response (5). Importantly, the embodied skills learned through practicing Tai Chi may represent a foundation for sustainable self-regulation and self-efficacy, and thereby enable patients to actively contribute to disease management. Finally, potentiation of the practice-associated, long-lasting behavioral changes counts as crucial aspect for management of complex diseases including COVID. Thus, an individual practicing of Tai Chi would in turn significantly reduce the burden for the health care system related to increasing demand for post-COVID rehabilitation.

TAI CHI POTENTIALLY IMPROVES LONG COVID SYMPTOMS

A severe COVID-19 disease course can lead to fibrotic changes in the lung (2) that could possibly cause a long-term impairment of the lung function. In COVID patients, spots of inflammation are frequently observed in CT images of the lower lung lobes (6). These patches might make it difficult to breathe during sustained exercise and if unresolved can potentially lead to fibrotic changes. Diaphragmatic breathing learned during Tai Chi encourages air into the lower lobes thus counteracting the inflammatory process. Therefore, exercise becomes an essential rehabilitation tool after acute care and this window of opportunity should be proactively and efficiently used to improve pulmonary function and counteract potential fibrotic changes. It has been shown that Qigong breathing used in Tai Chi leads to a 125 to 145% increase in lung capacity (7). Usually, lung capacity decreases with age due to decreasing tissue elasticity related to fibrotic changes. However, up to 70-year-old Qigong practitioners showed the same lung capacity as 20-year-old non-Qigong practitioners (7).

Recently it has been shown that relaxation response training upregulates genes associated with energy metabolism and mitochondrial function while downregulating genes linked to inflammatory response and stress-related pathways (8). Such boosting of mitochondrial fitness has been speculated to enhance anti-inflammatory effects, which may prevent the occasionally occurring destructive cytokine storm in COVID-19 (9). In addition, it has been demonstrated that Tai Chi modulates the immune response in general by downregulating cytokines such as interleukin-6 that has been implicated in scaring of the lung during COVID-19 (2, 10).

The inflammatory response during COVID-19 is tightly connected with the oxidative stress response leading to accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), by inducing mitochondrial dysfunction and secretion of proinflammatory cytokines. Moreover, ROS also activate transforming growth factor b (TGFb), a key factor for developing lung fibrosis.

While occasional high-intensity physical activity has been shown to promote oxidative stress, regular exercise with moderate intensity (40–59% VO_{2max}) decreases the ROS load and DNA damage, respectively, and stimulates key antioxidant enzymes (11). The same form of training intensity is recommended for the elicitation of physiological benefits and the promotion of better health. Thus, the moderate-intensity exercise Tai Chi would represent a suitable training option for improving health status in individuals suffering from post COVID symptoms.

One of the most debilitating long COVID signs is fatigue, which is often occurring in attacks of severe physical and mental tiredness that might result in mental health deterioration such as development of anxiety or depression (12). It has been reported that the fatigue may persist longer than a year post-COVID-19. However, there is an indication that it may last even longer, since 40% of survivors from previous coronavirus outbreaks such as the SARS (severe acute respiratory syndrome) epidemics in 2003 suffered from chronic fatigue and mental illnesses up to 4 years after the disease, which has led to a high unemployment rate and social stigmatization (13).

In addition, a recent study has shown that insomnia, anxiety and depression are very prevalent among the general population during the COVID-19 pandemics with twice as high prevalence as compared to non-pandemic periods and even higher among patients with COVID-19 (14). These observations indicate an urgent need to prevent long-term adverse outcomes associated with insomnia and mental health problems.

Initiation of Tai Chi practice soon after recovering from acute COVID-19 could potentially decrease the risk for developing long-term COVID. Tai Chi improves both blood and energy flow, activates the relaxation response and thus balances the autonomic nervous system (15) and can thereby potentially counteract fatigue and improve cognitive function as well as anxiety and depression (3, 4), all common long COVID symptoms. In addition, the practice has shown to have beneficial effects on cardiovascular health (4), hence, potentially decreasing the risk for COVID-19-associated stroke. Finally, Tai Chi has been shown to improve exercise capacity, balance and posture/neuromuscular control, which may occur in COVID-19 patients (3, 4).

A CALL FOR ACTION

Tai Chi potentially improves lung function by counteracting the fibrotic scar formation and decreasing long-term COVID fatigue and thereby the risk for development of mental disorders. Moreover, the practice is at the same time likely to increase muscular strength, mobility and vitality, which should in turn empower the individuals affected by COVID-19 to actively contribute to their recovery. Hence, implementation of Tai Chi in rehabilitation of COVID-19-affected individuals, for both short- and long-term disease courses, can be highly recommended.

AUTHOR CONTRIBUTIONS

MZ and JC designed the manuscript. MZ wrote the manuscript together with JC and MK. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: JC is holding rehabilitation classes at Fundación Neumológica Colombiana for COPD and post COVID patients. In addition, he has his own Tai Chi classes.

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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Socioeconomic Inequalities in COVID-19 Incidence During Different Epidemic Phases in South Korea

*Dae-sung Yoo[1,2], Minji Hwang[1,3], Byung Chul Chun[1,3,4], Su Jin Kim[5], Mia Son[6], Nam-Kyu Seo[7] and Myung Ki[1,3,4]**

[1] Department of Public Health, Korea University Graduate School, Seoul, South Korea, [2] Veterinary Epidemiology Division, Animal and Plant Quarantine Agency, Gimcheon, South Korea, [3] BK21FOUR R&E Center for Learning Health Systems, Korea University, Seoul, South Korea, [4] Department of Preventive Medicine, College of Medicine, Korea University, Seoul, South Korea, [5] Department of Emergency Medicine, College of Medicine, Korea University, Seoul, South Korea, [6] Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, South Korea, [7] Department of Non-Benefits Management, National Health Insurance Service/Health Insurance Policy Research Institute, Wonju, South Korea

Objective: Area-level socioeconomic status (SES) is associated with coronavirus disease 2019 (COVID-19) incidence. However, the underlying mechanism of the association is context-specific, and the choice of measure is still important. We aimed to evaluate the socioeconomic gradient regarding COVID-19 incidence in Korea based on several area-level SES measures.

Methods: COVID-19 incidence and area-level SES measures across 229 Korean municipalities were derived from various administrative regional data collected between 2015 and 2020. The Bayesian negative binomial model with a spatial autocorrelation term was used to estimate the incidence rate ratio (IRR) and relative index of inequality (RII) of each SES factor, with adjustment for covariates. The magnitude of association was compared between two epidemic phases: a low phase (<100 daily cases, from May 6 to August 14, 2020) and a rebound phase (>100 daily cases, from August 15 to December 31, 2020).

Results: Area-level socioeconomic inequalities in COVID-19 incidence between the most disadvantaged region and the least disadvantaged region were observed for nonemployment rates [RII = 1.40, 95% credible interval (CrI) = 1.01–1.95] and basic livelihood security recipients (RII = 2.66, 95% CrI = 1.12–5.97), but were not observed for other measures in the low phase. However, the magnitude of the inequalities of these SES variables diminished in the rebound phase. A higher area-level mobility showed a higher risk of COVID-19 incidence in both the low (IRR = 1.67, 95% CrI = 1.26–2.17) and rebound phases (IRR = 1.28, 95% CrI = 1.14–1.44). When SES and mobility measures were simultaneously adjusted, the association of SES with COVID-19 incidence remained significant but only in the low phase, indicating they were mutually independent in the low phase.

Conclusion: The level of basic livelihood benefit recipients and nonemployment rate showed social stratification of COVID-19 incidence in Korea. Explanation of area-level inequalities in COVID-19 incidence may not be derived only from mobility differences in Korea but, instead, from the country's own context.

Keywords: COVID-19, inequality, mobility, SARS-CoV2, social distancing, socioeconomic, spatial analyses

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Roger Nlandu Ngatu,
Kagawa University, Japan

Reviewed by:
Olalekan A. Ayo-Yusuf,
University of Pretoria, South Africa
Charles J. Vukotich,
University of Pittsburgh, United States

***Correspondence:**
Myung Ki
myungki@korea.ac.kr

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INTRODUCTION

Since the first case, reported in December 2019 in China, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2; COVID-19) pandemic has caused unprecedented global challenges due to rapid interpersonal transmission. This virus causes symptoms ranging from mild, such as sore throat and fever, to severe pneumonia resulting in death (1). Due to a higher transmission rate than other coronaviruses (reproduction ratio: 2.44–4.18) and a high proportion of asymptomatic infectious people (2), the global pandemic has grown significantly, causing nearly 271.4 million cases with 5.3 million deaths (as of 16th December 2021) according to the World Health Organization (3).

In Korea, since the first case of COVID-19 in a person who visited China was identified on January 20, 2020, multiple clustered outbreaks associated with religious followings, call centers, and courier services led to a surge in the number of disease occurrences; this was followed by enhanced strict counteractive measures, including social distancing, that were enforced by health authorities, which reduced the weekly average number of cases to single digits (4). However, due to increased outdoor activities, large-scale gatherings during the holiday season and seasonality, the number of newly infected cases grew dramatically to more than 1,000 cases daily, mostly driven by a substantial increase in infections in the capital region, where 25.92 million people live within 11,851.26 km², one of the most densely populated areas in the world.

Historically, disadvantaged people have been highly vulnerable to emerging infectious diseases, especially when they become a persistent epidemic (5). In recent studies on COVID-19, historic evidence showed that socioeconomically vulnerable individuals were more likely to have higher incidence and case-fatality rates of COVID-19 (6, 7). This indicates that underlying socioeconomic gradients are strongly associated with the distribution of incidence and fatality rates of COVID-19, due to variations in personal hygiene, access to testing and treatment, compliance level with social distancing policy, and the ability to work remotely (8). In recent studies regarding COVID-19 in the United States, low-income individuals were less able to reduce their mobility or maintain social distancing, indicating that economic activity is highly associated with behavioral responses to social distancing policy (9, 10).

In addition to individual socioeconomic vulnerability, area-level socioeconomic disadvantages have consistently been associated with COVID-19 incidence. Area-level socioeconomic status (SES) tends to depend on territory-based communities that characterize human society because of a shared socioeconomic basis, commonality in available services, living culture, and lifestyle (11). Area-level socioeconomic measures have been identified in various ways and typically measured using an aggregate variable (e.g., median household income) or a composite measure (e.g., deprivation index). Each measure represents a unique contribution to the socioeconomic association. Specifically, associations with COVID-19 were consistently observed for median household income (12, 13) and minor ethnicity (1, 14, 15) but findings for deprivation index (16, 17) and unemployment rate (13, 14) were inconsistent, indicating that area-level SES measures have different values across time and place and that how they are measured is important (18).

Individuals from lower SES areas are more likely to be infected for various reasons; however, in most studies, the primary cause was the lack of mobility reduction resulting in the inability to maintain social distancing. However, the mediating role of mobility was advocated in other studies to explain area-level socioeconomic inequalities in COVID-19 infection based on the high correlation between area-level SES and mobility reduction (10, 16, 19, 20). Despite wide acceptance of the explanation, studies in which the underlying relationship was investigated using both measures are scarce. Thus, firm empirical evidence is lacking on whether the effect of area-level SES on COVID-19 incidence depends on the level of mobility. This concept may be particularly relevant in countries like Korea, where socioeconomic inequalities in COVID-19 incidence may not be straightforward because affluent areas are also a central business place.

As noted below, Korea had been undergone a relatively lower level of COVID-19 incidence compared to other countries (21). Nevertheless, a better understanding of regional disparity in COVID-19 incidence is a huge challenge because it is essential to monitor the pattern of spread into subsegment of the population, let alone the incidence from the entire population. Thus, we investigated the socioeconomic inequalities in COVID-19 incidence at the level of a primary administrative unit of local government in Korea, using a diverse range of socioeconomic indicators including a mobility measure. In this study, we investigated (1) whether area-level socioeconomic measures are associated with COVID-19 incidence at the municipality level; (2) whether the associations' differences in the association between socioeconomic inequalities and COVID-19 incidence in two different epidemic phases with disparate social distancing enforcement; and (4) whether socioeconomic inequalities in COVID-19 infection are mainly due to mobility differences.

MATERIALS AND METHODS

Study Base

Overall, Korea experienced favorable outcomes of COVID-19 compared with other countries in terms of incidence and mortality through the pandemic and the study period (21, 22). To evaluate the effects of socioeconomic inequalities on COVID-19 incidence at different epidemic levels, the epidemic period was divided into two phases based on the daily number of cases and the accompanying social distancing intensity level as shown in **Figure 1**: low phase (from May 6 to August 14, 2020) in which less than 100 mean daily cases were confirmed with the eased social distancing regulation (level 1) and rebound phase (from August 15 to December 31, 2020) in which more than 100 mean daily cases were reported with stricter distancing imposed (level 2). Because the early phase of the epidemic was induced by a specific religious congregation concentrated in very limited

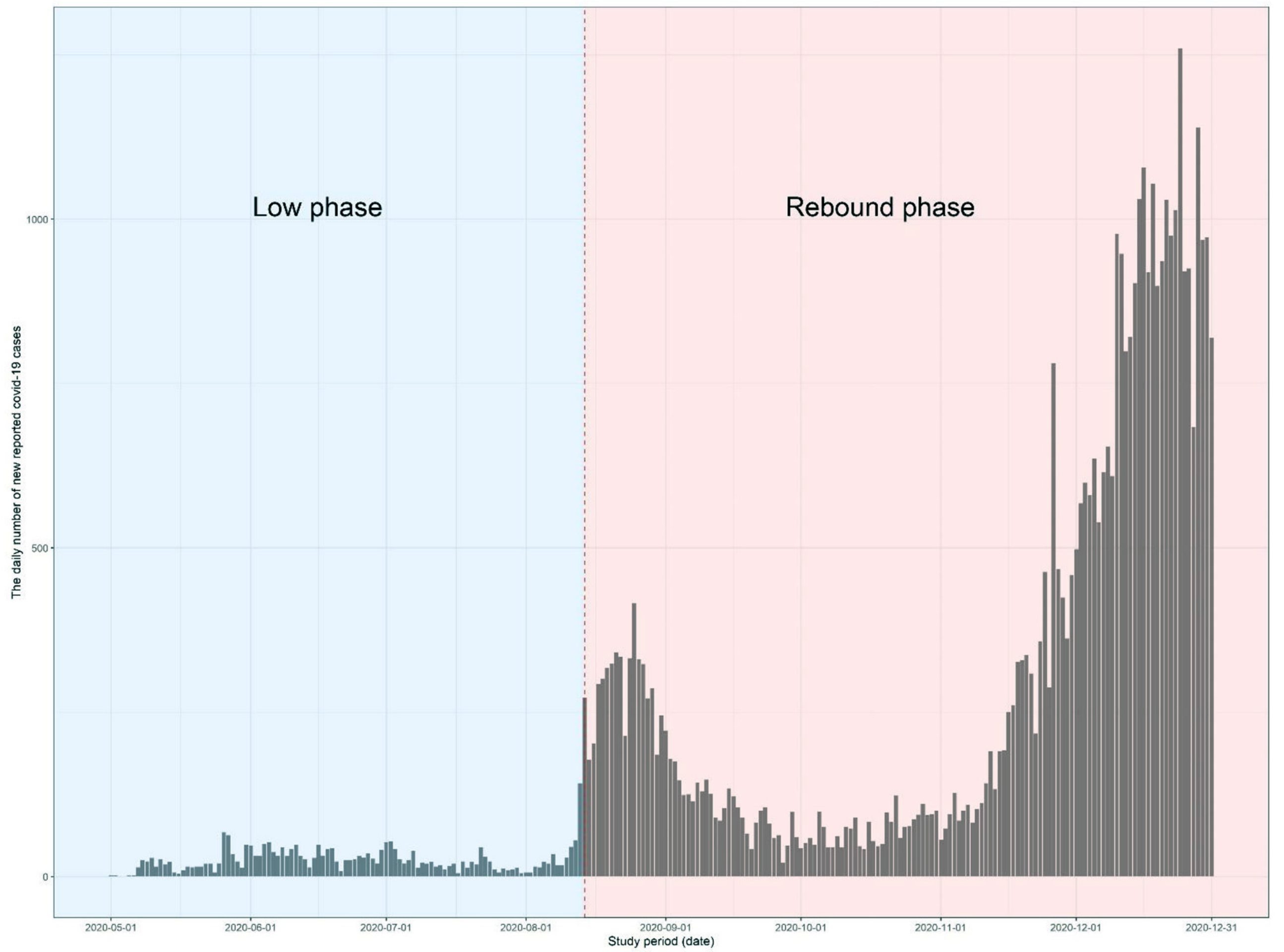

FIGURE 1 | The epidemic curve of coronavirus disease 2019 (COVID-19) in the Korea during the study period (from May 1 to August 14, 2020, for low phase and from August 15 to December 31, 2020, for rebound phase). The gray bar represents the daily number of newly reported COVID-19 cases.

municipalities, the starting time point in this study was March 5, 2020, to ensure the validity of the results (23).

The social distancing level enforced by the Korean government was classified into two levels during the study period through the guidelines underwent several changes afterward. For example, under level 2 social distancing, the use of face masks in public became mandatory, social gatherings with more than a certain number of individuals were prohibited and restaurants must be closed after a specific time point but without movement restriction. Lower social distancing regulation (i.e., level 1) began from May 6 to August 14, 2020, and stricter social distancing measure (i.e., level 2) was enacted from August 15, 2020.

Socioeconomic Status Measures and Covariates

The information on COVID-19 incidence as an outcome variable was collected from 229 municipalities and compiled from the KCDC and the local administration's official websites. As listed in **Table 1**, six area-level (i.e., municipality) socioeconomic factors were used to investigate the effects of inequality on the incidence of COVID-19 in Korea. The indicators were classified into two subcategories, SES, and economic activity, based on the corresponding attributes. SES measures included the following: national insurance contributions as the proxy of area-specific income level; material deprivation index (MDI); nonemployment rate; the proportion of basic livelihood security recipients; financial autonomy of the area. Economic activity included mobility at risk. Data on national insurance contributions in the first quarter of 2020 were obtained from the Korean National Health Insurance Services. MDI for each area was a composite index derived from the sum of standardized Z-scores for eight measures based on data from the national population and housing census conducted by the National Statistical Office of Korea; the proportion of nonemployed males, manual laborers, households under the minimum housing standard, nonsecured housing tenure, nonapartment housing, lower educational level (≤middle school), single-parent household and school dropouts

TABLE 1 | Description of the variables used in the study with the source of data.

Category	Variable (units)	Description	Source (period)
Outcome	COVID-19 (No. of Cases)	The sum number of cases of COVID-19 by municipality	Korean center for disease control and local administration (May 6, 2020 – December 31, 2020)
Socioeconomic status	National insurance contributions (US Dollar)	Average amount of personal national insurance contributions per month by municipality	Korean national health insurance services (1st quarter of 2020)
	Material deprivation index (Z-score)	Composite index derived from the sum of standardized Z-scores for eight measures; the proportions of nonemployed males, manual class, households under the minimum housing standard, insecure housing tenure, living apartment, nonapartment housing, lower educational achievement (≤middle school), single-parent household, school drop-out between 9 and 24. Data were driven from the National population and housing census by the National Statistical Office of Korea by municipality	National population and housing census of the National Statistical Office of Korea (2015)
	Nonemployment rate (%)	The proportion of individuals who were unemployed or out of the labor force aged from 30 to 64 years	National population and housing census of the National Statistical Office of Korea (2015)
	Basic livelihood security recipient (%)	The total number of households receiving basic livelihood security over total number of households according to national basic living security act	Korea social security information service (2019)
	Financial autonomy (%)	The ratio of revenue generation to total expense by municipality	Korean statistical information service (2020)
Economic activity	Mobility at risk (Z-score)	The volume of public transportation times works related movement divided by total amount of traffic volume	Korean Transport Institute (2018)
Covariates	Population density (No. of inhabitants /km^2)	Human population on resident registry over the land size estimated	Korean statistical information service (2020)
	Median age (years)	Median age of residents in registry by municipality	Korean statistical information service (2020)
	Health care workforce (No. of health care workers per 1,000 persons)	The sum of total number of medical doctors, dentists, pharmacist, and health care worker	Korean statistical information service (2020)

between 9 and 24 years of age (24). The higher the MDI score, the more the area is deprived. The nonemployment rate was calculated as the proportion of individuals who were unemployed or out of the labor force (e.g., early retirement, studying, and disability) between 30 and 64 years of age (25), based on data from the National Population and Housing Census in 2015. The proportion of basic livelihood security recipients at the area level in 2019 was retrieved from the Korea Social Security Information Service. Financial autonomy for each area was defined as a ratio of total revenue generation to the total expenditure per municipality as provided by the Korean Statistical Information Service for 2019. To determine the socioeconomic strata of socioeconomic factors, those continuous values of socioeconomic factors were converted into quintiles of their distribution (i.e., each stratum accounted for 20% of the number of municipalities) (26).

In addition, the municipality-specific economic activity variable, including the volume of traffic for mobility at risk represented by a Z-score, was added. Mobility at risk was equal to the proportion of the traffic volume of work-related movement utilizing public transportation, which was calculated by multiplying the volume of public transportation and the volume of works-related traffics (e.g., commuting to work and field trips). This variable was obtained from a transportation survey conducted by the Korean Transport Institute in 2018. Finally, three covariates, namely, municipality-specific median age, population density, and the number of healthcare workers per 1,000 inhabitants, were used to adjust for the demographic composition and the local health care capacity of the areas in our analysis. The variables were derived from the data obtained from the Korean Statistical Information Service for 2020. The data in our study were extracted from open sources, which are aggregated by administrative subdivisions. Therefore, do not contain any information that is indicative of information about personal or household level. The Institutional Review Board (IRB) of Korea University granted an exemption for this study (IRB exemption number: KUIRB-2020-0297-01).

Statistical Analyses

Several steps of the analytical process were applied to examine socioeconomic inequalities in COVID-19 incidence. Due to the nature of spatial data, spatial autocorrelation on the

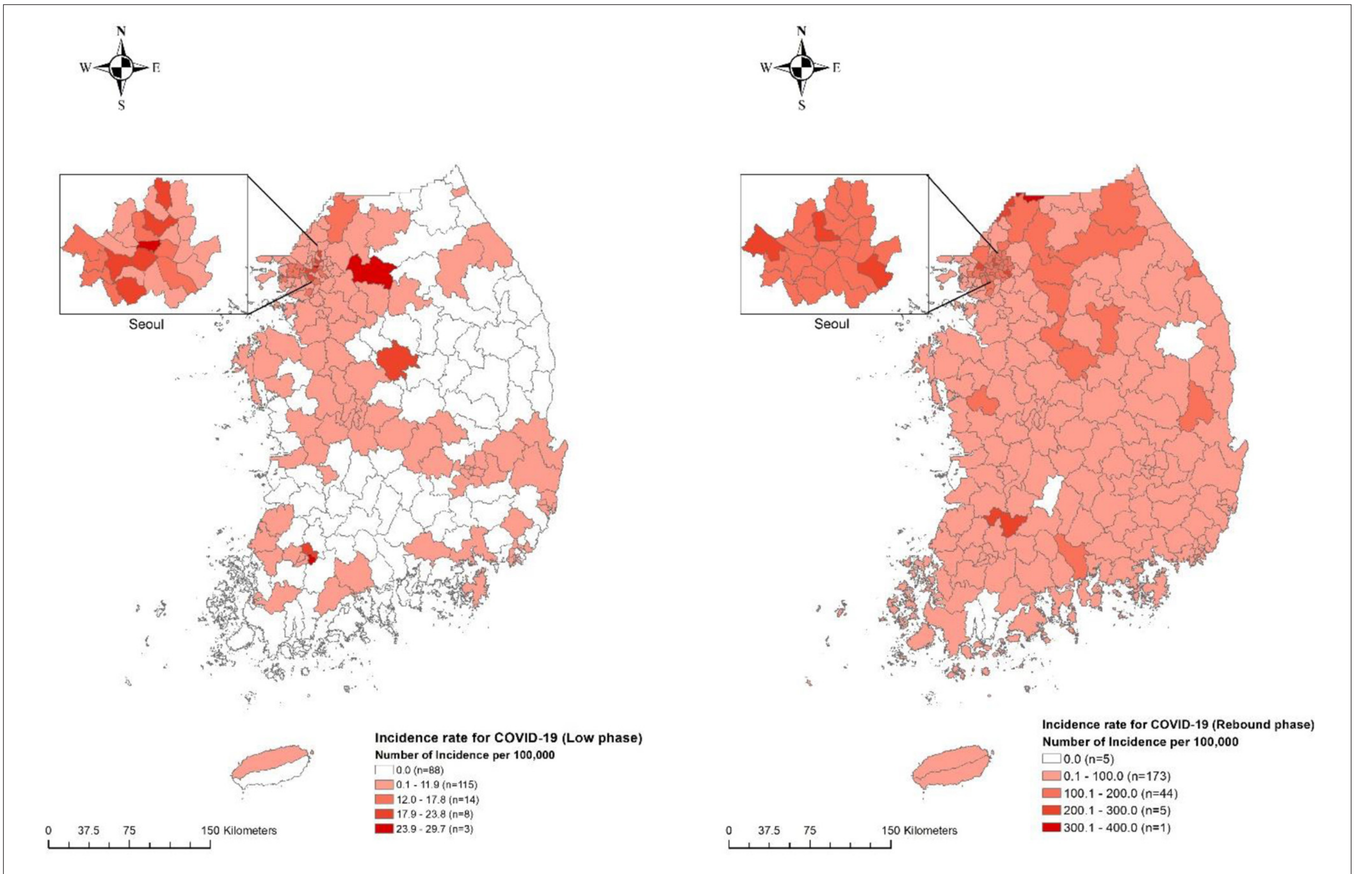

FIGURE 2 | Geographical distribution of municipality-specific incidence rate for COVID-19 in Korea between two epidemic phases. The number of incidences for COVID-19 per 100,000 inhabitants at the municipality level is denoted by five different color levels in the low phase of COVID-19 (**left**) and rebound phase of COVID-19 (**right**). Darker red shedding represents the highest strata, whereas brighter red shedding denotes the lowest strata along with white color representing noncase.

SES variables and three covariates were examined using Global Moran's I test before investigating the association between SES measures and COVID-19 incidence. The statistical significance of the Global Moran's I was estimated with 999 simulations. Following identification of the presence of spatial autocorrelation in socioeconomic indicators, the association between socioeconomic measures and COVID-19 incidence was estimated as an incidence rate ratio (IRR) using a spatial negative binomial model with marten correlation function for spatial correlation term (Model 1). To account for potential confounding factors, adjustment was initially made for three covariates (i.e., median age, population density, and healthcare workforce at the area-level) (Model 2). In addition, we conducted a regression with a further adjustment for economic activity to evaluate the mediating effect of mobility on the association between area-level SES and COVID-19 incidence (Model 3).

We built a Bayesian generalized linear model to estimate the posterior marginal distribution of IRR of each SES measure. Because the observed incidence rate by the municipality, used as the outcome of interest, was overdispersed, it was modeled as a negative binomial random variable with overdispersed variance instead of Poisson regression. In addition, the Besag, York, and Mollié (BYM) model was used to account for spatial autocorrelation of residuals by adding a spatial random effect using intrinsic conditional autoregressive (iCAR) function and extra residual term for spatially independent variation that was independent, identical, and normally distributed as follows:

$$Y_i \sim NB\left(\pi_i, r_i\right), Y_i\text{: Number of COVID} - 19 \text{ cases by municipality } i$$

$$\pi_i = \frac{r_i}{r_i + \lambda_i}, E\left(Y_i\right) = \lambda_i$$

$$\log\left(\lambda_i\right) = \alpha + \log\left(\mathbf{population}_i\right) + \beta_1 \times SES_{i,k} + \sum_{j=2}^{N} \beta_j \times covariate_i + u_i + \varepsilon_i$$

$$u_{1:229} \sim ICAR\left(W, \sigma_u^2\right)$$

$$\varepsilon \sim N\left(0, \sigma_\varepsilon^2\right)$$

$$u \sim N0,\ I - C^{-1} \times M, C = \gamma \times W, M = I \times \sigma_u^2$$

where u_i is the conditional autocorrelation regression term, the covariance matrix of the parameters calculated based on the neighboring regions, ε_i is the nonspatial structured term, u

is the spatial correlated random effect calculated by averaging neighboring random effects, I is the identity matrix, and W is the spatial weights matrix constructed by an inverse distance function with the exponents followed by row-standardized such that each row sums to 1 for interpretation of the parameters (27). The neighboring region at each municipality was defined as the administrative division located within the geographical distance that was not spatially correlated in a variogram generated using a Bayesian generalized linear model without the spatial correlation term. The spatial correlation parameter denoted as γ was set to 1.

The models were run with three chains with different starting values in which sampling values in the MCMC process with a burn-in of 4,000 iterations and a thinning rate of 10, and 50,000 iterations were used for each posterior distribution of parameters for SES and covariates. Convergence of the chains was assessed by visual inspection of the posterior distributions and computation of the Gelman–Rubin statistic. The Deviance Information Criterion (DIC) was used to measure and compare the goodness of fit for the model. The prior distribution for each parameter and hyperparameter is described in the **Supplementary Material**. R2WinBUGS R software package version 2.1 (28) with WinBUGS software version 1.4.3 was used to carry out given statistical approaches (29). The map presented in this study was created by Esri ArcGIS software version 10.8.1 using the South Korea map which is publicly available (30). All analyses were separately performed for two different phases of the COVID-19 pandemic; the low and rebound phases.

We repeated a similar analysis to estimate the relative index of inequality (RII) as a supplementary measure of inequalities in the COVID-19 incidence rate at the area level. RII is a commonly used measure of health inequalities that summarizes the distribution of a health outcome measure against an SES as a relative difference of the least and most deprived subgroups (31). RII in this study corresponds to the relative risk of the incidence for COVID-19 in the lowest and the highest socioeconomic strata and, therefore, is directed by changes in two strata (**Supplementary Material**). The RII was also estimated using a spatial negative binomial model with marten correlation function for spatial correlation term, 95% CI was estimated by bootstrap. RII estimation was made as follows.

$$\boldsymbol{Y_i} \sim \boldsymbol{NB}\left(\pi_i, \boldsymbol{r_i}\right), \boldsymbol{Y_i}\text{: } \textbf{\textit{Number of COVID}} - \textbf{\textit{19 cases by municipality i}}$$

$$\pi_i = \frac{\boldsymbol{r_i}}{\boldsymbol{r_i} + \lambda_i}, \boldsymbol{E}\left(\boldsymbol{Y_i}\right) = \lambda_i$$

$$\log\left(\lambda_i\right) = \alpha + \log\left(\boldsymbol{population_i}\right) + \beta_{\boldsymbol{1}} \times \boldsymbol{SES_{i,k}} + \sum_{j=2}^{N} \beta_j \times \boldsymbol{covariate_i} + \boldsymbol{u_i} + \varepsilon_i$$

$$\boldsymbol{u_{1:229}} \sim \boldsymbol{ICAR}\left(\boldsymbol{W}, \sigma_{\boldsymbol{u}}^{\boldsymbol{2}}\right)$$

$$\varepsilon \sim \boldsymbol{N}\left(\boldsymbol{0}, \sigma_{\varepsilon}^{\boldsymbol{2}}\right)$$

$$\boldsymbol{u} \sim \boldsymbol{N}(\boldsymbol{0}, \ (\boldsymbol{I}-\boldsymbol{C})^{-\boldsymbol{1}} \times \boldsymbol{M}), \boldsymbol{C} = \gamma \times \boldsymbol{W}, \boldsymbol{M} = \boldsymbol{I} \times \sigma_{\boldsymbol{u}}^{\boldsymbol{2}}$$

where x_i denotes the mid-point of municipality i in socioeconomic class k with number 1 assigned to the highest class of SES, as opposed to the lowest strata. The mid-point was derived for each SES class. In addition, SES variables are likely to be mutually correlated. Thus, Spearman's correlation coefficient between two paired SES variables was estimated to exclude the correlated combinations for subsequent multivariate analyses.

RESULTS

Overview of COVID-19 Incidence and Socioeconomic Characteristics

The COVID-19 epidemic in Korea showed two distinctive phases in terms of the incidence level over the study period as illustrated in **Figure 1**. In the low phase (from May 6 to August 14, 2020), 2,906 cases were reported in 141 municipalities with 28.8 daily new cases for 100 days, in which no escalating pattern was observed in the epidemic curve. In contrast, in the rebound phase (from August 15 to December 31, 2020), 40,545 cases were reported in 224 municipalities with 291.7 daily cases for 139 days, in which two distinctive peaks were observed in the epidemic curve.

Geographically, a significant difference was observed in the area-level COVID-19 incidence rate as shown in **Figure 2**. On average, 12.7 cases were reported per area [minimum (min) – maximum (max) = min – max = 0–127 cases] in the low phase and 177.1 cases (min – max = 0–1,653 cases) were reported in the rebound phase. The majority of COVID-19 cases were reported in the Seoul metropolitan area (81.8% in the low phase and 72.8% in the rebound phase) where 50.28% of the total Korean population resides within 11,851.26 km^2 (11.8% of the land size of Korea). The average nonemployment rate was 13.9 and 4.9% of households received basic livelihood security (**Table 2**). All variables, in particular, economic activity, showed significant spatial autocorrelation in the Global Moran's I test indicating that the association of those variables with COVID-19 should be measured with consideration of spatial autocorrelation.

Generally, socioeconomic measures were significantly correlated with each other (**Figure 3**) but heterogeneous in direction. For example, national insurance contributions as the proxy of personal income level had a negative correlation with indicators of social exclusion and poverty [e.g., MDI (Spearman coefficient = −0.84], the proportion of basic livelihood security recipients [Spearman coefficient = −0.75), and the nonemployment rate (Spearman coefficient = −0.13)]. Notably, a negative correlation of economic activity (i.e., mobility at risk) was observed with indicators of social exclusion and poverty such as the proportion of basic livelihood security recipients (Spearman coefficient = −0.38) but not with nonemployment rate (Spearman coefficient = 0.69), and a positive correlation of mobility at risk was shown with national insurance contribution (Spearman coefficient = 0.69), indicating economic activity (i.e., mobility at risk) was characteristic of affluent areas.

TABLE 2 | Overview of socioeconomic status measures, economic activity variables, and covariates for 229 municipalities in Korea.

Variables	Descriptive statistics					
	Mean	SD	Min	Max	CV	Global morans'I†
Socioeconomic status (unit)						
National insurance contributions (US dollars)	43.18	10.58	27.76	100.43	0.25	0.71 (0.001)
Material deprivation index (Z-score)	0.00	5.61	−12.41	14.59	-	0.48 (0.001)
Nonemployment rate (%)	13.86	3.12	4.53	24.10	0.23	0.34 (0.001)
Basic livelihood security recipient (%)	4.48	1.57	1.27	9.79	0.26	0.62 (0.001)
Financial autonomy (%)	24.96	12.60	6.60	68.00	0.33	0.57 (0.001)
Economic activity						
Mobility at risk (Z-score)	0.00	1.00	−1.48	2.84	-	0.87 (0.001)
Covariates						
Population Density (No. of inhabitant/km^2)	45.78	87.66	0.20	516.19	1.92	0.36 (0.001)
Median Age (years)	47.47	6.08	37.20	61.00	0.13	0.49 (0.001)
Health care workforce (No. of workers per 1,000 persons)	8.21	6.87	2.57	54.02	0.84	0.23 (0.002)

SD, standard deviation; Min, minimum; Max, maximum; CV, coefficient of variance = standard deviation/mean.
† The significance of the statistics of Global Morans'I was estimated with 999 simulations, expressed in parenthesis.

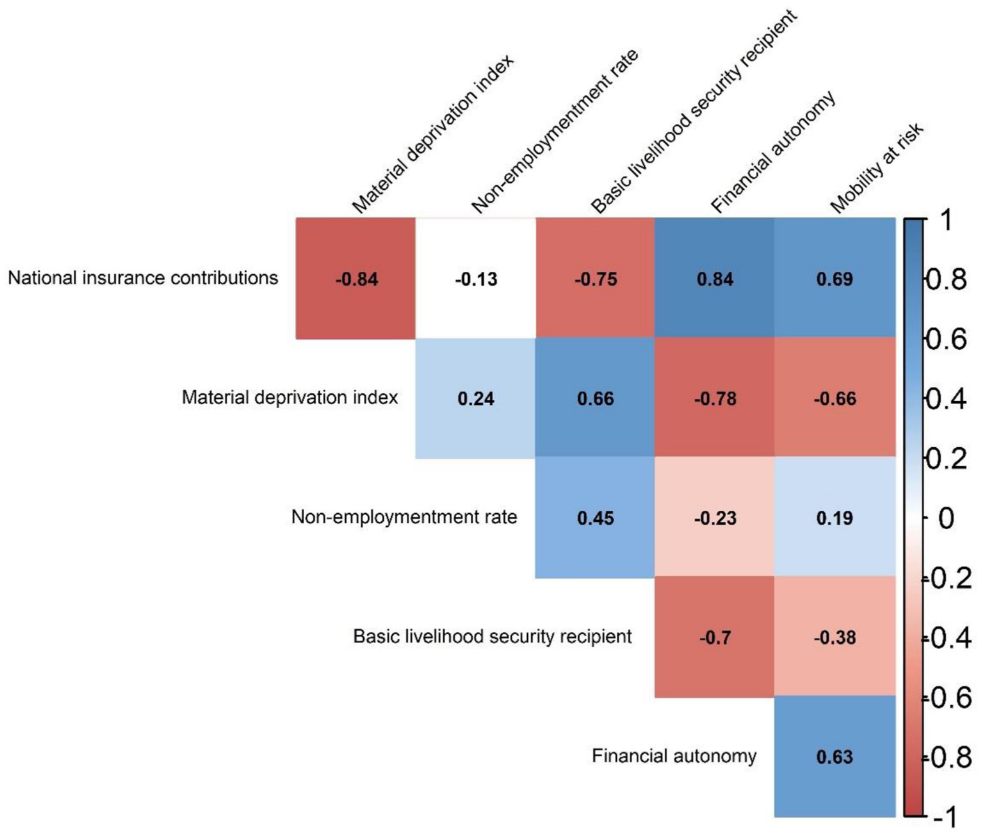

FIGURE 3 | Correlation plot between socioeconomic status and economic activity variables. The number inside the cell corresponded to Spearman correlation coefficient estimates. The intensity of correlation was expressed by colored gradient where dark blue represented one (a complete positive correlation) and dark red represented minus one (a complete negative correlation). All correlation coefficients estimates were statistically significant ($p < 0.05$).

TABLE 3 | Incidence rate ratios for the association between socioeconomic status and economic activity and incidence for COVID-19 over the low and rebound phase in 229 municipalities in Korea.

Variables	Low phase (no. of cases = 2,906)			Rebound phase (no. of cases = 40,545)		
	Model 1 †	Model 2 ‡	Model 3§	Model 1 †	Model 2 ‡	Model 3§
Socioeconomic status						
National insurance contributions	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)	-	1.01 (1.00, 1.02)	1.07 (0.82,1.40)	-
Material deprivation index (Z-score)	0.99 (0.95, 1.02)	0.98 (0.92, 1.04)	-	0.99 (0.97, 1.01)	1.00 (0.97,1.02)	-
Nonemployment rate	1.11 (1.06, 1.17)	1.20 (1.13, 1.28)	1.61 (1.09, 1.25)	1.02 (0.99, 1.05)	1.05 (1.02, 1.08)	1.02 (0.99, 1.06)
Basic livelihood security recipient	1.10 (1.02, 1.18)	1.23 (1.07, 1.40)	1.16 (1.02, 1.32)	1.04 (1.02, 1.06)	1.35 (0.93, 1.93)	1.04 (0.98, 1.09)
Financial autonomy	1.00 (0.98, 1.01)	0.98 (0.97, 1.00)	-	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	-
Economic activity						
Mobility at risk	1.69 (1.23, 2.35)	1.67 (1.26, 2.17)	1, 59 (1.22, 2.06)	1.23 (1.05, 1.46)	1.28 (1.14, 1.44)	1.26 (1.13, 1.41)
Covariates						
Population density	1.00 ¶ (1.00, 1.00 ¶)	-	-	1.00 ¶ (1.00, 1.00 ¶)	-	-
median age	0.99 (0.95, 1.03)	-	-	0.99 (0.97, 1.00)	-	-
Health care workforce	1.02 (1.01, 1.04)	-	-	1.01 (1.00, 1.02)	-	-

The incidence rate ratio (IRR) was estimated using a Spatial and Bayesian negative binomial model with marten correlation function and BYM for spatial correlation term, 95% confidence interval was estimated by bootstrap, denoted in the parenthesis.

† Model 1: unadjusted model.

‡ Model 2: socioeconomic indicators were remained to estimate the associations, adjusting for covariates (human density, median age, and health care workforce).

§ Model 3: two significant variables in Model 2 were retained to estimate the associations, adjusting for covariates from Model 2+ mobility at risk, separately. In turn, the incidence rate ratio for mobility at risk returned two estimates for each of two corresponding socioeconomic status variables. The incidence rate ratio of mobility at risk in this table was given as an adjustment factor for basic livelihood security recipients variable.

¶ denotes a given value is >1.

Associations Between Area-Level Socioeconomic Measures and COVID-19 Incidence

Table 3 shows the estimation of IRR for the association between area-level SES measures and COVID-19 incidence using a Bayesian negative binomial regression. Overall, two area-level SES measures, nonemployment rate and the proportion of basic livelihood security recipients, were consistently associated with COVID-19 incidence based on unadjusted and adjusted modeling in the low and rebound phases. Specifically, in the low phase, the adjusted IRR corresponding to an increase in 1% of the nonemployment rate and the proportion of basic livelihood security recipients was estimated as 1.20 (95% credible interval (Crl) = 1.13–1.28) and 1.23 (95% Crl = 1.07–1.40), respectively (Model 2). In the rebound phase, the same SES measures presented inconsistence association with COVID-19 incidence. For example, the nonemployment rate showed a significantly negative association with COVID-19 incidence adjusted for only covariates (model 2), but for both covariates and mobility at risk (model 3), while the proportion of basic livelihood security recipients had an only univariate association with COVID-19 incidence (model 1) (**Figures 4**, **5**).

An economic activity indicator (i.e., area-level mobility at risk) was positively associated with COVID-19 incidence rate in both the low (IRR = 1.67, 95% Crl = 1.26–2.17) and rebound phases (IRR = 1.28, 95% Crl = 1.14–1.44). When assessing the mediation of mobility at risk in the association between two SES measures and COVID-19 incidence, the magnitude of the associations was attenuated but remained significant in the low phase, but no associations were observed in the rebound phase (Model 3). For instance, the area with a higher nonemployment rate had a higher risk of COVID-19 incidence in the low phase (IRR = 1.61, 95% Crl = 1.09–1.25) but independent associations were not observed in the rebound phase (IRR = 1.02, 95% Crl = 0.99–1.06). When assessed with RII, nonemployment rate and the proportion of basic livelihood recipients showed a similar pattern of associations with COVID-19 incidence (**Supplementary Table**).

DISCUSSION

In this study, a significantly positive association was found between area-level nonemployment rate and the population share of basic livelihood security recipients and COVID-19 incidence. However, area-level socioeconomic effects were stronger in the low phase when the prevalence of COVID-19 was low, with less strict governmental measures (**Figures 4**, **5**). In other words, the strength of the association of those SES measures decreased as the level of COVID-19 incidence rate across the country increased. Similarly, the inequalities in the COVID-19 incidence rate concerning nonemployment and basic livelihood security recipients were significantly high in the low phases. In addition, higher mobility at risk, indicating active economic activity at the area level, increases the risk of COVID-19 incidence in both phases. In this context, when both area-level SES measures and mobility were simultaneously adjusted, SES measures remained significant in the low phase, suggesting they were independent of each other in the low-risk period. However, in the rebound phase, adjustment for economic activity variables showed no association between SES measures and COVID-19 incidence. Overall, partial existence of COVID-19 inequalities in some measures may have occurred as a result of counteraction between risk raising and lowering area-level effects (e.g., poor communities are less mobile).

Among five measures of area-level SES, the areas with a higher level of basic livelihood security recipients and nonemployment rate showed a higher risk of COVID-19 incidence; however, an association was not observed for other area-level socioeconomic measures. A partial observation of area-level socioeconomic inequalities in COVID-19 incidence differs from most previous studies from the United States (32), the United Kingdom (20), and Spain (33, 34), and is similar to a previous Korean study (35) in which no or a partial association was observed. Inconsistency in inequalities in COVID-19 incidence across measures may possibly be interpreted using the socioeconomic context of Korea. Korean government measures were impartially imposed regarding case-identifying processes, awareness of the process, access to COVID-19 testing, and contact tracing, which may provide a relatively equal chance of being diagnosed. Close supervision by national mandatory conduct systems was uniformly applied regardless of area-level SES. This universal approach is not exclusive to Korea, but the outcome may be proequity in countries with high levels of public support for strong governmental measures. In addition, inequalities may be greater in places where COVID-19 diagnostic testing is often delayed, and choosing which patient to care for first is an issue when the number of patients is overwhelming (36). In contrast, Korea has maintained a lower COVID-19 incidence by enhancing rigorous contact tracing and extensive testing with no discrimination, which may have minimized some forms of socioeconomic disparity across areas. Inconsistent inequalities may be also explained by different conceptualizations of the five area-level SES measures. Basic livelihood security recipients are mostly older adults, and the age composition of this measure better reflects diagnosed COVID-19 cases; the majority (35.1% in the low phase and 31.6% in the rebound phase) were older adults ($\geq$60 years of age), according to the Korea Central Disease Control Headquarters (http://ncov.mohw.go.kr/en/). This finding is in agreement with an individual-based Korean study in which higher SES was associated with higher COVID-19 incidence in the older population, and both higher and lower SES were associated with the younger population (37). Similarly, the area-level nonemployment rate largely depends on the proportion of individuals who are not in the labor force. However, the national health insurance premium and financial autonomy address directly the income level of the working population. The deprivation index is a composite measure developed using six variables of material circumstances. Deriving the material deprivation index by assigning the same weight to each individual variable may mask socioeconomic patterns existing in the COVID epidemic (18).

In this study, a high level of mobility was associated with an increased risk of COVID-19 incidence, consistent with recent studies from the United States. However, this study results are in contrast to previous studies in terms of which areas are more mobile. In most previous studies, socioeconomically disadvantaged areas were reportedly more likely to have higher mobility (9, 10); however, this study results showed that a high level of mobility was characteristic of affluent areas in Korea. This finding is understandable because mobility using public transport is concentrated in densely populated areas in the capital and large cities in Korea and within-city mobility is distributed across places of social gatherings and business meetings.

High mobility observed in affluent areas may offer another plausible explanation as to why socioeconomic inequalities differ based on the measure. Collectively, area-level socioeconomic disadvantages concerning COVID-19 incidence were mixed with lower economic activity in poor communities. Notably, when simultaneously adjusted for mobility, SES measures of basic livelihood security recipients and the nonemployment rate remained significant in the low phase but not in the rebound phase. This result indicates that mobility is a major contributing factor to the association between area-level SES and COVID-19 incidence in the rebound phase, but mobility alone does not fully explain the association; other vulnerabilities (e.g., a larger poor older population) are likely to be involved.

The area-level socioeconomic effect was stronger in the low phase, when the prevalence of COVID-19 was low, with less strict governmental measures, indicating that the area-level socioeconomic gradient is less likely to affect the variation in COVID-19 occurrence. Hypothetically, the socioeconomic inequalities in COVID-19 incidence were not exacerbated in the rebound phase. A larger inequality in the low phase may be attributed to people in poor communities being less responsive to an initial spread of COVID-19 when government public health measures were not sufficiently implemented nationwide. With progression to a widespread stage (rebound phase), the Korean government launched the testing and contact tracing system as a key part of the control strategy. The relatively effective performance of the strong government measures, with public compliance, applied in a nondiscriminatory manner, irrespective of SES, led to subsequent improvement in regional variations in incidence.

The strength of this study includes the use of nationwide incidence data and various socioeconomic measures. In

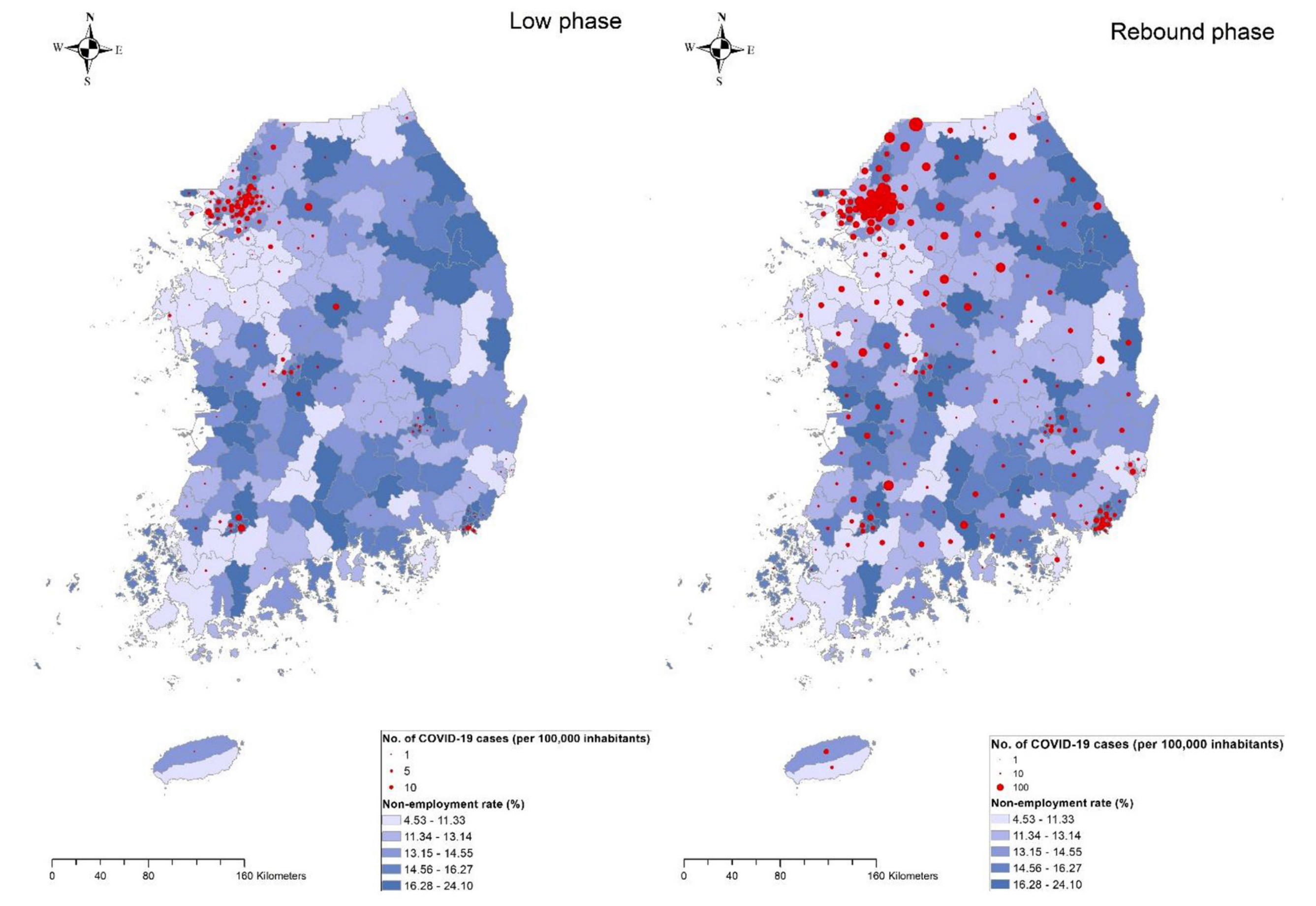

FIGURE 4 | Geographical distribution of nonemployment rate coupled with COVID-19 incidence rate by 229 municipalities during the low phase of the epidemic (**left**) or the rebound phase (**right**). The size of the circle is proportional to the cumulative number of reported COVID-19 cases per 100,000 inhabitants during the corresponding period. Blue gradient represents the magnitude of the nonemployment rate.

particular, concurrent use of SES measures with mobility measures enabled us to obtain a better-fitted model and identify any existing associations. This study had several limitations. First, the mobility measure was obtained from the previous year and does not reflect the mobility changes induced by the COVID-19 pandemic. However, to some degree, the use of previous mobility data may serve as a proxy indicator in this interpretation because mobility change depending on SES appears minimal in Korea. The only study in which the average mobility patterns were compared during the COVID-19 period in Korea showed no significant change in mobility shaped by socioeconomic differences (38). Second, the findings in this study are limited to area-level interpretation, due to the inherent nature of ecological studies, which could not be directly applied at an individual level. Third, the variables associated with living conditions, such as poor hygiene conditions and overcrowding, could not be included due to data availability, although this would be relevant information regarding the association between SES and COVID-19 incidence. Furthermore, it is noteworthy to investigate the impact of inequalities on the incidence of COVID-19 in countries with a relatively lower number of cases and during the post-vaccination period to understand the direct effect of SES disparity on the infection adjusted for vaccination coverage.

In conclusion, COVID-19 does not occur randomly but follows socioeconomic patterns; socioeconomic inequalities in COVID-19 incidence occur concerning the unique context of a society in response to the pandemic. Despite similar contexts, each SES measure represents a specific factor and has a different ability to identify socioeconomic stratification caused by COVID-19. In Korea, where government control measures were effectively applied, with high compliance and with relatively low incidence, SES measures, such as basic livelihood security recipients, reflecting age stratification, may be preferable. Mobility was associated with COVID-19 incidence and partly explains the correlation between area-level SES and COVID-19 incidence during a high incidence period in countries such as Korea, where mobility is characteristic of affluent areas. The results confirm the necessity for emergency policy priorities concerning the older population in disadvantaged areas, including faster vaccination, and underscore a further need for socioeconomic support, including emergency relief funds.

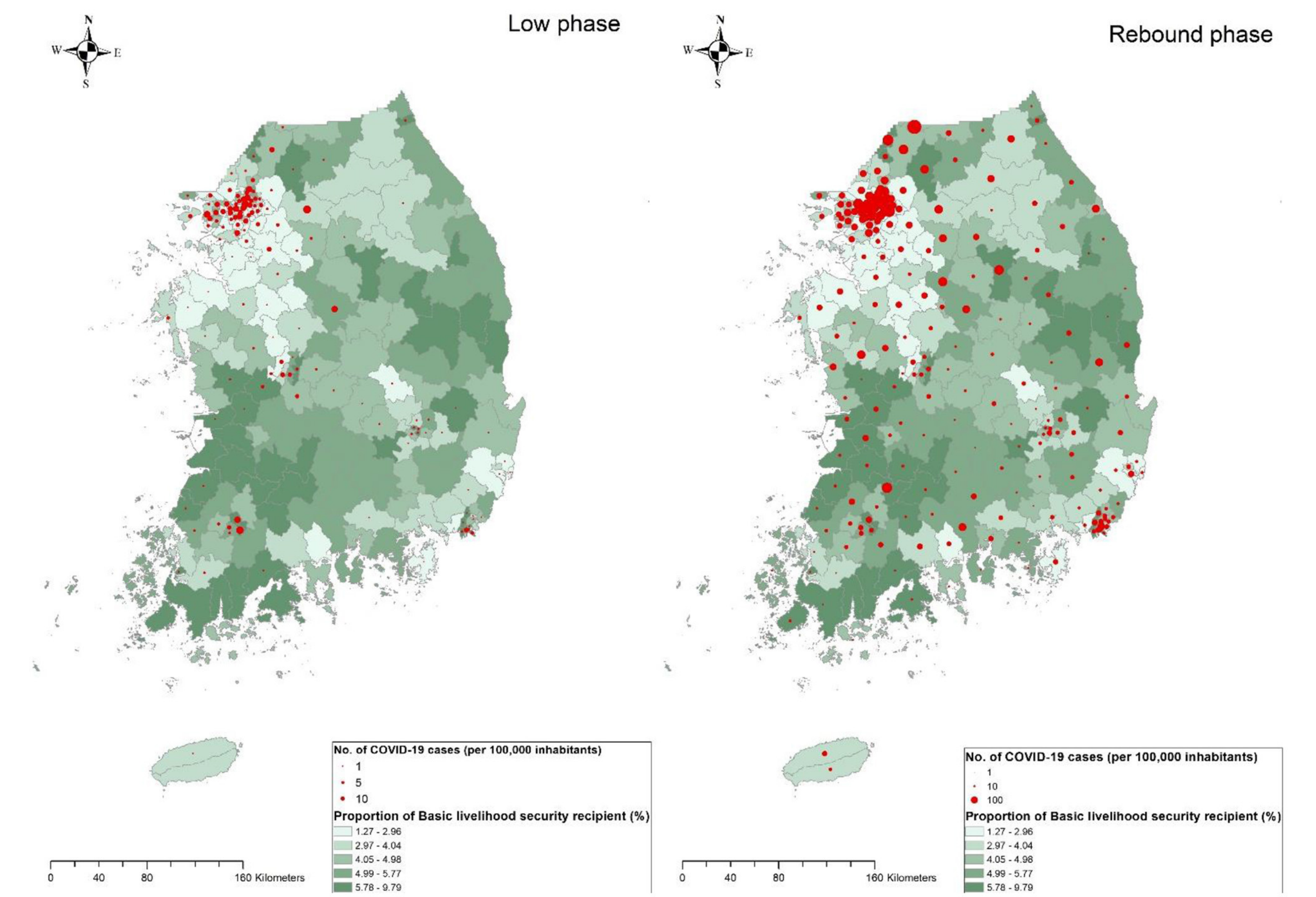

FIGURE 5 | Geographical distribution of the proportion of basic livelihood security recipients with COVID-19 incidence rate by 229 municipalities during the low phase of the epidemic (**left**) or the rebound phase (**right**) The size of the circle is proportional to the cumulative number of reported COVID-19 cases per 100,000 inhabitants during the corresponding period. Green gradient represents the magnitude of the nonemployment rate.

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

D-sY conceived and designed the study. D-sY and MK acquired the data and wrote the original draft. MS and N-KS supported data collection. MH contributed data standardization. D-sY performed analyses. BC, MH, MS, N-KS, and SK edited the subsequent drafts. All authors read and approved the final manuscript.

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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.2022.840685/full#supplementary-material

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Factors Related to Non-compliance With Non-pharmaceutical Interventions to Mitigate the Spread of SARS-CoV-2: Results From a Survey in the Swiss General Adult Population

Michael P. Hengartner, Gregor Waller and Agnes von Wyl*

School of Applied Psychology, Zurich University of Applied Sciences, Zurich, Switzerland

Background: Non-pharmaceutical interventions (NPI) play an important role in national efforts to control and contain the spread of SARS-CoV-2, but some people do not comply with these public health measures. The aim of this study was thus to describe this group of noncompliant people.

Methods: A random sample of 1,157 people was drawn from the adult general population of Switzerland based on a three-stepped quota scheme considering the variables age (18–31, 32–45, 46–59, and ≥60 years), sex (male and female), and language region (German-, French-, and Italian-speaking Switzerland). We assessed a global scale of non-compliance with NPI based on several individual measures such as wearing face masks and social distancing. As predictor variables we included objective sociodemographic variables (e.g., age, sex) and easy measurable constructs (e.g., fears and worries about COVID-19, trust in medical experts).

Results: Out of 14 predictor variables tested, seven were statistically significantly associated with increased non-compliance with NPI: male sex, younger age, self-identification as low-risk group, judging the consequences of an infection with SARS-CoV-2 as non-serious, less worries and fears about the pandemic, not obtaining regular information from health authorities, and not trusting in medical experts. The most parsimonious multivariable prediction model included the variables younger age, low appraisal of negative consequences, less fear and worries, not obtaining regular information from health authorities, and not trusting in medical experts. The model accounted for 27.9% of variance explained in non-compliance with NPI.

Conclusion: Young adults who perceive COVID-19 as mostly harmless/inconsequential and who ignore and/or mistrust information from health authorities and medical experts, are the population most likely to be noncompliant with NPI. These findings may help to target a group of people at high risk of infection and to efficiently concentrate educational and interventional public health measures.

Keywords: SARS-CoV-2, COVID-19, non-pharmaceutical interventions, compliance, public health measure

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Roger Nlandu Ngatu,
Kagawa University, Japan

Reviewed by:
Daniela Thais Zapata Sifuentes,
Universidad Ricardo Palma, Peru
Amir Mohsenpour,
Bielefeld University, Germany

****Correspondence:***
Michael P. Hengartner
heng@zhaw.ch

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INTRODUCTION

Non-pharmaceutical interventions (NPI) such as social distancing, wearing face masks, canceling of public events, and restrictions on private gatherings have been shown to be effective and play an important role in national efforts to mitigating the spread of SARS-CoV-2 infections (1–4). Although safe and effective vaccines are available (5–7), in various countries vaccination rates are rather low, especially in younger adults (https://graphics.reuters.com/world-coronavirus-tracker-and-maps/vaccination-rollout-and-access/). It has further been shown that vaccines are less effective in preventing infections with the predominant Delta variant and that protection against asymptomatic infections wanes quite rapidly after a few months, even though the vaccines still effectively prevent hospitalizations for severe COVID-19 (6, 8, 9). NPI thus complement national vaccination strategies, but not all people comply with them.

Previous research has consistently shown that younger age, male sex, low educational attainment, lack of trust in medical experts and science, and a underestimation of the harms/seriousness of COVID-19 are significantly associated with non-compliance with NPI (10–13). Nivette et al. previously examined non-compliance with NPI in a Swiss sample, but this study was restricted to people aged 22 years living in the city of Zurich (14). To the best of our knowledge, a comprehensive analysis of non-compliance with NPI in the Swiss general adult population has not been published thus far.

A reliable description of factors associated with non-compliance with NPI in the general Swiss adult population may help the Swiss government and public health authorities to effectively target prevention and awareness campaigns. The aim of the present study was thus to examine which individual factors are associated with non-compliance to NPI in the general adult population in Switzerland to better define this group at high risk of infection.

METHODS

Sample Recruitment

A survey was conducted in collaboration with the market research institute Respondi. The Swiss online panel of Respondi comprises about 20,000 people broadly representative of the Swiss general population. Only people aged 18 and older were contacted to participate in the present survey. In total 2,515 people responded to the invitation by Respondi to participate. Sample recruitment was based on a three-stepped quota scheme considering the variables age (18–31, 32–45, 46–59, and ≥60 years), sex (male and female), and language region (German-, French-, and Italian-speaking Switzerland). Altogether 1,006 people were excluded because the quota size was already reached, and 352 people were excluded because they did not complete the questionnaire. Therefore, the final sample comprised 1,157 people representative of the Swiss adult population according to the distribution of age, sex, and region. All surveys were completed between December 11, 2020 and January 5, 2021. Formal approval by a national Ethics Committee was not required according to Swiss law as no health-related data were assessed.

Measures

The survey assessed several constructs from the fields of media psychology, health psychology, personality psychology, and ecological psychology. The dependent variable was a global scale of non-compliance with NPI. This included the following public health measures: (1) If possible, I keep the necessary social distance to other people (1.5 m) in public; (2) When meeting friends or relatives, I keep the necessary social distance (1.5 m); (3) I wash my hands regularly; (4) If possible, I avoid public transportation; (5) If I have (cold) symptoms, I stay at home; (6) If I have (cold) symptoms, I make a SARS-CoV-2 test; (7) If possible, I avoid congregations of people; (8) If possible, I refrain from travels abroad; (9) I wear a mask in public when social distancing is not possible; (10) When I mix with people, I activate the Swiss COVID-19 tracing app; (11) I try to reduce private gatherings to a minimum. All items were rated on a five-point Likert scale ranging from 1 ("not at all true") to 5 ("definitely true"). The global measure of non-compliance was built by computing the inverse mean score across all individual measures. Thus, the scale had a possible range from 1 (complete compliance with NPI) to 5 (complete non-compliance with NPI). The internal consistency of this scale was good (Cronbach's $\alpha = 0.82$), but item 10 (activating the Swiss COVID-19 tracing app) was poorly correlated with the total scale score (corrected item-scale correlation: $r = 0.28$). Moreover, compliance with this measure was also very poor (50% indicated they would rather or definitely not activate the tracing app). After removing this item, the internal consistency of the scale was slightly improved (Cronbach's $\alpha = 0.84$) and all items were moderately to highly correlated with the total scale score (range of corrected item-scale correlation: $r = 0.38$ to $r = 0.68$). For a list of all public health measures included (see **Table 1**).

As predictor variables we included only variables that can be assessed objectively (e.g., age, sex, educational attainment) or that are easily measurable with a few simple questions (e.g., fear and worries about COVID-19 pandemic, obtaining information from health authorities, trust in medical experts). The following variables were selected according to these criteria: (1) sex (male vs. female); (2) age (continuous measure in years); (3) nationality (Swiss vs. other); (4) educational attainment (low, medium, high corresponding broadly to high school, college, and higher education); (5) self-perceived high-risk group (yes vs. no based on age and chronic health conditions); (6) I personally know someone who had COVID-19 (yes vs. no); (7) I personally know someone who died of COVID-19; (8) I personally had COVID-19 (yes vs. no); (9) personal existence threatened by COVID-19 pandemic (yes vs. no based on perceived threats to occupational and financial situation); (10) appraisal of negative consequences of SARS-CoV-2 infection [based on the mean score across two items enquiring about the negative consequences of an infection with SARS-CoV-2 with and without regularly wearing a face mask; both rated on a six-point Likert scale ranging from 1 ("very mild") to 6 ("very serious")]; (11) fears and worries about the COVID-19 pandemic [mean score across the

TABLE 1 | Non-compliance with non-pharmaceutical interventions to mitigate the spread of SARS-CoV-2 ($n = 1157$).

Indicator	Response category	*N* (%)
If possible, I keep the necessary social distance to other people (1.5 m) in public	Definitely not true	19 (1.6%)
	Rather not true	33 (2.9%)
	Undecidedly true	41 (3.5%)
	Rather true	306 (26.4%)
	Definitely true	756 (65.3%)
	Missing	2 (0.2%)
When meeting friends or relatives, I keep the necessary social distance (1.5 m)	Definitely not true	67 (5.8%)
	Rather not true	145 (12.5%)
	Undecidedly true	125 (10.8%)
	Rather true	371 (32.1%)
	Definitely true	448 (38.7%)
	Missing	1 (0.1%)
I wash my hands regularly	Definitely not true	8 (0.7%)
	Rather not true	36 (3.1%)
	Undecidedly true	51 (4.4%)
	Rather true	273 (23.6%)
	Definitely true	784 (67.8%)
	Missing	5 (0.4%)
If possible, I avoid public transportation	Definitely not true	128 (11.1%)
	Rather not true	135 (11.7%)
	Undecidedly true	81 (7.0%)
	Rather true	248 (21.4%)
	Definitely true	559 (48.3%)
	Missing	6 (0.5%)
If I have (cold) symptoms, I stay at home	Definitely not true	31 (2.7%)
	Rather not true	88 (7.6%)
	Undecidedly true	106 (9.2%)
	Rather true	335 (29.0%)
	Definitely true	590 (51.0%)
	Missing	7 (0.6%)
If I have (cold) symptoms, a make a SARS-CoV-2 test	Definitely not true	200 (17.3%)
	Rather not true	146 (12.7%)
	Undecidedly true	236 (20.4%)
	Rather true	239 (20.7%)
	Definitely true	332 (28.7%)
	Missing	3 (0.3%)
If possible, I avoid congregations of people	Definitely not true	29 (2.5%)
	Rather not true	38 (3.3%)
	Undecidedly true	67 (5.8%)
	Rather true	264 (22.8%)
	Definitely true	755 (65.3%)
	Missing	4 (0.3%)
If possible, I refrain from travels abroad	Definitely not true	42 (3.6%)
	Rather not true	36 (3.1%)
	Undecidedly true	81 (7.0%)
	Rather true	173 (15.0%)
	Definitely true	822 (71.0%)
	Missing	3 (0.3%)
I wear a mask in public when social distancing is not possible	Definitely not true	34 (2.9%)
	Rather not true	41 (3.5%)
	Undecidedly true	37 (3.2%)
	Rather true	177 (15.3%)
	Definitely true	867 (74.9%)
	Missing	1 (0.1%)
I try to reduce private gatherings to a minimum	Definitely not true	56 (4.8%)
	Rather not true	100 (8.6%)
	Undecidedly true	102 (8.8%)
	Rather true	364 (31.5%)
	Definitely true	531 (45.9%)
	Missing	4 (0.3%)

items "I worry about the coronavirus and the current situation"; "I feel uncomfortable thinking about the coronavirus"; "I fear that I could get severe COVID-19"; "I fear that someone close to me could get severe COVID-19"; "The news and stories I hear about the coronavirus in the media make me nervous or anxious"; all rated on a five-point Likert scale ranging from 1 ("definitely not true") to 5 ("definitely true")]; (12) I obtain regular information from health authorities, e.g., Swiss federal office of public health, cantonal health department, WHO (yes vs. no, if information obtained daily or several times per week); (13) I obtain regular information from social media channels, e.g., Facebook, Instagram, Twitter (yes vs. no, if information obtained daily or several times per week); and (14) I trust in medical experts [yes vs. no, if score on a seven-point Likert scale ranging from 1 ("no trust at all") to 7 ("very high trust") was at least 5]. A brief description of all predictor variables is given in **Table 2**.

Statistical Analysis

To further verify that the individual NPI measures form a unidimensional scale we conducted two principal factor analyses, one with Varimax rotation and another with Promax rotation. We also conducted a series of two-step cluster analyses to examine whether there are distinct groups of people according to non-compliance with specific NPI measures (rather than uniform compliance across individual NPI measures). To do so we conducted a series of models with two to six fixed clusters.

We used generalized linear models with maximum likelihood estimation where non-compliance with NPI was entered as the outcome variable, applying an inverse-Gauss (Wald) distribution and an identity link-function. In a first step we tested all predictor variables separately (univariable model; crude effects) and then, in a second step, entered all variables simultaneously (multivariable model; fully adjusted effects). In a third step, we build a model that included only predictors that were statistically significant in the fully adjusted multivariable model. We did

TABLE 2 | Predictor variables associated with non-compliance with non-pharmaceutical interventions to mitigate the spread of SARS-CoV-2 (n = 1,157).

Predictor	%/mean (SD)	Crude effect B (95%-CI)	Fully adjusted effect[#] B (95%-CI)
Sex	Male (50.4%)	0.09 (0.01 to 0.17)*	0.06 (−0.00 to 0.12)
	Female (49.6%)	Reference	Reference
Age (18–90 years)	Mean = 46.3 (SD = 0.70)	−0.01 (−0.01 to −0.01)***	−0.01 (−0.01 to −0.00)***
Swiss nationality	Yes (85.0%)	−0.04 (−0.15 to 0.08)	0.01 (−0.07 to 0.10)
	No (15.0%)	Reference	Reference
Educational attainment	High (32.0%)	0.08 (−0.01 to 0.18)	0.03 (−0.04 to 0.10)
	Medium (29.0%)	0.02 (−0.08 to 0.12)	−0.02 (−0.09 to 0.05)
	Low (39.1%)	Reference	Reference
Self-perceived high-risk group	Yes (30.3%)	−0.26 (−0.34 to −0.18)***	0.03 (−0.05 to 0.11)
	No (69.7%)	Reference	Reference
Personally knows someone who had COVID-19	Yes (50.2%)	−0.04 (−0.12 to 0.04)	−0.04 (−0.10 to 0.03)
	No (49.8%)	Reference	Reference
Personally knows someone who died of COVID-19	Yes (10.2%)	−0.09 (−0.22 to 0.04)	0.03 (−0.06 to 0.12)
	No (89.8%)	Reference	Reference
Personally had COVID-19	Yes (7.4%)	0.15 (−0.01 to 0.32)	0.04 (−0.08 to 0.16)
	No (92.6%)	Reference	Reference
Personal existence threatened by COVID-19 pandemic	Yes (27.8%)	0.05 (−0.04 to 0.14)	0.06 (−0.01 to 0.13)
	No (72.2%)	Reference	Reference
Appraisal of negative consequences of SARS-CoV-2 infection (severity: 1–6)	Mean = 3.51 (SD = 1.28)	−0.17 (−0.20 to −0.15)***	−0.07 (−0.10 to −0.04)***
Fears and worries about COVID-19 pandemic (severity: 1–5)	Mean = 3.14 (SD = 0.95)	−0.27 (−0.31 to −0.24)***	−0.18 (−0.23 to −0.14)***
Obtains regular information from health authorities	Yes (35.9%)	−0.30 (−0.37 to −0.22)***	−0.14 (−0.20 to −0.08)***
	No (64.1%)	Reference	Reference
Obtains regular information from social media channels	Yes (34.0%)	−0.05 (−0.13 to 0.03)	0.02 (−0.05 to 0.08)
	No (66.0%)	Reference	Reference
Trusts in medical experts	Yes (69.2%)	−0.36 (−0.45 to −0.26)***	−0.21 (−0.28 to −0.13)***
	No (30.8%)	Reference	Reference

[#] *Includes all predictor variables simultaneously.*
$*p < 0.05$.
$**p < 0.01$.
$***p < 0.001$.

not explore interaction terms due to their many inherent issues arising from power failure, measurement error, multiple testing, and overfitting, ultimately resulting in severely inflated type I errors (15, 16). Non-linear effects (e.g., quadratic, cubic) were tested by categorizing continuous variables through quartile split. The proportion of variance explained was determined with McFadden's pseudo-R^2. The level of statistical significance was set at $\alpha = 0.05$. We additionally present results based on a Bonferroni correction for multiple testing, where the level of statistical significance was $\alpha = 0.004$.

All statistical analyses were conducted with SPSS version 28 for Windows.

RESULTS

The sample (n = 1,157) consisted of 49.6% women and 50.4% men. The majority (85.0%) was of Swiss nationality, and the mean age was 46.3 years (range: 18–90 years, SD = 16.5 years). More information is provided in **Table 2**. Non-compliance with individual NPI is shown in **Table 1**. The highest non-compliance was found with respect to avoiding public transportation (22.7% were rather or definitely noncompliant) and making a SARS-CoV-2 test when having (cold) symptoms (29.9% were rather or definitely noncompliant). Scores on the global measure of non-compliance with NPI ranged from 1 (complete compliance) to 5 (complete non-compliance), with a median score of 1.6 and a modal score of 1. The lower quartile score was 1.3 and the upper quartile score was 2.1. This indicates that about 75% of Swiss people reported good or very good compliance with NPI, but a small minority of about 5% was remarkably noncompliant. A graphical depiction is provided in **Figure 1**.

Both principal factor analyses and two-step cluster analyses confirmed that the global scale of non-compliance with NPI is unidimensional. The principal factor analyses yielded one latent factor with an eigenvalue >1 onto which all individual NPI measures loaded. The different cluster solutions of the two-step cluster analyses likewise showed that increasing the number of clusters merely captured the uniform degree of non-compliance across all individual NPI measures (e.g., uniformly

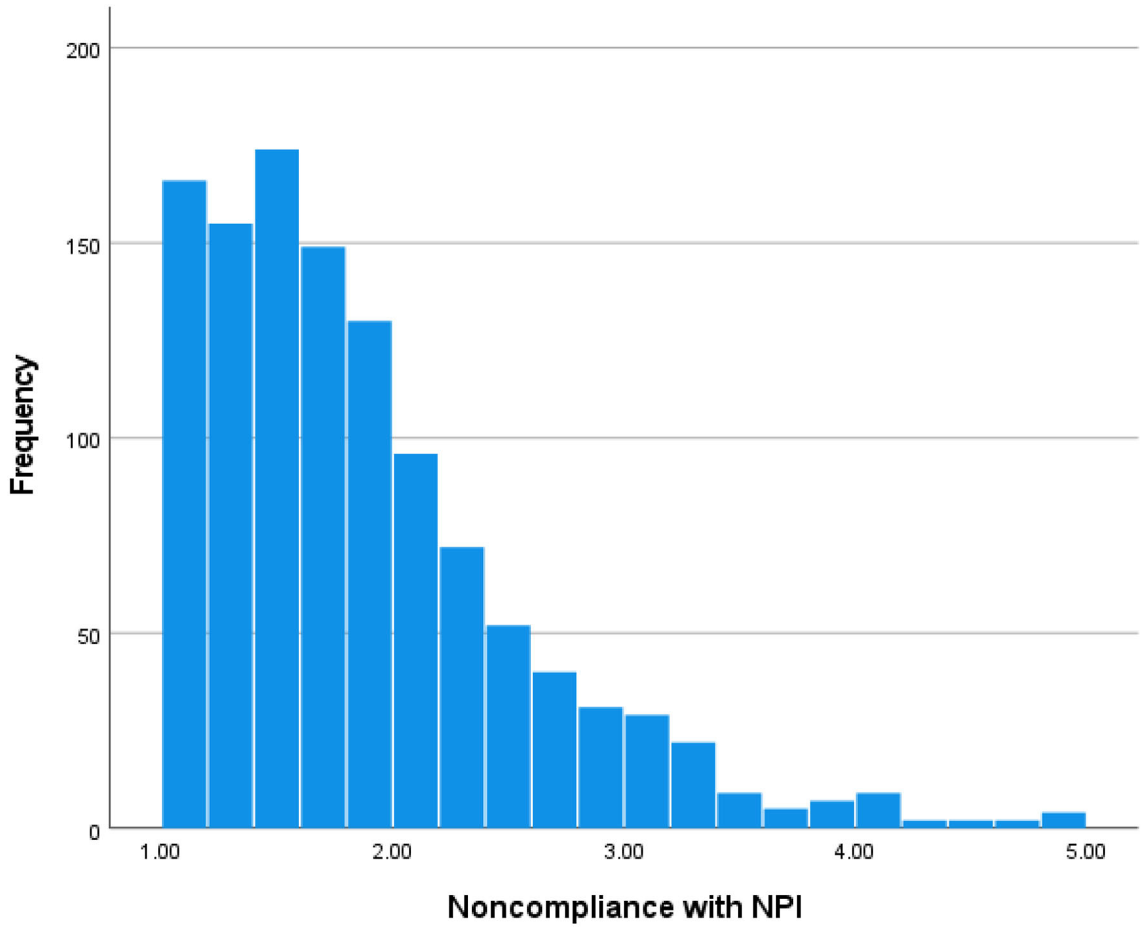

FIGURE 1 | Scores on the global scale of non-compliance with non-pharmaceutical intervention (NPI). Scale ranges from 1 (complete compliance) to 5 (complete non-compliance); scores smaller than 3 indicate a tendency to compliance and scores >3 indicate a tendency to non-compliance.

low, moderate, or high non-compliance). This indicates that people differ based on their uniform level of compliance across all NPI measures. That is, people who are rather noncompliant with a specific public health measure compared to the average person also tend to be relatively noncompliant with any other public health measure.

Out of 14 predictor variables tested, seven were statistically significantly associated with increased non-compliance with NPI (see **Table 2**). Men were slightly more noncompliant than women. A relatively strong effect was found for age: non-compliance declined with age, indicating that the youngest adults were the most noncompliant. People who self-identified as high-risk group were less noncompliant. People who judged to consequences of an infection with SARS-CoV-2 to be serious and people who were anxious about the pandemic reported considerably lower non-compliance with NPI. Finally, people who obtained regular information from health authorities and people who trusted in medical experts also reported lower non-compliance. Except for sex, all predictor variables remained statistically significant after controlling for multiple testing.

The multivariable model based on all 14 predictor variables accounted for 27.9% of variance explained in non-compliance with NPI. Five predictor variables remained statistically significant at $p < 0.05$, that is, younger age, low appraisal of negative consequences, less fear and worries, not obtaining regular information from health authorities, and not trusting in medical experts. These variables were also significantly related to non-compliance with NPI after correcting for multiple testing ($p < 0.004$). Notably, belonging to a self-perceived high-risk group completely lost its association with non-compliance with NPI after controlling for age and the other predictor variables. We did not detect quadratic or cubic effects. All continuous predictor variables showed linear associations with non-compliance with NPI.

We then build a model that included only the five significant predictor variables from the fully adjusted multivariable model reported above. All predictor variables remained statistically strongly associated with non-compliance with NPI: younger age ($p < 0.001$), low appraisal of negative consequences ($p < 0.001$), less fear and worries ($p < 0.001$), not obtaining regular information from health authorities ($p < 0.001$), and

TABLE 3 | Final multivariable prediction model of non-compliance with non-pharmaceutical interventions to mitigate the spread of SARS-CoV-2 (n = 1,157).

Predictor	B (95%-CI)	*P*
Age (18–90 years)	−0.006 (−0.008 to −0.005)	<0.001
Appraisal of negative consequences of SARS-CoV-2 infection (severity: 1–6)	−0.070 (−0.098 to −0.041)	<0.001
Fears and worries about COVID-19 pandemic (severity: 1–5)	−0.184 (−0.225 to −0.142)	<0.001
Obtains regular information from health authorities (yes vs. no)	−0.135 (−0.197 to −0.073)	<0.001
Trusts in medical experts (yes vs. no)	−0.203 (−0.279 to −0.127)	<0.001

McFadden pseudo-R^2: 0.272.

not trusting in medical experts ($p < 0.001$). The regression coefficients with their 95% confidence intervals are shown in **Table 3**. This more parsimonious five-variable model accounted for 27.2% of variance explained in non-compliance with NPI and the regression coefficients were virtually identical compared to the less parsimonious 14-variable model.

DISCUSSION

Our survey in a representative sample of the Swiss adult general population showed that, after multivariable adjustment, younger age, low appraisal of negative consequences of SARS-CoV-2 infection, low fears and worries about the pandemic, not obtaining regular information from health authorities, and low trust in medical experts, independently predicted non-compliance with NPI to mitigate the spread of SARS-CoV-2. These factors largely replicate the findings from previous studies (10–13). However, in contrast to previous studies, we did not find that men and people with lower educational attainment were more noncompliant than women and people with higher educational attainment (e.g., ref. 10). This could be due to cultural characteristics of the Swiss general adult population, differences in the educational and occupational system, or uncontrolled confounders in previous studies (e.g., fears and worries about COVID-19).

Assuming the detected effects are additive, it follows that young adults who perceive COVID-19 as mostly harmless/inconsequential and who ignore and/or mistrust information from health authorities and medical experts, are the population most likely to be noncompliant with NPI. Given that the vaccines currently available in Switzerland only partially protect against infection with the predominant Delta variant, and that vaccine-induced immunity seems to wane over time (6, 8, 9), these findings have important implications for national efforts to contain SARS-CoV-2 infections and to mitigate the ensuing public health consequences (e.g., overcrowding of intensive care units).

Research has shown that this population of seemingly mistrustful and unconcerned young adults is also hesitant to get a COVID-19 vaccine (17, 18). This group therefore constitutes a high-risk population that is opposed to both vaccines and NPI. Governments and health authorities are advised to concentrate their public campaigns, including both education and intervention programs, on this group. Failure to reach these people may compromise the control (and containment) of the COVID-19 pandemic.

The strength of our study is its large and broadly representative sample and a comprehensive range of objective and/or easily measurable characteristics. However, three limitations need to be taken into account. First and foremost, compliance with NPI fully relied on self-report. Due to social desirability, it is possible that the indicated compliance with NPI deviates from the actual behavior in some people. Second, the survey took place before vaccines were available in Switzerland. Therefore, controlling for current vaccine status may influence the factors associated with non-compliance to NPI. The factors associated with vaccine hesitancy/refusal and non-compliance to NPI are largely similar, but we cannot firmly exclude that controlling for current vaccine status would alter our prediction model. Only a future study with full assessment of vaccination status will be able to answer this crucial question. Third, only adults were included in this study, thus we cannot generalize our findings to children and adolescents. In future studies it would be worthwhile to also assess non-compliance with NPI in minors.

In conclusion, the results of the current study indicate that young adults who are not troubled or anxious about COVID-19, and people who do not obtain information from health authorities and who mistrust medical experts, are the most noncompliant with NPI. These findings may help to target a group of people at high risk of infection and to efficiently concentrate educational and interventional public health efforts to contain the spread of SARS-CoV-2. Future studies that also consider the current vaccination status should preferably assess the reasons for non-compliance with NPI, so that health authorities not only have information in which groups they should intervene, but also how.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MH designed the study, conducted all statistical analyses, and wrote the first manuscript draft. GW and AvW participated in development of the survey questionnaire, data interpretation, and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Epidemiological Dynamics of SARS-CoV-2 Variants During Social Protests in Cali, Colombia

*Luz H. Patiño[1], Sergio Castañeda[1], Marina Muñoz[1,2], Nathalia Ballesteros[1], Angie L. Ramirez[1], Nicolas Luna[1], Enzo Guerrero-Araya[2,3], Julie Pérez[4], Camilo A. Correa-Cárdenas[4], Maria Clara Duque[4], Claudia Méndez[4], Carolina Oliveros[4], Maryia V. Shaban[5], Alberto E. Paniz-Mondolfi[6] and Juan David Ramírez[1,6]**

[1] Centro de Investigaciones en Microbiología y Biotecnología-UR (CIMBIUR), Facultad de Ciencias Naturales, Universidad del Rosario, Bogotá, Colombia, [2] Agencia Nacional de Investigación y Desarrollo (ANID)—Millennium Science Initiative Program—Millennium Nucleus in the Biology of the Intestinal Microbiota, Santiago, Chile, [3] Microbiota-Host Interactions and Clostridia Research Group, Facultad de Ciencias de la Vida, Universidad Andrés Bello, Santiago, Chile, [4] Grupo de Investigación en Enfermedades Tropicales del Ejército (GINETEJ), Laboratorio de Referencia e Investigación, Dirección de Sanidad Ejército, Bogotá, Colombia, [5] Incubadora Venezolana de la Ciencia (IVC), Centro de Investigaciones Biomédicas IDB, Barquisimeto, Venezuela, [6] Molecular Microbiology Laboratory, Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Edited by:
Benjamin Longo-Mbenza, Walter Sisulu University, South Africa

Reviewed by:
Keun Hwa Lee, Hanyang University, South Korea
Lina Martinez, ICESI University, Colombia
Diana Carolina Lopez, National University of Colombia, Colombia

***Correspondence:**
Juan David Ramírez
juand.ramirez@urosario.edu.co; juan.ramirezgonzalez@mountsinai.org

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Background: The third wave of the global health crisis attributed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus reached Colombia in March 2021. Over the following 6 months, it was interpolated by manifestations of popular disapproval to the actual political regime—with multiple protests sprouting throughout the country. Large social gatherings seeded novel coronavirus disease 2019 (COVID-19) variants in big cities and propagated their facile spread, leading to increased rates of hospitalizations and deaths.

Methods: In this article, we evaluate the effective reproduction number (Rt) dynamics of SARS-CoV-2 in Cali, Colombia, between 4 April 2021 and 31 July 2021 based on the analysis of 228 genomes.

Results: Our results showed clear contrast in Rt values between the period of frequent protests (Rt > 1), and the preceding and following months (Rt < 1). Genomic analyses revealed 16 circulating SARS-CoV-2 lineages during the initial period—including variants of concern (VOCs) (Alpha, Gamma, and Delta) and variants of interest (VOIs) (Lambda and Mu). Furthermore, we noticed the Mu variant dominating the COVID-19 distribution schema as the months progressed. We identified four principal clusters through phylogenomic analyses—each one of potentially independent introduction to the city. Two of these were associated with the Mu variant, one associated with the Gamma variant, and one with the Lambda variant.

Conclusion: Our results chronicle the impact of large group assemblies on the epidemiology of COVID-19 during this intersection of political turmoil and sanitary crisis in Cali, Colombia. We emphasize upon the effects of limited biosecurity strategies (which had characterized this time period), on the spread of highly virulent strains throughout Cali and greater Colombia.

Keywords: SARS-CoV-2, COVID-19, effective reproduction number, lineages, Cali

INTRODUCTION

In December 2019, the identification of an amply transmissible and highly virulent member of the *Coronaviridae* family (coronavirus disease 2019, COVID-19) in Wuhan, China informed the world of a novel pathogen which would seed an ensuing pandemic (1). As of 10 December 2021, laboratory diagnoses have confirmed 269,021,697 cases and more than 5 million deaths proceeding from COVID-19 universally.[1] This statistic is dominated by the American continent, with Colombia being one of the countries most impacted by the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): 5,089,695 confirmed cases and 129,011 deaths.[2]

Colombia has faced three separate "waves" throughout the COVID-19 epidemic (May–September 2020; December 2020–February 2021; and March–August 2021). These delineations are correlated with the restraining and relaxing of social distancing measures implemented by the government in efforts to maintain balance between the health care burden and the precarious economic situation experienced by public and private enterprises (2). In the midst of the third wave (March–August 2021), a series of demonstrations took place throughout the country. Between 28 April 2021 and 31 July 2021, Colombians actively protested a new taxation proposal, inadequate federal management of the pandemic and ensuing poverty and unemployment seen throughout the country. At the moment of these protests, vaccination levels remained still low (with only 12,179,103 people, or 23.9% of the population having received both doses) and the clear infringement upon advisable social distancing protocol set off alarm in the public health sphere, as more people took to the streets disrespecting standards of biosecurity.[3]

The three largest cities in Colombia: Bogotá, Medellín, and Cali, then witnessed increase in the weekly averages of cases and deaths by SARS-CoV-2, as well as a concerning presence of novel viral lineages: Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), and Mu (B.1.621) (see text footnote 2) (3).

Around the world, neither the onset of the pandemic, nor stringent lockdown protocols ever truly arrested the demonstration of public disagreement with modern social structures. From marches for the *Black Lives Matter* movement, to public activism in support of labor laws, economic equality, and environmental concerns, the past years have witnessed ample protests in the United States, Southeast Asia, and Latin America. Yet, the true epidemiological impact of gathering in support of social justice has seldom been analyzed (4, 5). In the unique Colombian example, a recent study (pre-print) tracked the effects on transmission rates of COVID-19 in five highly populated cities. It showed that of these, Cali and Bucaramanga experienced the closest correlations between increase in disease spread and rising social fervor (6).

Cali is the capital of the Valle del Cauca (VAC) department of Colombia. It is considered one of the country's largest cities with approximately 2,227,642 inhabitants. Cali is also the city with the highest accumulated number of natural infections and deaths by SARS-CoV-2 in VAC as of 15 November 2021: 285,199 cases and 7,468 deaths, with a fatality rate of 2.62%[4] and a seroprevalence of 30% (CI: 27–33%).[5] Throughout the course of the third pandemic wave in 2021, Cali, along with other Colombian cities witnessed a number of protests and anti-government demonstrations that led to a major state of social unrest. However, Cali, the capital city of Valle del Cauca was home to the largest and most violent and unremitting demonstrations countrywide, thus being considered the epicenter of the protests. In fact, the continued and escalating state of civil arrest in Cali prompted the government to deploy the Armed Forces and block access to the city in an effort to contain protesters.

Taking into consideration this sustained increase in cases and deaths by SARS-CoV-2 during the protest period, as well as our still-precarious understanding of the epidemiological dynamics of the virus and variants of concern/of interest (VOC/VOIs), we planned a study evaluating the epidemiological and genomic behavior of SARS-CoV-2 from 4 April 2021 through 31 July 2021. To this end, we (i) evaluated circulating lineages, their phylogenomic relationships, and any clades circulating within the city and (ii) we deconstructed the mutational profile of each isolate, throughout the entire viral genome. Our results showed an undeniable relationship between these social gatherings and the increased incidence of COVID-19. Further, we identified four clusters (two of them associated with the Mu variant) with potential independent introductions in the city of Cali. Finally, we attempt to explain the decrease in number of circulating lineages (Mu variant dominance), during the time that the protests took place.

[1]https://coronavirus.jhu.edu/map.html

[2]https://www.ins.gov.co/Noticias/Paginas/Coronavirus.aspx

[3]https://www.minsalud.gov.co/salud/publica/Vacunacion/Paginas/Vacunacion-covid-19.aspx

[4]https://www.ins.gov.co/Noticias/Paginas/coronavirus-filtro.aspx

[5]https://www.ins.gov.co/estudio-nacional-de-seroprevalencia/reporte.html#curso

MATERIALS AND METHODS

Epidemiological Data and Study Population

We analyzed case counts of Cali and Medellin from data deposited in the database of the Instituto Nacional de Salud, which can be accessed at: https://www.datos.gov.co/Salud-y-Protecci-n-Social/Casos-positivos-de-COVID-19-en-Colombia/gt2j-8ykr/data (accessed on 20 October 2021), as well as case counts of Bogota deposited in a public data source repository,[6] from 4 April 2021 through 31 July 2021 (although this study focused on Cali, we wanted to include general estimates of similar populated cities for sake of comparison). This time period embraced a time of social unrest against the government dominated by riots, massive mobilizations, protests and walks that led to increased population circulation in the streets of different cities under deficient biosecurity conditions and lack of personal protective equipment. This database is available for public consultation and contains all variables used in our research, such as case notification date and deaths. Notification date corresponds to the date on which each suspect case was identified and reported to the Public Health System, and subsequently confirmed as positive. The metadata of cases, deaths and the estimated Rt value for each day and period evaluated in Cali city are described in the **Supplementary Table 1**.

Likewise, vaccination data was obtained from an open public data source,[7] in which all vaccination events are recorded and its information used to determine the cumulative doses administered during a given period of time. Of note, accumulated doses included at this site, does not discriminate between first and/or second doses.

Effective Reproduction Number Estimation

The effective reproduction number (Rt) was calculated using a Bayesian framework following the Cori et al. method (7) implemented in the Epyestim package[8] with piecewise constant estimates on fixed arbitrary time intervals coinciding with the events (sub-periods previously described) of citizen protests occurring in all three main cities of Colombia where the largest riots occurred (Cali, Bogotá, and Medellin).

Effective reproduction number (Rt) was calculated based on the inference of infection events derived from SARS-CoV-2 positive cases designed as follows: New COVID-19 detected cases were smoothed using a LOWESS filter with a 21-day window and were subjected to two deconvolutions to infer the time series of infection events. The first deconvolution considers the delay from infection with SARS-CoV-2 to symptom presentation following a Gamma distribution with Alpha = 1.35 and scale = 3.77 (8). The second deconvolution considers the delay from symptom onset to detection by a test following a negative binomial distribution with Mu = 5.25 and Alpha = 1.57 (8).

[6]https://datosabiertos.bogota.gov.co/dataset/44eacdb7-a535-45ed-be03-16dbbea6f6da?_external=True

[7]https://datos.cali.gov.co/dataset/registros-de-vacunas-para-covid-aplicadas

[8]https://github.com/lo-hfk/epyestim

Sequencing and Bioinformatics Analysis

Samples for sequence analysis were obtained from patients attending the Dirección de Sanidad del Ejército. Nasopharyngeal swabs were placed in viral transport media LABG&M (Microgen Ltda., Colombia), and nucleic acid extraction was performed using the Quick-RNA Viral kit from ZYMO Research® in a Hamilton Microlab Prep extraction platform, or Biomek i5 Nucleic Acid Extraction platform of Beckman Coulter, as well as b-Aid Virus RNA Extraction kit in a Lab-Aid 824s Nucleic Acid Extraction System of ZEESAN Biotech Co., following manufacturer's recommendations. For the eluted RNA, SARS-CoV-2 detection was carried out by reverse transcription and multiplex amplification by Real-Time PCR (qPCR) using the VIASURE® Kit (CerTest/Biotec) screening for ORF1ab and N gene targets (interpreting as positive those samples with a positive result for either of the two markers), or Allplex™ SARS-CoV-2 Assay of Seegene, in lyophilized format, with a mix of enzymes, primers, probes, buffer, dNTPs, stabilizers and an exogenous internal control by test. A positive test result was considered when both RdRp/ORFB1 and N genes were detected. Limit of detection (LOD) was 20 genome copies per reaction. Samples with a positive result and a Ct value <29 were stored at $-20°C$. Available samples were then grouped by epidemiological week and randomly selected for genomic sequencing. A total of 124 sequences were obtained from 4 April 2021 through 31 July 2021.

Whole genome sequencing of SARS-CoV-2 was performed using Oxford Nanopore's MinION platform, using the MinKNOW application (v1.5.5) according to an established protocol.[9] Bioinformatics analysis was performed as described in the ARTIC bioinformatics pipeline.[10] Once the assemblies were obtained, typing was performed based on the Pangolin COVID-19 Lineage Assigner (Phylogenetic Assignment of Named Global Outbreak LINeages). The mutation search was performed by means of Clade assignment, mutation calling, and sequence quality checks NextClade v 1.5.4.[11] A total of 228 sequences from Cali were herein obtained and analyzed from 4 April 2021 to 31 July 2021 (124 sequences sequenced in this study, and 104 sequences publicly available in the Global Initiative on Sharing All Influenza Data (GISAID) database in the same time period and the same location). For the moment of the data collection there were not genomes reported from Cali for the date 4 April 2021. Further information of the dates and genomes included in the analysis are included in the **Supplementary Table 2**. The abundance of SARS-CoV-2 variants over time was calculated from the complete Cali city genomes database ($n = 228$). The results were represented using the R software (9).

Phylogenomic and Mutational Analysis

A dataset with 5,283 sequences was established with the aim of comparing the phylogenomic relationships of SARS-CoV-2 circulating in Cali (Colombia), and to infer the potential introduction dates for the most recent common ancestor (tMRCA). This data set included: (i) 228 sequences from Cali;

[9]https://artic.network/ncov-2019

[10]https://artic.network/ncov-2019/ncov2019-bioinformatics-sop.html

[11]https://clades.nextstrain.org/

(ii) 3,270 sequences from other areas of Colombia, including 170 from VAC, the greater geographical area which includes Cali (its capital city) (all the genomes available until the last date of our analysis, 31 July 2021); and 1,785 reference genomes representing the diversity of SARS-CoV-2 lineages available in the NextClade tool. All publicly available genomes were downloaded from the GISAID database (10). The new set of genomes was uploaded with the numbers registered in the **Supplementary Table 2**.

The complete dataset was aligned using MAFFT v7.40755 (11) with FFT-NS-2 algorithm and other parameters by default. The 5′- and 3′-untranslated regions were manually trimmed in Uniprot UGENE software v39.0[12] considering the ORFs described for the reference strain Wuhan-1 (NC_045512.2). A maximum likelihood (ML) tree was then built in IQtree2 v.1.6.1 (12), using the best substitution model, default heuristic search options, and ultrafast bootstrapping with 1,000 replicates and other parameters by default as was previously described (13). A time-scaled ML phylogeny was then constructed in TreeTime (14) using the conditions: collection date as constraint and other parameters previously reported (15). All trees obtained were graphically represented in the Interactive Tree Of Life online tool (16).

Single-nucleotide polymorphism (SNP) analysis was performed by comparing the 228 genomes from Cali downloaded from the GISAID database (ranged from 4 April 2021 to 31 July 2021) with the reference genome from Wuhan, China (hCoV-19/Wuhan/Hu-1/2019, GenBank accession number: NC_045512.2) using the NextClade tool v 1.5.4 (see text footnote 11) (10), and the UGENE v.33.0 software (17). Additionally, the SNPs over time were evaluated (since 4 April 2021 to 31 July 2021).

[12]http://ugene.net/

Statistical Analysis

A descriptive analysis of the sociodemographic variables collated in the databases was performed. The quantitative variables were summarized in terms of means or medians and standard deviation or interquartile range, based on their distribution. Qualitative variables were summarized as frequencies and proportions. Statistical analyses were carried out using R software. For continuous values, normality hypotheses were evaluated using the Kolmogorov–Smirnov test. All tests of significance, parametric or non-parametric tests, were two-tailed, and p-values < 0.05 were considered statistically significant.

RESULTS

Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 in Cali City

We analyzed SARS-CoV-2 cases reported from 4 April 2021 through 31 July 2021, in Cali, Colombia (**Figure 1A**). A total of 115,167 positive cases and 2,795 deaths were reported during the period of active protests. On June 17, the city reached its

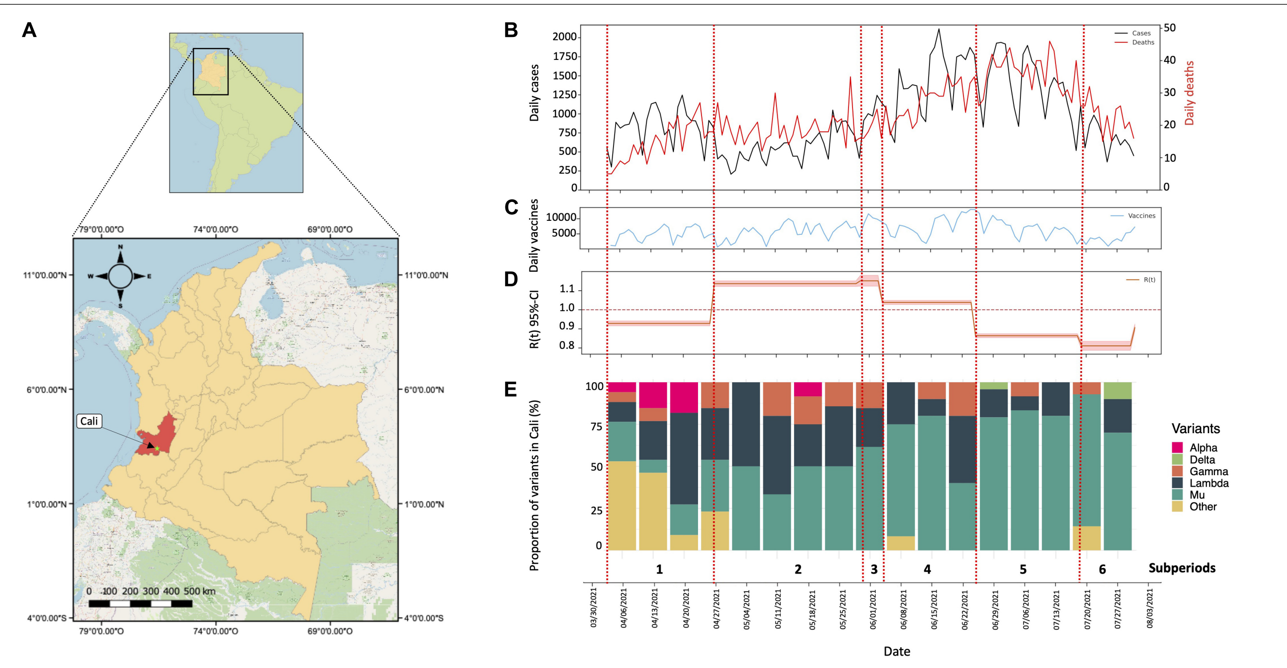

FIGURE 1 | Genomic surveillance and epidemic model of SARS-CoV-2 in Cali from 4 April 2021 to 31 July 2021. **(A)** Geographical location of the department of Valle del Cauca and its capital Cali. The map was constructed using the QGIS tools (QGIS Geographic Information System, Open-Source Geospatial) version 3.20.3-Odense. Foundation Project (http://qgis.osgeo.org). **(B)** Number of cases (black line) and deaths (red line) for SARS-CoV-2 reported daily in Cali from 4 April 2021 to 31 July 2021. **(C)** Number of vaccines applied per day in Cali from 4 April 2021 to 31 July 2021. **(D)** Value Rt calculated from 4 April 2021 to 31 July 2021. **(E)** Distribution of SARS-CoV-2 variants in Cali, Colombia. Proportion of VOC/VOI and other variants in Cali, Colombia from 4 April 2021 to 31 July 2021.

COVID-19 incidence peak: with a total 2,117 confirmed cases (7 weeks after onset of protests) (**Figure 1B**). The highest number of virus-related deaths in this period occurred on July 12th, totaling 46 (11 weeks after protests began) (**Figure 1B**). Of the total number of cases reported during our study interval, 53% corresponded to female patients and 47% to male patients. The median age was 38 years (IQR: 27–52 years). Within the deceased group ($n = 2,795$), a higher proportion of male than female deaths (59%) was noted with a median age of 68 years (IQR: 58–79 years). The daily incidence was consistent with following mortality events (as shown in **Figure 1B**). It is important to highlight that throughout the time period studied, 720,325 total vaccine doses were dispensed to the population of Cali, corresponding to first and second doses (**Figure 1C**).

Effective Reproductive Number (Rt) and Infection Dynamics

Based on information released by the government and media in relation to mass mobilizations and protests with highest popular circulation in the streets, we defined six sub-periods within our study-time interval (red dashed lines in **Figures 1B–E**). The initial sub-period: between April 4 and April 27 (prior to the beginning of the protests in the city). A second period, between 28 April 2021 (when the national strike began) and 30 May 2021 (when the mass mobilizations halted). A temporary arrest in mobilizations due to government negotiations with protesters defined a third sub-period from May 31 to June 4. Subsequent reactivation of the protests between June 5 and June 25, marked the fourth sub-period. Later, a new "return to normal" took place between June 26 and July 19, marked by a re-establishment of dialogs between the government and citizens (fifth sub-period). However, due to an incapacity for agreement, massive demonstrations reignited in July 20 through July 31 setting the sixth sub-period. July 31 thus defines the ultimate date for this analysis.

Based on these sub periods, the analysis of the effective reproduction number (Rt) was calculated using a Bayesian framework following the Cori et al. method (7). This method allows understanding changes in the Rt value at discretized times such as those herein established. The Rt values were significantly different between the time periods evaluated (Kruskal–Wallis Chi-squared = 112.5, $p < 0.05$) in this study (**Figure 1D**). Prior to the beginning of the national strike in Colombia, the city of Cali had an Rt of 0.89 and short after the initiation of unrest this value steadily increased through the second and third sub periods, exceeding the threshold of 1 (1.12 and 1.13, respectively), being statistically higher for both cases (Kruskal–Wallis Chi-squared = 112.5, $p < 0.05$. Dunn–Bonferroni *post hoc* Test, $p < 0.05$). Likewise, during cessation of the strikes between June 26 and July 19, a decrease in the Rt value to 0.84 was noted, even lower than in the previous periods marked by massive mobilizations greater circulation of people in the streets (Kruskal–Wallis Chi-squared = 112.5, $p < 0.05$. Dunn–Bonferroni *post hoc* Test, $p < 0.05$) (**Figure 1D**). These results contrast with those observed in Bogotá (**Figure 2A**) and Medellin (**Figure 2B**) were the largest riots occurred, exhibiting just a slight increase in the Rt value (very close to 1), both prior to the beginning of the protests as in the period of largest mobilizations (**Figure 2**).

Based on the analysis of SARS-CoV-2 genome assemblies, available during the six evaluated sub-periods (4 April 2021 and 31 July 2021), we identified circulation of 16 SARS-CoV-2 lineages (with a lineage proportion of 50.44% lineage B.1.621, 24.12% C.37, 7.46% P.1, 4.39% B.1.1.348, 3.95% B.1.621.1, 2.63% B.1.1.7, 1.32% B.1, 0.88% lineages A.2.5, B.1.1, B.1.625, and B.1.623; and with a proportion of 0.44% the lineages AY.20, AY.26, B.1.1.487, C.37.1, and P.1.10), with the greatest diversity of lineages (9 lineages circulating) being represented in the first sub-period (between 4 April 04 2021 and 27 April 2021) when protests had yet not started. At this time, approximately 50% of the variants were classified as VOCs/VOIs with the remaining 50% classified as B.1.625, B.1.1, and some of its descendant lineages (e.g., B.1.1.348 and B.1.1.487) (**Figure 1E**). Throughout the second sub-period (28 April 2021), we noted a decrease in the number of circulating lineages, as well as an increase in prevalence of VOCs and VOIs, specifically, of Lambda, Gamma, and Mu variants. Interestingly we observed a significant increase in the number of cases associated to the Mu variant (**Figure 1E**); particularly 2 weeks after initiation of the national strike (second sub period), a trend that was maintained during the remaining periods evaluated.

Phylogenomic Relationships and Potential Introduction Dates

The alignment obtained from the complete dataset ($n = 5,823$) including 228 genome sequences available from Cali, and 170 from the greater Valle del Cauca (labeled set as VAC) was used to infer a ML phylogeny in IQtree2. Tree topology revealed that the SARS-CoV-2 genome sequences from Cali mostly grouped ($n = 179$) into four main clusters, with the remaining 49 genomes being heterogeneously distributed (**Figures 3A,B**). Two of these clusters (C1 and C2, where the Mu variant predominated) were closely related. In the case of C1, this included 57 sequences mostly from Colombian genomes, with 21 sequences from VAC (9 from Cali and 12 from elsewhere in the department). The second cluster (C2), whose predominant variant was Gamma, comprised 1,140 sequences, including 109 genomes from VAC (54 from Cali and 55 from other regions of VAC) plus six reference genomes mostly from United States ($n = 7$) and one from England. The third cluster (C3), whose predominant variant was Lambda, contained 395 genomes comprising 18 from VAC (6 from Cali and 12 from other regions of VAC), 61 reference sequences mostly from United States, and only three genomes from South America (two from Brazil and one from Uruguay), with the reminder genomes deposited from European countries. Lastly, the fourth cluster (C4) embraced 147 sequences with 61 from VAC (37 from Cali and 24 from its department), that were closely related with 31 reference genomes mostly from United States ($n = 35$) and 2 from Peru. All genomes not mentioned during the description of the clusters belonged to different departments of Colombia, with a predominant profile from Antioquia (Northwestern Colombia).

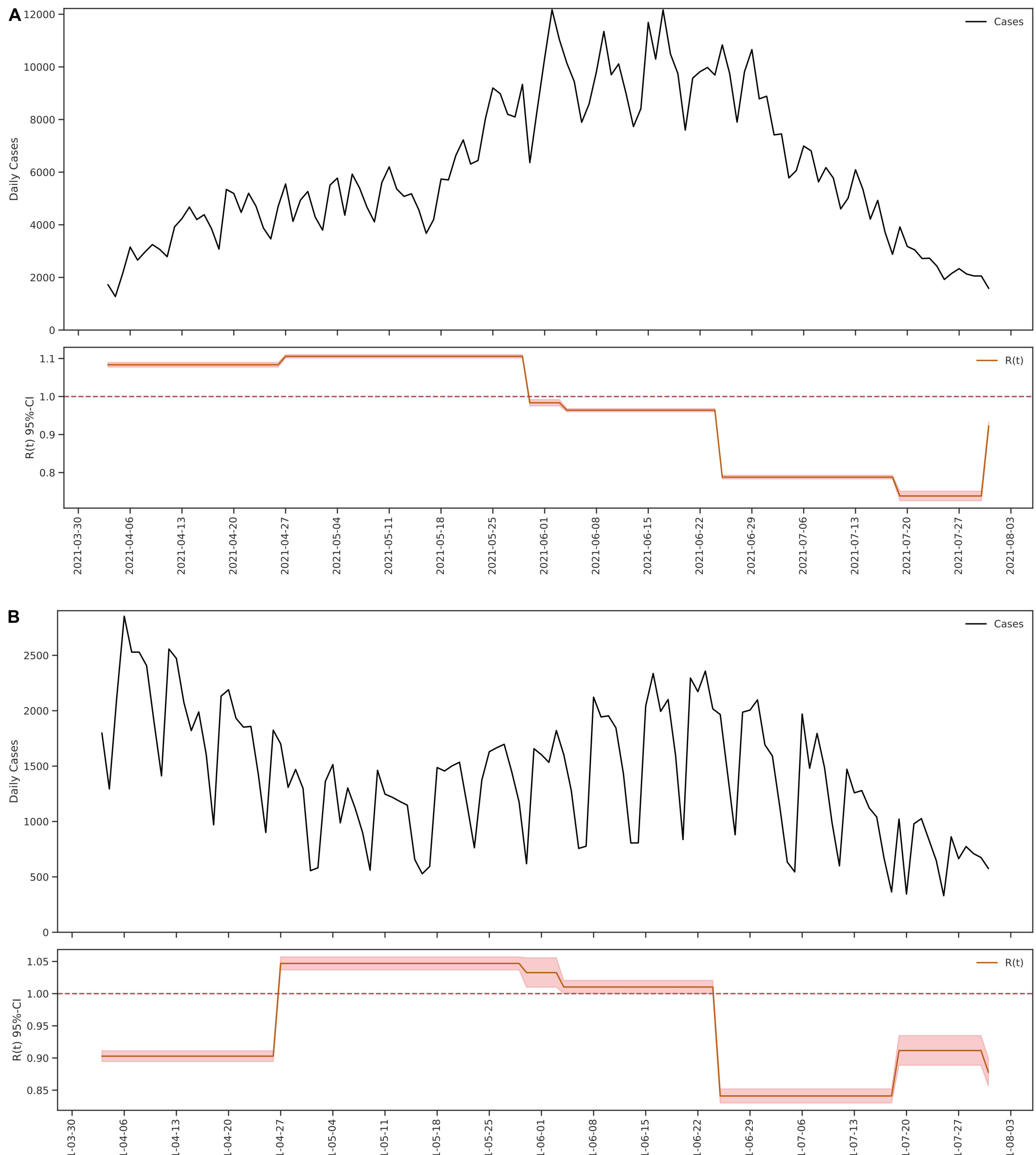

FIGURE 2 | Epidemic model of SARS-CoV-2 in Bogota and Medellin from 4 April 2021 to 31 July 2021. The figure shows the number of cases for SARS-CoV-2 reported daily and the value Rt calculated from 4 April 2021 to 31 July 2021, in the cites of Bogota **(A)** and Medellin **(B)**.

In addition, tMRCA for the VOCs/VOIs identified in the 228 genomes from Cali, was inferred using TreeTime (**Figure 3B**). The results showed two potential introduction events for the Mu variant (C1 and C2), the first on January 6 2021 (95% CI = December 7 2020 to February 10 2021) and the second on November 3 2020 (95% CI = September 22 2020 to November 24 2020). These genomes were closely related to other Colombian genomes suggesting that these two independent introductions occurred most probably from other departments. On the other hand, the putative introduction for Gamma variant (C3) was estimated in December 27 2020 (95% CI = December 12 2020 to January 13 2021) and for the Lambda variant (C4) in August 24 2020 (95% CI = January 26 2020 to November 24 2020); with genomes in close relationship to those from other countries

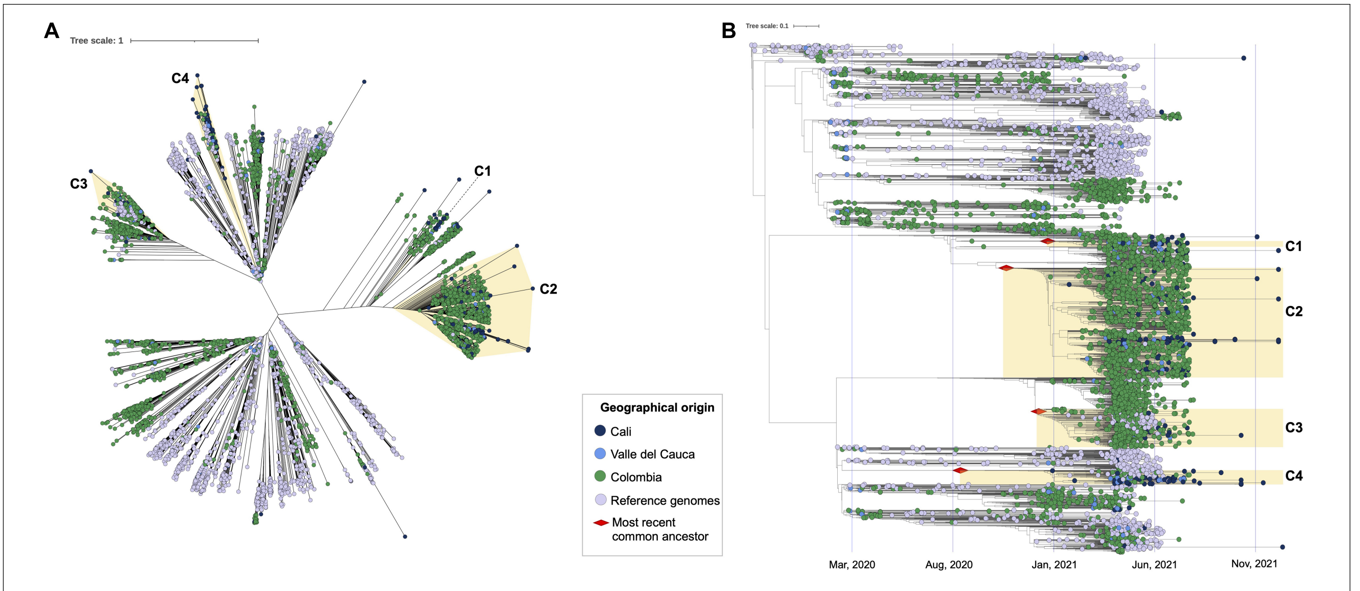

FIGURE 3 | Phylogenomic relationships of evaluated SARS-CoV-2 genomes in the global context, identification of the most recent common ancestor (tMRCA). **(A)** Phylogenomic relationships between the 5,283 genome sequences analyzed, which included 228 sequences from Cali (blue dots) 3,270 sequences from other areas of Colombia [green dots, including Valle del Cauca (magenta dots)]; and 1,785 reference genomes (purple dots). The clusters consisting of 179 of the 228 genomes from Cali are highlighted in light yellow (C1–C4). **(B)** Phylogenomic relationships between the 5,283 genome sequences analyzed with the identification of the most recent common ancestor (tMRCA). The red diamond represents the putative introduction date per each cluster.

(United States, Brazil, Uruguay, Europe, and Peru), suggesting independent introductions to Cali from those countries.

Mutational Analysis

Fifty-eight SNPs and three deletions over more than 10% of SARS-CoV-2 genomes from Cali ($N = 228$) were identified (**Figure 4**). Thirty-three of the substitutions (57%) were identified as non-synonymous substitutions, most of them identified in VOC as Alpha and Gamma and in VOI as Lambda and Mu variants. Additionally, the analysis of these mutations through time (April 4 2021 and July 31 2021) revealed that the substitution A15002G (ORF1b) was introduced on May 18 2021 and was maintained during the analyzed period (**Figure 4**).

DISCUSSION

According to the Armed Conflict Location & Event Data Project (ACLED), more than 100 countries have been witnessed to internal civil disorder. Of these, India, Israel, and Mexico have been most afflicted by such events in relation to the development of the COVID-19 pandemic within their borders (18). Extensive domestic and international debates of "right-and wrong" have been encouraged by media outlets documenting these country-specific social issues. Yet, conversations concerning the true impact of civil unrest on the epidemiology of COVID-19 remain poorly discussed. In this article, we investigated the epidemiological and genomic behavior of SARS-CoV-2 as it was forcibly integrated into the population by social turmoil in Cali, Colombia. We chose to examine this particular city for several reasons. Primarily because Cali was the third city, after Bogotá and Medellin with the highest accumulated number of natural infections and deaths by SARS-CoV-2 during the study period (April 4 2021 to July 31 2021). In addition, Cali was the city where the majority and most severe acts of vandalism and convulsed demonstrations occurred, leading to sustained chaos while anticipating a potential rebound for virus transmission.

Among the analyses central to the conclusions of this article, we highlight the Rt values in Cali, Colombia, gathered from the periods during, and prior-to/post the most significant period of demonstrations (April 28 2021 to June 25 2021) (**Figure 1D**). The Rt value being greater than one during this period, as opposed to less than one at other times. We can make an association between the assembly of large groups, and the heightened incidence of COVID-19 cases with the support of these Rt values and with the evidence of a peak in daily cases documented 2 weeks after the largest protests took place (**Figure 1B**). However, it is important to note that other events, such as the lifting of the restrictions, which took place in a moderate and staggered manner and the Easter holidays (March 28–April 4) could have had effect in the increase of Rt value.

Our findings are aligned with the findings by Moreno-Montoya et al. (6) and Valentine et al. (5), which describe a positive growth in the occurrence of COVID-19 cases after the protests; but were contrary to those of Neyman et al. (4), which indicated that each individual protestor did not significantly contribute to the COVID-19 case rate in affected countries. Nor did our findings align with previous studies by Bui et al. (19)—which did not reveal a significant relationship between protests and COVID-19 hospitalization rates within California counties. Some possible explanations for these disparities may include a greater neglect of social distancing guidelines experienced during

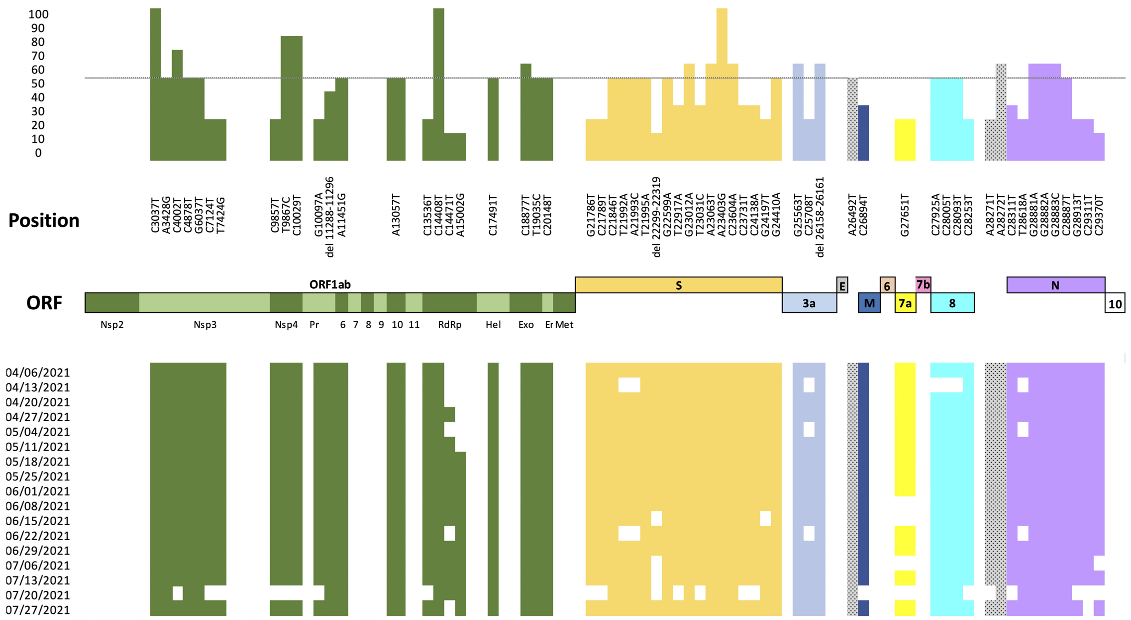

FIGURE 4 | Nucleotide diversity of the Cali genomes. Analysis of nucleotide diversity by comparing the 228 Cali SARS-CoV-2 genomes and the Wuhan reference sequence (hCoV-19/Wuhan/Hu-1/2019), GenBank accession number: NC_045512.2 over time. The upper panel represents in the *X*-axis the position of each mutation within the SARS-CoV-2 genome and in the *Y*-axis the percentage of genomes with the mutation. The lower panel shows the presence (represented with color) or absence (represented without color) of each substitution found in the 228 Cali genomes analyzed between April 4 2021 and July 31 2021.

the dissents in Colombia, failure to use personal protective equipment, inadequate ventilation among areas shared by the large groups, the lower vaccination rate within this city: (720,325), which corresponds to 32% of the total population (**Figure 1C**) and the high rate of transmissibility of SARS-CoV-2, which has been associated with the ability of this virus to replicate extensively in bronchial and alveolar epithelia, the high "silent" presymptomatic transmission (20) and the reproductive number R0 (average number of secondary cases generated per typical infectious case), which for SARS-CoV-2 present a median point estimate of 3.1 (21). Additionally, we consider that Mother's Day celebration (May 9 2021), which coincided with the period of protests could have contributed to increased SARS-CoV-2 transmission due to greater family gatherings at that time, in a similar fashion to what has been reported for holiday gatherings in the United States (22). This could very well have augmented the statistic describing COVID-19 spread in the whole of the city during the evaluated period.

Our analysis of 228 SARS-CoV-2 genomes, revealed 16 independent lineages of the virus circulating in Cali at one time or another during the period of heaviest social demonstrations. These included three VOCs Alpha, Delta, and Gamma, and two VOIs Mu and Lambda (**Figure 1E**). These findings are significant given the increased infectivity and transmission potential, severe clinical outcomes, and evasion properties of protective antibodies from previous antigen exposure, which have all become defining signatures of these variants (22–25).

Of the 16 lineages, only 9 had been circulating in the initial weeks of the protests. As the months progressed, we saw a decrease in the number of lineages coupled to an increase in the number of cases attributed to the highly infections Mu variant (**Figure 1E**). Many infectious diseases propagate in a population when migration of masses of non-immune individuals enter the physical domain of people amongst whom herd immunity is attaining its first grip. Such is the case in support of our findings: the arrival of large numbers of people to Cali, during this period of turmoil (either those supporting protests against President Iván Duque, as in the case of *Minga* indigenous individuals from Cauca department –Southern VAC–, or those sent to control protesters as was seen with the arrival of military personnel from exterior municipalities) aided the profusion of SARS-CoV-2 throughout the city.

Sustained movements of people into and out of the city likely further favored the dispersion of the Mu variant in Cali and in other regions of Colombia. The Mu variant is thought to have been introduced to the city at two independent periods, preceding the protests, one on November 3 2020, and later on January 6 2021 (**Figure 3B**). It may be further inferred that these independent occasions primed the predominance of the Mu strain over all other lineages of SARS-CoV-2 and the 55% increase in the number of reported cases during the period in which the protests took place (**Figure 1E**).

In January 2021, the Mu variant (completely defined as B.1.621/B.1.621.1), was first identified in Colombia (26). To date, it has been described (with its sub-lineage B.1.621.1) in more than 30 countries including the United States, Spain, Mexico, Hong Kong, Netherlands, and Denmark (27, 28). Its remarkable efficiency of transmission in a population might be explained by an excellent immune-evasion capacity of 0.38 (CrI: 0.32–0.43), as compared against the Gamma variant: 0.30 (CrI: 0.24–0.33)

(28). Further, the Mu variant evades both antibodies produced by natural infection, as well as those by induced immunization *via* vaccine—Mu variant being 12.4 times more resistant to neutralization by convalescent sera in the former case (28), and 7.6-fold more resistant to sera obtained from BNT162b2-vaccinated individuals, in the latter (28–30). It is thus important to note that the transmission behavior and potential of COVID-19 examined during these protests should be primarily, if not principally, attributed to the Mu variant.

Previous studies have speculated that the un-anticipated dominance of the Mu strain over other VOCs and VOIs, proceeds from its unique capacity to evade the immune system (26). Despite a subpar transmission index (1.34; CrI:1.22–1.43), as compared with the Gamma variant (1.86; CrI:1.63–1.90) (28), it seems that the aforementioned serum antibody resistance confers evolutionary advantage in populations among which other VOCs circulate still. The Gamma variant was introduced to Cali at about the same time as was the Mu variant (**Figure 3B**) yet viral spread in Cali was superseded by Mu during the full course of the period of fervent demonstrations. Further advanced studies are needed to make more poignant claims on possible correlations between the molecular makeup of Mu, and its persistence in a population. In this context, we emphasize that it is indispensable to follow through with SARS-CoV-2 genomic surveillance and vaccination programs in Colombia. This is reinforced by the recent emergence of the omicron lineage—which yet remains a mystery as it quickly continues to propagate worldwide.

This is the first such report of the epidemiological and genomic behavior of SARS-CoV-2 in the framework of Colombia's recent turbulent period of popular protests against the government. The results of our study demonstrate that these large group assemblies in Cali, together with the mass movements into and out of the city during the summer of 2021 favored the spread of SARS-CoV-2 (specifically of the Mu variant). The heightened spread of COVID-19, increased hospitalizations in Cali and consequently saturated the city's intensive care units (95% saturation). At present, 48.1% of the Colombian population is vaccinated and VOCs like Alpha, Gamma, and Delta, along with VOIs like Mu and Lambda co-circulate in our country. We consider therefore, that persistent dialogue between the public health directory in the government, and the Colombian people is imperative in order to halt further transmission chains.

Finally, we note some limitations to our study: we recognize a very probable under-reporting of the true number of COVID-19 cases in Cali during the period of interest. The abstinence of these cases from the true percentage of people infected during the summer of 2021 in Cali may be attributed to asymptomatic carriers of the virus. Second, we remain in the dark about many phenotypic characteristics of the SARS-CoV-2 strains assessed as new strains appear in the global circuit as the character of those evolutionarily preceding them is still being elucidated. Thus, we may be missing key points about virulence, transmission, and immune evasion which would have better explained the dynamics of viral spread in Cali during the period in question. Third, with a rather low number of SARS-CoV-2 genomes sequenced, we were only allowed to have a snapshot of the greater picture. This may have been a sample which coincidentally drew one conclusion in place of another. Finally, the environment of Cali may have favored one dispersion outcome over others possibly driven by the nature of the variants, had they been distributed in a different setting. The scenario presented here portrays a clear example on the significance of the interplay between viruses, environment and their interactions with host populations, particularly in context of complex human interfaces as seen during social conflict.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Universidad del Rosario Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LP conceived and designed the study, analyzed and interpreted the data, and prepared the manuscript. SC and EG-A carried out the bioinformatic analysis. MM carried out the phylogenomic analysis. NB, AR, NL, JP, CC-C, MD, CM, CO, MS, and AP-M critically revised the manuscript and made important suggestions. JR conceived and designed the study, and prepared and revised the manuscript. All authors have reviewed and approved the manuscript.

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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.2022.863911/full#supplementary-material

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Chest Computed Tomography Is an Efficient Method for Initial Diagnosis of COVID-19: An Observational Study

Waldonio de Brito Vieira[1], Karen Margarete Vieira da Silva Franco[1], Apio Ricardo Nazareth Dias[1,2], Aline Semblano Carreira Falcão[2], Luiz Fábio Magno Falcão[2], Juarez Antonio Simões Quaresma[1,2] and Rita Catarina Medeiros de Sousa[1]*

[1] *Núcleo de Medicina Tropical, Universidade Federal do Pará, Belém, Brazil,* [2] *Centro de Ciências Biológicas e da Saúde, Universidade do Estado do Pará, Belém, Brazil*

Coronavirus disease (COVID-19) is an infectious disease that can lead to pneumonia, pulmonary oedema, acute respiratory distress syndrome, multiple organ and system dysfunction, and death. This study aimed to verify the efficacy of chest computed tomography (CT) for the initial diagnosis of COVID-19. This observational, retrospective, cross-sectional study included 259 individuals who underwent clinical evaluation, blood collection, chest CT, and a reverse transcription polymerase chain reaction (RT-PCR) diagnostic test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during their course of treatment at a reference hospital in Belém, Pará, Brazil between April and June 2020. Inclusion criteria were flu-like symptoms in adults of both sexes. Individuals with an inconclusive COVID-19 molecular test or who had artifacts in the chest CT images were excluded. Parametric data were analyzed using Student-*t*-test and non-parametric data were analyzed using average test and Fisher exact test. Participants were divided into two groups: Group 1 (COVID-19 positive), $n = 211$ (124 males, 87 females), 51.8 ± 17.9 years old and Group 2 (COVID-19 negative), $n = 48$ (22 males, 26 females), 47.6 ± 18.6 years old. Most frequent symptoms were cough [Group 1 $n = 199$ (94%)/Group 2 $n = 46$ (95%)], fever [Group 1 $n = 154$ (72%)/Group 2 $n = 28$ (58%)], myalgia [Group 1 $n = 172$ (81%)/Group 2 $n = 38$ (79%)], dyspnoea [Group 1 $n = 169$ (80%) / Group 2 $n = 37$ (77%)], headache [Group 1 $n = 163$ (77%)/Group 2 $n = 32$ (66%)], and anosmia [Group 1 $n = 154$ (73%)/Group 2 $n = 29$ (60%)]. Group 1 had a higher proportion of ground-glass opacity [Group 1 $n = 175$ (83%)/Group 2 $n = 24$ (50%), 0.00], vascular enhancement sign [Group 1 $n = 128$ (60%)/Group 2 $n = 15$ (31%), 0.00], septal thickening [Group 1 $n = 99$ (47%)/Group 2 $n = 13$ (27%), 0.01], crazy-paving pattern [Group 1 $n = 98$ (46%) / Group 2 $n = 13$ (27%), 0.01], consolidations [Group 1 $n = 92$ (43%)/Group 2 $n = 8$ (16%), 0.00], and CO-RADS 4 and 5 [Group 1 $n = 163$ (77.25%)/Group 2 $n = 24$ (50%), 0.00] categories in chest CT. Chest CT, when available, was found to be an efficient method for the initial diagnosis and better management of individuals with COVID-19.

Keywords: COVID-19, severe acute respiratory syndrome, computed tomography, diagnosis, lung injury, CO-RADS

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****Correspondence:***
Juarez Antonio Simões Quaresma
juarez.quaresma@gmail.com

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INTRODUCTION

Coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is characterized by a flu-like syndrome, with the most common initial symptoms being fever, cough, sore throat, fatigue, headache, anosmia, myalgias, and diarrhea (1–6). Although many individuals develop a mild form of the infection and have a good prognosis, COVID-19 can progress to more severe forms with the development of pneumonia, pulmonary oedema, acute respiratory distress syndrome, multiple organ and system dysfunction, and death (7–9). Severe acute respiratory syndrome (SARS) is an important complication in patients with severe disease, and it sets in as soon as individuals progress to dyspnoea and hypoxemia (6).

COVID-19 related-pneumonia is a complication of moderate and severe forms of the disease and are characterized by a higher incidence of bilateral infiltrates, mainly ground-glass opacities and consolidations on chest computed tomography (chest CT) (10, 11). CT scan findings are often used for diagnostic confirmation through protocols such as COVID-19 Reporting and Data System (CO-RADS), which classifies the image findings in CO-RADS categories in accordance with their characteristics, has a good application for triage in symptomatic individuals (12, 13), and helps to monitor the progression of the disease (14, 15).

COVID-19 needs a quick diagnosis, as the severe forms usually have a fast and aggressive progression. The results of the reverse transcriptase polymerase chain reaction (RT-PCR) test, the gold standard, take an average of 7 days to be released by the laboratories, and this time can be the difference between life and death for these patients. Hence, there is a need for a COVID-19 diagnostic method with faster results and good sensitivity.

Chest CT has the potential to quickly deliver a result of imaging patterns characteristic of COVID-19. Hence, this study aimed to verify the efficacy of chest CT for the initial diagnosis of COVID-19.

MATERIALS AND METHODS

Study Design, Ethical Aspects, and Settings

This was a retrospective, cross-sectional, observational study approved by the Research Ethics Committee of Hospital Universitário João de Barros Barreto (Protocol n. 4.010.595). A consent form for data use was obtained from the hospital where the participants were treated. This study was conducted in strict accordance with the principles of the Declaration of Helsinki and was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was carried out at a reference hospital in Belém, Pará, Brazil in the Brazilian Eastern Amazon.

Participants and Materials

All patients of both sexes with flu-like symptoms who underwent investigations including chest CT, blood tests, and nasal swab at the emergency room of the reference hospital were included in this study. Patients with inconclusive results, image artifacts on the chest CT, or incomplete filling of the medical records were excluded. A peripheral arterial oxygen saturation level $\leq$93% was one of the criteria used for hospital admission, according to the institutional protocol.

Data Collection and Description of the Processes

Symptoms, duration of symptoms, age, sex, peripheral oxygen saturation level at admission, presence of comorbidities, laboratory data, and diagnostic test results of RT-PCR for SARS-CoV-2 were collected from the electronic medical records from TASY^{TM} (Phillips Healthcare^{TM}, Amsterdã, Nederlands). All participants underwent a chest CT scan, performed without intravenous contrast in the supine position. Inside the GE Multislice Brightspeed Edge Select CT scanner (GE Healthcare, Chalfont St Giles, UK) using a tube kilovoltage (kV), 100–120 kV; tube current (mAs), automatic exposure control; collimation, 1.0 mm; pitch, 1; reconstruction algorithm, iterative-based reconstruction; reconstruction slice thickness, 0.5 mm; interslice gap, 0 mm and reformatted with lung (width, 1,500 HU; level, −500 HU), and soft tissue (width, 350 HU; level, 50 HU) window settings the patient was instructed to take a deep breath, followed by a momentary apnoea to obtain cross-sectional images of the chest with slices of 1-mm collimation.

The scans were analyzed using the Osirix MD 11.0^{TM} software (Pixmeo Company, Bernex, Suiça) by two radiologists with experience in chest CT, without previous knowledge of the RT-PCR results of the individual patients. Chest tomography analysis was performed according to the qualitative visual assessment of the types of opacities, specifying their morphology, distribution and percentage of involvement of the lung parenchyma, and classification according to the CO-RADS categories.

The chest CT findings were classified as follows: (a) ground-glass opacity, defined as increased density of the lung parenchyma that retains the visible contours of the vessels and bronchi inside the affected area; (b) vascular enhancement sign (VES), vascular enlargement inside the lesion resulting from congestion and dilation of small vessels; (c) septal thickening; (d) crazy-paving pattern appearing as thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacity; (e) consolidation, when the air in the alveolar space is supplanted by a pathological product; and (f) parenchymal band, appearing as a linear opacity, usually 1–3 mm thick and up to 5 cm long that usually extends to the visceral pleura (16–18).

Chest CT was classified into categories of the Coronavirus disease 2019 Reporting and Data System (CO-RADS). This protocol provides a level of suspicion for pulmonary involvement of COVID-19, based on features seen in the high-resolution chest CT. The level of suspicion gradually increases from CO-RADS 0 to CO-RADS 6 [(12); **Table 1**].

The following parameters were also manually measured at CT scans using the Osirix MD 11.0^{TM} software (Pixmeo Company, Bernex, Suiça): diameter of the pulmonary artery trunk whose value when equal to or $>$29 mm was predictive of pulmonary arterial hypertension (19); dimensions of the left atrium whose

TABLE 1 | The coronavirus disease 2019 reporting and data system (CO-RADS).

CO-RADS classification	Interpretation
CO-RADS 0	-Non interpretable CT Scan or technically insufficient to determine COVID-19
CO-RADS 1	-Normal CT Scan
CO-RADS 2	-Low compatible with COVID-19 CT Scan
CO-RADS 3	-Equivocal or Unsure COVID-19 CT Scan
CO-RADS 4	-High suspicious for COVID-19 CT Scan
CO-RADS 5	-Very High or typical for COVID-19 CT Scan
CO-RADS 6	-Typical COVID-19 CT Scan with RT-PCR confirmation

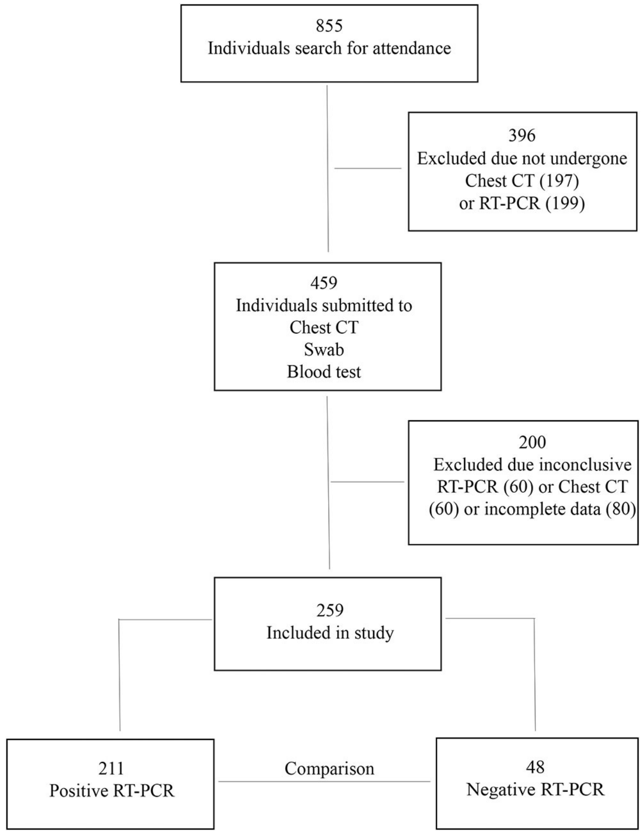

FIGURE 1 | Flowchart of the study.

hypertrophy was related to systemic arterial hypertension (20); and evaluation of the average density of the hepatic parenchyma, whose densities when <45 Hounsfield Units (HU) suggested hepatic steatosis (21, 22).

According to the results of the RT-PCR tests for SARS-CoV-2, the patients were divided into two groups, Group 1 (COVID-19 positive) and Group 2 (COVID-19 negative), for the purpose of data comparison.

Statistical Analysis

All the information collected was recorded in spreadsheets of Excel 2007™ software (Microsoft Corporation, Redmond, USA) and analyzed using Graphpad prism 5.0™ (Graphpad software, Inc., San Diego, USA). Lilliefors test was used to assess the normality of the sample. Student t-test was used for the analysis of variables with normal distribution, and the average test and Fisher exact test were used for the analysis of the non-parametric variables. The kappa test was used to analyze the interobserver concordance. The α level of 0.05 was adopted to reject the null hypothesis.

RESULTS

From 1 April to 30 June 2020, 855 individuals with flu-like symptoms were evaluated (anamnesis and physical examination). Of these, 459 individuals were suspected to have SARS-CoV-2 infection and were subjected to chest CT, blood collection, and nasal swab. Of these, 200 individuals were excluded, 60 owing to inconclusive RT-PCR, 60 owing to image artifacts on the chest CT, and 80 owing to incomplete filling of the medical record. A total of 259 patients were finally included in the study, 211 with a confirmed diagnosis of COVID-19 by RT-PCR and 48 with a negative diagnosis of COVID-19 by RT-PCR (**Figure 1**).

The study groups were homogeneous in relation to the sex of the individuals (male: Group 1, $n = 124$/Group 2, $n = 22$, $p = 0.1$ and female: Group 1, $n = 87$/Group 2, $n = 26$, $p = 0.1$), age (Group 1: 51.8 ± 17.9/Group 2: 47.6 ± 18.6, $p = 0.14$) and age groups (until 59 years old: Group 1, $n = 140$/Group 2, $n = 35$, $p = 0.4$ and 60 years-old or more: Group 1, $n = 71$/Group 2, $n = 13$, $p = 0.4$).

The clinical evaluation showed that there was no statistically significant difference regarding the time of symptom onset in the two groups [Group 1: 8.7 ± 2.8/ Group 2: 9.1 ± 1.9, $p = 0.2$]. However, most individuals were treated at the emergency room between 6 and 10 days after the onset of symptoms. The most common symptoms were cough [Group 1, $n = 199$ (94%)/Group 2, $n = 46$ (95%), $p = 1$], fever [Group 1, $n = 154$ (72%)/Group 2, $n = 28$ (58%), $p = 0.05$], myalgia [Group 1, $n = 172$ (81%)/Group 2, $n = 38$ (79%), $p = 0.83$], dyspnoea [Group 1, $n = 169$ (80%)/Group 2, $n = 37$ (77%), $p = 0.69$], headache [Group 1, $n = 163$(77%)/Group 2, $n = 32$ (66%), $p = 0.13$], and anosmia [Group 1, $n = 154$ (73%)/Group 2, $n = 29$ (60%), $p = 0.11$]. Fever shows a trend of association to Group 1, and ageusia occurred only among individuals in Group 1.

Regarding comorbidities, prevalence of diabetes mellitus and systemic arterial hypertension was similar in both the groups, but obesity was more frequent in Group 1 [Group 1, $n = 48$ (22%)/Group 2 $n = 2$ (4%), $p = 0.00$]. Peripheral oxygen saturation levels below 93% were also more frequent in this group [Group 1, $n = 115$ (54%)/Group 2, $n = 18$ (37%), $p = 0.03$], as well as minor lymphocite levels at initial attendance [Group 1: 1,344 ± 578/Group 2: 1,932 ± 405, $p < 0.01$], leukopenia (leucocytes level <4,000/mm^3) [Group 1, $n = 56$ (26%)/Group 2, $n = 4$ (8%), $p = 0.00$], higher levels of C-reactive protein [Group 1, 64 ± 29/Group 2 51 ± 24, $p < 0.01$], and

TABLE 2 | Epidemiological, clinical, and laboratorial characteristics of study participants (Belém, Pará, Brazil, 2020).

	Group 1 $n = 211$ (81.4%)	Group 2 $n = 48$ (19.6%)	Total $n = 259$ (100%)	p-value
Sex of participants				
Male	124 (58.7%)	22 (45.8%)	146 (56.3%)	0.1
Female	87 (48.7%)	26 (54.2%)	113 (43.7%)	
Age (mean ± sd)	51.8 ± 17.9	47.6 ± 18.6	51 ± 18.1	0.14
Symptoms time in days, (mean ± sd)	8.7 ± 2.8	9.1 ± 1.9	8.8 ± 2.6	0.2
Symptoms time in days				
Until 5	26 (12.3%)	0 (0%)	26 (10%)	0.00*
6–10	132 (62.6%)	38 (79%)	170 (65%)	0.00*
≥1	53 (25.1%)	10 (21%)	63 (25%)	0.00*
Symptoms				
Cough, *n* (%)	199 (94%)	46 (95%)	245 (94%)	1
Fever, *n* (%)	154 (72%)	28 (58%)	182 (70%)	0.05
Myalgia, *n* (%)	172 (81%)	38 (79%)	210 (81%)	0.83
Dyspnoea, *n* (%)	169 (80%)	37 (77%)	206 (79%)	0.69
Headache, *n* (%)	163 (77%)	32 (66%)	195 (75%)	0.13
Anosmia, *n* (%)	154 (73%)	29 (60%)	183 (70%)	0.11
Odynophagy, *n* (%)	139 (65%)	28 (58%)	167 (64%)	0.40
Runny nose, *n* (%)	52 (24%)	9 (19%)	61 (23%)	0.45
Diarrhea, *n* (%)	16 (7%)	2 (4%)	18 (6%)	0.54
Abdominal pain, *n* (%)	30 (14%)	2 (4%)	32 (12%)	0.055
Ageusia, *n* (%)	24 (11%)	0 (0%)	24 (9%)	0.01*
Comorbities				
DM, *n* (%)	30 (14%)	4 (8%)	34 (13%)	0.34
SAH, *n* (%)	45 (21%)	7 (14%)	52 (20%)	0.32
Obesity, *n* (%)	48 (22%)	2 (4%)	50 (19%)	0.00*
SpO2 ≤ 93%, *n* (%)	115 (54%)	18 (37%)	133 (52%)	0.03*
Leukocytes at initial attendance				
<4,000/(mm^3), *n* (%)	56 (26%)	4 (8%)	60 (23%)	0.00*
4,000–10,000/(mm^3), *n* (%)	58 (27%)	27 (56%)	85 (33%)	0.00*
>10,000/(mm^3), *n* (%)	97 (47%)	17 (35%)	114 (44%)	0.20
Lymphocytes at initial attendance (mm^3), mean ± sd	1,344 ± 578	1,932 ± 405	1,453 ± 578	<0.01#
C-reative protein at initial attendance/ (mg/dL), mean ± sd	64 ± 29	51 ± 24	62 ± 29	<0.01#
Hospital admission	124 (58.7%)	19 (39.5%)	143 (55.2%)	0.02*
Nursery, *n* (%)	71 (33%)	11 (23%)	82 (31%)	0.17
ICU, *n* (%)	53 (25%)	8 (16%)	62 (23%)	0.26

Group 1, COVID-19 positive; Group 2, COVID-19 negative; DM, diabetes mellitus; SAH, systemic arterial hypertension; SpO_2, peripheral oxygen saturation; PCR, C-reactive protein; ICU, intensive care unit. #ANOVA ($p < 0.05$).
**Fisher exact test ($p < 0.05$).*

hospital admission [Group 1, 124 (58.7%)/Group 2, 19 (39.5%), $p = 0.02$] (**Table 2**).

The interobserver concordance between the two radiologists who analyzed the chest CT images was 93% ($k = 0.9304$) and was determined by a kappa test. The main pulmonary findings on chest CT were ground-glass opacity [Group 1: 175 (83%)/Group 2: 24 (50%), $p = 0.00$], vascular enhancement sign [Group 1: 128 (60%)/Group 2: 15 (31%), $p = 0.00$], septal thickening [Group 1: 99 (47%)/Group 2: 13 (27%), $p = 0.01$], crazy-paving pattern [Group 1: 98 (46%)/ Group 2: 13 (27%), $p = 0.01$], and consolidations [Group 1: 92 (43%)/Group 2: 8 (16%), $p = 0.00$], all being more frequent among individuals in Group 1 (**Table 3**). Individuals in Group 1 also presented with a higher frequency of bilateral [Group 1: 150 (71%)/Group 2: 23 (48%), $p = 0.00$] and lower lobe injuries [Group 1: 143 (67%)/Group 2: 20 (41%), $p = 0.00$], as well as the involvement of more than 50% of the lung parenchyma [Group 1: 60 (28%)/Group 2: 7 (14%), $p = 0.00$] when compared to individuals in Group 2. There was the presence of other radiological findings, left atrium hypertrophy (Left atrium diameter > 40 mm) [Group 1: 65 (31%)/Group 2: 10 (21%), $p = 0.21$], increase in the pulmonary artery trunk diameter (diameter > 29 mm) [Group 1: 104 (49%)/Group 2: 20 (41%), $p = 0.42$] (**Figure 2**), and reduction in the density of the liver parenchyma (<45 UH) [Group 1: 122 (57%)/Group 2: 22 (46%), $p = 0.14$), but none showed any statistically significant difference between the two groups (**Table 3**).

Chest CT scans of each patient were analyzed based on the description of the parenchymal injuries and classified into a CO-RADS category (**Figure 3**).

TABLE 3 | Main findings at Chest CT in symptomatic individuals by group (Belém, PA, Brazil-2020).

	Group 1 ($n = 211$)	Group 2 ($n = 48$)	Total ($n = 259$)	p-value
Pulmonary findings				
Ground-glass opacity, *n* (%)	175 (83%)	24 (50%)	199 (76%)	0.00*
VES, *n* (%)	128 (60%)	15 (31%)	143 (55%)	0.00*
Septal thickening, *n* (%)	99 (47%)	13 (27%)	112 (43%)	0.01*
Crazy-paving pattern, *n* (%)	98 (46%)	13 (27%)	111 (42%)	0.01*
Consolidation, *n* (%)	92 (43%)	8 (16%)	100 (38%)	0.00*
Parenchimal bands, *n* (%)	62 (29%)	8 (16%)	70 (27%)	0.07
Distribution of injuries				
Bilateral injuries, *n* (%)	150 (71%)	23 (48%)	173 (66%)	0.00*
Lower lobe injuries, *n* (%)	143 (67%)	20 (41%)	163 (63%)	0.00*
Opacities < 25%, *n* (%)	76 (36%)	30 (62%)	106 (40%)	0.00*
Opacities 25–50%, *n* (%)	75 (35%)	11 (23%)	86 (33%)	0.00*
Opacities > 50%, *n* (%)	60 (28%)	7 (14%)	67 (27%)	0.00*
Other radiological findings				
Left Atrium > 40 mm, *n* (%)	65 (31%)	10 (21%)	75 (28%)	0.21
PAT diameter, mean ± sd	28.5 ± 5.2	26.8 ± 5.3	28.1 ± 5.2	0.06
PAT diameter ≥ 29 mm, *n* (%)	104 (49%)	20 (41%)	124 (47%)	0.42
Hepatic parenchyma density ≤ 45 UH, *n* (%)	122 (57%)	22 (46%)	144 (59%)	0.14

Group 1, COVID-19 positive; Group 2, COVID-19 negative; CO-RADS, The Coronavirus disease 2019 (COVID-19) Reporting and Data System; UH, Unidade Hounsfield; CT, computed tomography; VES, vascular enhancement sign; PAT, pulmonary arterial trunk.
**Fisher exact test ($p < 0.05$).*
Opacities: findings as ground-glass opacity, consolidation, and crazy paving pattern.*

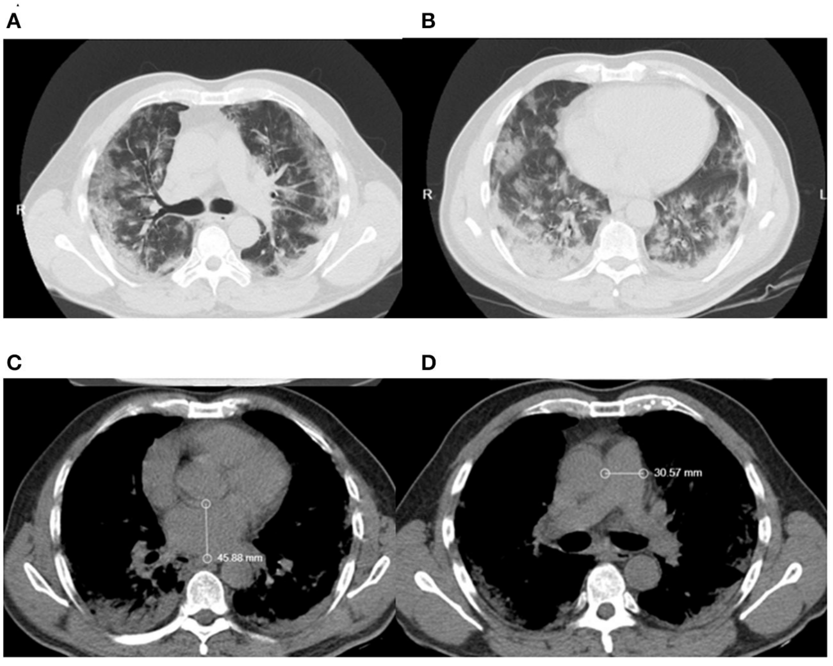

FIGURE 2 | Patients chest CT showing **(A)** vascular enhancement sign **(B)** ground-glass opacities **(C)** left atrium diameter **(D)** pulmonary artery trunk diameter.

There was a relationship between the CO-RADS category on chest CT and the results of the RT-PCR diagnostic tests for SARS-CoV-2, with a higher proportion of individuals with CO-RADS categories 4 and 5 in Group 1 [Group 1: 163(77.25)/Group 2: 24(50), $p = 0.00$] (**Table 4**).

DISCUSSION

The individuals evaluated in this study were in the acute phase of the disease with a predominance of respiratory symptoms, such as cough, fever, myalgia, dyspnoea, and headache. There was no predominance of individuals with associated comorbidities, diabetes mellitus, or systemic arterial hypertension. Changes in other systems, in this initial assessment, seem to have no observable repercussions on imaging examinations. The individuals in Group 1 had a higher incidence of imaging findings compared to those in Group 2, and the main findings on chest CT were ground-glass opacity, vascular enhancement sign, and septal thickening. The presence of CT scans classified as CO-RADS 4 and CO-RADS 5 was significantly higher in Group 1, so was the presence of a higher percentage of parenchyma involvement.

Comorbidities such as diabetes mellitus and systemic arterial hypertension have been reported to be associated with a higher probability for the development of severe forms of COVID-19 and SARS (23); however, there was no difference in the proportion of individuals with comorbidities between the groups in this study. The search for hospital care was initiated after the 6th day of symptoms by 90% of the study subjects, and the most severe respiratory symptoms of COVID-19, such as dyspnoea and hypoxemia, were noted to start on the 7th day of infection. In a study involving 138 patients, 20% of the individuals developed SARS within 8 days after the onset of symptoms and 12.3% required invasive mechanical ventilation (24). Another study reported that of the 201 patients hospitalized with COVID-19 in Wuhan, 41% developed acute respiratory distress syndrome (23).

COVID-19 has flu-like characteristics and symptoms and the most common symptoms in individuals with COVID-19-related pneumonia were fever, cough, expectoration, and myalgia. Less common symptoms were headache, dyspnoea, abdominal pain/diarrhea, pharyngeal discomfort, and chest pain (4, 11). Associated with these symptoms, many individuals also complained of loss of smell and taste, denominated as anosmia and ageusia, respectively (25–27). Lung injuries were predominantly bilateral and in the lower lobes. Ground-glass opacity in the peripheral areas is the characteristic pattern of COVID-19 (28) and is also characterized by being symmetrical and basal (5, 8, 24, 29–31).

These findings tend to change according to the stage of the disease. In the first 4 days, ground-glass opacities are the most common (76.5%); between 10 and 14 days of illness, crazy-paving pattern is the most common (62.7%); between 15 and 21 days, consolidation (75%) is commonly noted; between 22 and 28 days, linear opacities (83.1%) are seen; and in individuals over 28 days, the most common findings are ground-glass opacities [98.1%; (32)]. The pulmonary manifestations of COVID-19 can be lasting, with the presence of sequelae and residual lesions in a significant portion of the survivors (33).

Computed tomography has great sensitivity for detecting patterns related to COVID-19, but a low specificity therefore is recommended to be used in combination with a more specific

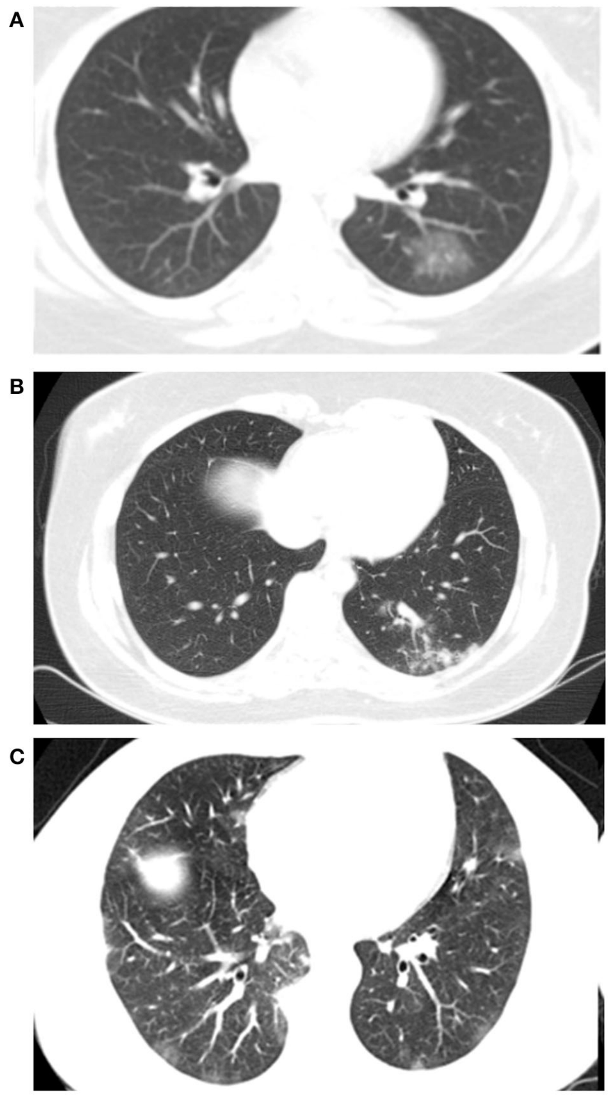

FIGURE 3 | Patients chest CT showing coronavirus disease 2019 reporting and data system **(A)** CORADS 3. **(B)** CORADS 4. **(C)** CORADS 5.

TABLE 4 | CO-RADS of chest CT in symptomatic individuals by group (Belém, PA, Brazil-2020).

	Group 1 ($n = 211$)	Group 2 ($n = 48$)	Total ($n = 259$)	*p*-value
CO-RADS 4 ou 5, *n* (%)	163 (77.25)	24 (50)	187 (72.20)	0.00*
CO-RADS 3, *n* (%)	16 (7.58)	0 (0)	16 (6.17)	0.04*
CO-RADS 1, *n* (%)	32 (15.16)	24 (50)	56 (21.62)	0.00*
Total	211	48	259	

CT, computed tomography; Group 1, COVID-19 positive; Group 2, COVID-19 negative; CO-RADS, The Coronavirus disease 2019 Reporting and Data System; CO-RADS 4, 5, high, very high suspicious for COVID-19; CO-RADS 3, equivocal or unsure; CO-RADS 1, very low or normal.

*Fisher exact test ($p < 0.05$).

diagnostic method (34–36). In a study on 1,014 patients in Wuhan who underwent RT-PCR and chest CT for COVID-19 assessment, a positive COVID-19 chest CT had a sensitivity of 97% using RT-PCR as a reference; however, the specificity was only 25% (14). CT, despite not being a completely reliable diagnostic tool, is useful in determining the severity of COVID-19 in clinical practice (37).

CO-RADS and other protocols were created by radiological societies around the world within the scope of the COVID-19 pandemic, such as the protocol created by Radiological Society of North America, both of which classify pulmonary involvement as typical, indeterminate, atypical, or negative (12, 38) and are comparable with each other in sensitivity and reliability (12, 39, 40). CT reports usually also include the estimate of pulmonary involvement, reported in percentage (41). This degree of involvement is often useful in determining severity and estimating the prognosis (37, 42). Chest CT is an important auxiliary tool in the diagnosis and acts as an indicator of the severity of pulmonary involvement in COVID-19 (43).

Computed tomography alone does not provide a reliable diagnostic confirmation. Multimodality imaging assessment in patients with COVID-19 has been shown to be useful to assess cardiac complications in this population (44). CT has the advantages of rapid application and high image resolution and can be used, among other things, for the evaluation of cardiac chambers (45–47). The findings of pulmonary artery trunk diameter with dimensions above 29 mm and left atrium hypertrophy are suggestive of cardiovascular affection, despite this, there was no statistical difference in comparison to Group 2.

As it is a systemic inflammatory disease, COVID-19 affects, among others, the gastrointestinal system (48). Individuals who developed the severe form of the disease had pathological tissue changes in the liver parenchyma, developing liver cirrhosis and non-alcoholic liver steatosis (49). An increased liver parenchyma density is suggestive of hepatic steatosis and was observed in 57% of individuals in Group 1. However, this also did not show a statistically significant difference in relation to Group 2.

The early diagnosis of COVID-19 is essential for better management of the patient, be it the decision to carry out more detailed monitoring in moderate forms, to ensure social isolation, and to prevent the spread of the disease. The gold standard diagnostic methods have high sensitivity and specificity; however, they have a turn-around time of at least 7 days.

This study reinforces the importance of CT as a rapid diagnostic adjunctive method for COVID-19. Its use allows for better decision-making by the health team, indicating the best measures to be taken according to the clinical picture and tomographic patterns of each patient, as well as, determining with greater sensitivity the suspected cases of COVID-19, leading to greater assertiveness in its handling.

Future studies must focus on the follow-up of individuals who have recovered from COVID-19 to help determine the relationship between the sequelae of the infection and imaging patterns observed in various health services. We highlight that the main limitations of this study was the small sample size and the fact that this group of patients represents those seen in only one health service; therefore, the results can possibly not be generalized to the city's population.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee from Hospital Universitário João de Barros Barreto (Protocol n. 4.010.595). A consent form for data use was obtained from the hospital where the participants were treated.

AUTHOR CONTRIBUTIONS

WV, KF, LF, JQ, and RS contributed to conception and design of the study. AD and AF organized the database, figures, and performed the statistical analysis. WV and KF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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As Omicron Takes Hold and Other New Variants Arise, COVID-19 Testing Remains the Universally Agreed Tool to Effect Transition From Pandemic to Endemic State

Melissa B. Miller[1*], *Eng Eong Ooi*[2,3,4,5], *Daniel D. Rhoads*[6,7], *Martin Kulldorff*[8], *Danielle E. Anderson*[9], *Hyukmin Lee*[10], *Sunetra Gupta*[11] and *Krajden Mel*[12]

[1] Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, United States, [2] Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore, Singapore, [3] Viral Research and Experimental Medicine Centre, SingHealth Duke-NUS Academic Medical Centre, Singapore, Singapore, [4] Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore, [5] Department of Microbiology and Immunology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [6] Department of Pathology, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH, United States, [7] Department of Laboratory Medicine, Cleveland Clinic, Cleveland, OH, United States, [8] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States, [9] Department of Microbiology and Immunology, The University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia, [10] Department of Laboratory Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea, [11] Department of Zoology, University of Oxford, Oxford, United Kingdom, [12] British Columbia Centre for Disease Control Public Health Laboratory, Vancouver, BC, Canada

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***Correspondence:**
Melissa B. Miller
Melissa.Miller@unchealth.unc.edu

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The COVID-19 pandemic has caused more than 448 million cases and 6 million deaths worldwide to date. Omicron is now the dominant SARS-CoV-2 variant, making up more than 90% of cases in countries reporting sequencing data. As the pandemic continues into its third year, continued testing is a strategic and necessary tool for transitioning to an endemic state of COVID-19. Here, we address three critical topics pertaining to the transition from pandemic to endemic: defining the endemic state for COVID-19, highlighting the role of SARS-CoV-2 testing as endemicity is approached, and recommending parameters for SARS-CoV-2 testing once endemicity is reached. We argue for an approach that capitalizes on the current public health momentum to increase capacity for PCR-based testing and whole genome sequencing to monitor emerging infectious diseases. Strategic development and utilization of testing, including viral panels in addition to vaccination, can keep SARS-CoV-2 in a manageable endemic state and build a framework of preparedness for the next pandemic.

Keywords: SARS-CoV-2, screening, surveillance, diagnosis, public health, guidelines

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged at the end of 2019, causing a global pandemic with more than 448 million cases and 6 million deaths worldwide to date (1). Omicron is now the dominant variant of SARS-CoV-2, the virus that causes COVID-19. As of March 2022, omicron makes up more than 90% of cases in most countries reporting sequencing data (2). Approximately 65% of the world's population has been vaccinated against SARS-CoV-2 (1) and many have looked hopefully toward a return to pre-pandemic conditions. However, it is becoming increasingly apparent that SARS-CoV-2 will not be eradicated, but will transition to an endemic state (3). In the midst of this transition, new variants of concern continue to arise and challenges in public health remain central on the world stage. One topic of frequent debate has been the role of testing in the diagnosis, screening, and surveillance of COVID-19 (4). Clear public health recommendations on SARS-CoV-2 testing are needed to supplement guidance that has largely been focused on the treatment of COVID-19 (5).

This perspective is the result of a discussion between the authors, who represent thought leadership from a variety of disciplines as well as differing points of view ranging from limited isolation to complete lock-down on how to manage this pandemic. Importantly, all authors agree that careful management of an eventual transition from COVID-19 pandemic to endemicity requires continued use of SARS-CoV-2 testing. We address three critical topics pertaining to the transition from COVID-19 pandemic to endemic: defining the endemic state for COVID-19, highlighting the role of SARS-CoV-2 testing as endemicity is approached, and recommending parameters for SARS-CoV-2 testing once endemicity is reached.

DEFINING THE ENDEMIC STATE FOR COVID-19

The most important driver of the transition from pandemic to endemic will be immunity derived from vaccination or past infection coupled with proper public health control measures. Reported case rates will not necessarily be useful in determining endemicity, as the role of asymptomatic cases and seasonal fluctuations may be a natural part of endemic COVID-19, or may be indicators of concern.

Therefore, we propose a two-criteria framework for endemic COVID-19. First, low annual hospitalization and death rates must be reached. What defines sufficiently low will vary regionally according to demographics, access to resources, healthcare capacity, migration status, and cultural norms. Ideally, the World Health Organization should set out such criteria for its member states and provide technical guidance. Second, low hospitalizations and deaths must be maintained without the need for infection prevention measures in public areas such as facemasks, business closures, or restrictions on events.

ROLE OF TESTING DURING THE TRANSITION FROM PANDEMIC TO ENDEMIC

While vaccination efforts are the critical driver on the path to COVID-19 endemicity, they alone are insufficient for several reasons. We see vaccine hesitancy in many regions resulting in waning vaccination rates. In the United States, vaccination rates from July 2021 to February 2022 rank among the slowest of the world's seven wealthiest large democracies (6). Additionally, in certain regions there is continued opposition to public health measures such as mask-wearing. This combination of waning vaccination rates and resistance to public health measures results in suboptimal virus control.

Importantly, case rates are not permanently reduced by vaccination alone. In the United Kingdom, the daily COVID-19 case rate exceeds 42,000 per day despite 85.4% of their population aged 12 and up being fully vaccinated (7). Variants of concern can have differential response to the vaccines, with vaccine effectiveness against symptomatic infection by the omicron variant estimated at $\sim$40% and up to 71% after a booster (8). Given these factors, we believe testing will continue to play a crucial role in managing viral spread as we return to normalcy.

Three primary modes of testing have been important during the pandemic and will continue to be utilized—though to different extents—throughout the transition from pandemic to endemic state: diagnostic, screening, and surveillance testing (9). We define diagnostic testing as testing of patients who present with symptoms of acute respiratory illness, screening as testing of asymptomatic individuals in particular settings such as elder care, and surveillance as population-level testing of samples from symptomatic and asymptomatic people. The specific utility of each testing type will be dependent on regional rates of immunity and access to healthcare resources (see **Table 1**).

Demand for diagnostic testing will be sustained as immunity increases, but the type of test recommended will change. Specifically, in populations with high immunity, the value of polymerase chain reaction (PCR) tests will increase as the positive predictive value of rapid antigen diagnostic testing (RADT) decreases proportionally to decreasing viral loads (10). Regions with access to sufficient healthcare resources should seek to implement diagnostic PCR testing for SARS-CoV-2 as part of a respiratory panel including influenza A/B and respiratory syncytial virus (RSV). However, PCR panels may not be feasible in resource-restricted low- and middle-income countries (LMIC), where the focus should be on improving access to SARS-CoV-2 PCR testing via mobile PCR platforms and continuing to utilize RADT (11).

Screening will remain crucial particularly while vaccination rates and immunity improve. In addition to protecting the vulnerable, such as nursing home residents and migrant populations, and monitoring the global distribution of variants, screening will enable the comparison of reported infection rates between vaccinated and unvaccinated persons. The impact of immune escape of SARS-CoV-2 variants and the durability of immunity are two variables that are uncertain.

Surveillance testing is a crucially important yet underutilized tool in the transition to a manageable endemic state, particularly in LMICs. For effective surveillance, random samples should be collected consistently in different geographical areas and age groups. When paired with surveillance tests, whole-genome sequencing (WGS) can be powerful but is costly. In regions where the cost may be prohibitive, WGS can be reserved for the identification of "new" variants not identified by PCR panels. WGS will also be important as antiviral therapies become more widely available, to ensure that the antiviral targets have not mutated.

TABLE 1 | Variations in SARS-CoV-2 testing in regions with differential vaccination/immunity rates and access to healthcare resources.

		Sufficient access to healthcare resources	Limited access to healthcare resources
High immunity %	Diagnostic	Focus on increasing overall PCR capacity to accommodate SARS-CoV-2 and other molecular diagnoses Increase utilization of and reimbursement for respiratory panel tests	Focus on improving access to SARS-CoV-2 PCR testing and leveraging existing infrastructure and using RADTs to support already existing PCR testing
	Screening	Shift to PCR screening as the positive predictive value of RADT testing will decrease proportionally to decreasing viral loads Prioritize screening of those in contact with at-risk populations	Limit PCR-based screening investment to at-risk populations RADT or isothermal amplification (e.g., SHERLOCK) will be useful in venues with high capacities or that involve border control
	Surveillance	Governments, research institutions, and laboratories should collaborate to create standardized panel-based surveillance programs that will be useful to detect immunity-escaping variants and beyond SARS-CoV-2, including testing best practices and quality assurance methodology	
Low immunity %	Diagnostic	Focus on increasing overall PCR capacity; SARS-CoV-2 should become a standard part of a respiratory panel including influenza A/B and RSV	Focus on improving access to PCR testing specifically for SARS-CoV-2
	Screening	Incentivize screening as a measure to aid reopening and "returning to life" RADT screening will remain useful but may be insufficient in elderly care settings	RADT screening will remain useful but may be insufficient in elderly care settings
	Surveillance	In addition to the steps recommended for high vaccination settings,	
		Incentivize whole-genome sequencing of all SARS-CoV-2 positive tests to support variant surveillance	Conduct variant monitoring via reflex testing of all positives with a mutation panel

PCR, polymerase chain reaction; RADT, rapid antigen diagnostic test; RSV, respiratory syncytial virus.

DIFFERENTIAL VALUE OF RADT AND PCR TEST MODALITIES

Both RADT and PCR testing are needed during the transition to endemic COVID-19, although with differing applicability. Where feasible, diagnostic testing needs to shift toward PCR tests, which have greater sensitivity and specificity and are superior in diagnosing symptomatic and asymptomatic patients. PCR tests should be used to confirm a negative RADT in high-risk settings where consequences of a false negative result can be severe.

Screening via RADT will continue to provide useful insights in settings with high population density, regions with low immunity and high incidence, and in monitoring temporal and geographic fluctuations, at a potentially very low cost per test with a quick turnaround time. However, RADT are limited in their ability to provide "proof of negativity," and many entities (e.g., airlines) are increasingly requiring laboratory proof of negativity via PCR testing instead of RADT. One exception to this may be the BinaxNOW RADT, which has specificity close to 100% (12).

The expense of PCR testing compared to RADT is of particular consideration in low-resource settings and highly infectious contexts, as diagnostic labs with limited resources must balance competing needs to fulfill both SARS-CoV-2 and other testing needs. Therefore, RADTs or isothermal amplification tests (e.g., specific high-sensitivity enzymatic reporter unlocking [SHERLOCK]) can be used to support PCR, especially in situations where the testing demand exceeds the supply of PCR tests or when turnaround time is critical. However, RADT shortages, such as those being seen in the US, may also necessitate greater reliance on lab-based PCR tests (13).

TESTING DURING ENDEMICITY

Incentives for testing should continue once COVID-19 reaches an endemic equilibrium to raise awareness and education regarding the role of testing in protecting vulnerable populations. To avoid financial burden on individuals, tests need to be heavily or fully subsidized by governments, employers, or medical insurance. For example, if workers are required by their employer to be tested regularly, they should not have to pay for the tests themselves. The World Health Organization has established the Access to COVID-19 Tools Accelerator (ACT-A) to provide tests to LMIC; however, funding for ACT-A is an ongoing challenge (14). Multinational programs such as ACT-A could also play a role in standardizing testing protocols, streamlining data reporting, and disseminating information on best practices (15).

International travel will continue to be a useful opportunity for testing during endemic COVID-19. Requiring tests for travelers has been demonstrated to be a successful way to monitor variants such as omicron that may pose a challenge to herd immunity (16). Testing of travelers from regions where there is increased disease prevalence or variants of interest/concern can potentially reduce transmission (17). In addition, travel testing can monitor global disease prevalence and assess geographic and longitudinal trends (18).

Discrimination between SARS-CoV-2 and other respiratory viruses will continue to be important in optimizing patient care during endemic COVID-19. Therefore, multiplex PCR assays to detect SARS-CoV-2, influenza A/B, and RSV should become a routine part of clinical management of patients who present with acute respiratory illness (19). Surveillance testing for antibodies could also be useful to monitor if population immunity is waning over time. Studies have shown that the titer of anti-SARS-CoV-2 IgG antibody is detectable up to 15 months after recovery from COVID-19 (20).

QUALITY ASSURANCE AND LOOKING AHEAD TO FUTURE PANDEMICS

Quality assurance programs for SARS-CoV-2 tests are necessary due to global variability in test performance. Approval of a test for use during the pandemic has not necessarily equated to a high-quality test. For example, as of July 15, 2021, the US Food and Drug Administration had determined that 289 SARS-CoV-2 test kits should no longer be used or distributed due to failure to meet regulatory requirements (13). However, government intervention should be carefully designed so as not to limit the potential positive impacts of innovation (21).

In preparation for future pandemics and other infectious disease outbreaks, governments and global leaders need to invest in testing capacity and quality and also support the ability to rapidly scale testing when needed. We should capitalize on the current momentum to increase capacity for PCR-based testing and WGS to monitor emerging infectious diseases. SARS-CoV-2 is not going to exit the world stage soon, but strategic development and utilization of testing, including viral panels in addition to vaccination, can keep it in a manageable endemic state and begin preparing us for the next pandemic.

CONCLUSIONS

In this perspective, we have provided new insights into the evolving public health dialogue around COVID-19 by putting forth a definition of endemic COVID-19, outlining the role of SARS-CoV-2 testing throughout the transition from pandemic to endemic, and recommending parameters for testing during endemicity. Both rapid antigen and PCR tests will remain important testing modalities, with particular need for viral panels that include SARS-CoV-2 during endemicity.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

To prepare this article, two global advisory boards were sponsored by Thermo Fisher Scientific under their Thought Leader Advisory Program and moderated by Boston Strategic Partners. The authors represent thought leadership from a variety of disciplines and share differing points of view on how to manage this pandemic. This manuscript summarizes their collective views on how testing may be conducted as we approach a state of endemicity. All authors contributed to the manuscript. None of the authors received financial compensation for writing this article.

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Risk of SARS-CoV-2 Infection Among People Living With HIV in Wuhan, China

Mengmeng Wu[1,2†], *Fangzhao Ming*[3†], *Songjie Wu*[4†], *Yanbin Liu*[1], *Xiaoxia Zhang*[1], *Wei Guo*[5,6], *Gifty Marley*[7], *Weiming Tang*[8,9*] and *Ke Liang*[1,2,4,10*]

[1] Department of Infectious Diseases, Zhongnan Hospital of Wuhan University, Wuhan, China, [2] Wuhan Research Center for Infectious Diseases and Cancer, Chinese Academy of Medical Sciences, Wuhan, China, [3] Wuchang District Center for Disease Control and Prevention, Wuhan, China, [4] Department of Nosocomial Infection Management, Zhongnan Hospital of Wuhan University, Wuhan, China, [5] Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, China, [6] Department of Pathology, School of Basic Medical Sciences, Wuhan University, Wuhan, China, [7] School of Public Health of Nanjing Medical University, Nanjing, China, [8] Guangdong Second Provincial Central Hospital, Southern Medical University, Guangzhou, China, [9] University of North Carolina at Chapel Hill Project-China, Guangzhou, China, [10] Hubei Engineering Center for Infectious Disease Prevention, Control and Treatment, Wuhan, China

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***Correspondence:**
Weiming Tang
Weiming_tang@med.unc.edu
Ke Liang
keliang@whu.edu.cn

† These authors have contributed equally to this work and share first authorship

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Background: In the era of the COVID-19 pandemic, people living with HIV (PLWH) face more challenges. However, it is unclear if PLWH is more susceptible to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than HIV-negative individuals. This study aimed to explore the prevalence of the SARS-CoV-2 infection and the associated risk factors among PLWH.

Methods: From 1 to 30 May 2020, we conducted a cross-sectional survey that enrolled 857 PLWH and 1,048 HIV-negative individuals from the Wuchang district in Wuhan, China. Our data analysis compared the rate of the SARS-CoV-2 infection among PLWH and HIV-negative participants, and the proportions of symptomatic patients and asymptomatic infectors between the two groups. We also assessed the risk factors associated with the SARS-CoV-2 infection among PLWH.

Results: Overall, 14/857 (1.6%) PLWH and 68/1,048 (6.5%) HIV-negative participants were infected with SARS-CoV-2. Among the SARS-CoV-2-infected PLWH participants, 6/14 (42.8%) were symptomatic patients, 4/14 (28.6%) were SARS-CoV-2 nucleic acid-positive asymptomatic infectors, and 4/14 (28.6%) were serology-positive asymptomatic infectors. Among the infected HIV-negative participants, 5/68 (7.4%) patients were symptomatic and 63/68 (92.6%) were serology-positive asymptomatic infectors. The rate of the SARS-CoV-2 infection was lower among the PLWH than in the HIV-negative group (1.96% vs. 5.74%, $p = 0.001$) and the rate of morbidity among the symptomatic patients was similar between the two groups ($p = 0.107$). However, there were more serology-positive asymptomatic infectors among the infected HIV-negative participants than among the infected PLWH (0.54% vs. 5.46%, $p = 0.001$). Furthermore, being 50 years or older (aOR = 4.50, 95% CI: 1.34–15.13, $p = 0.015$) and having opportunistic infections (aOR = 9.59, 95% CI: 1.54–59.92, $p = 0.016$) were associated with an increased risk of SARS-CoV-2 infection among PLWH.

Conclusions: PLWH has more varied forms of the SARS-CoV-2 infection than the HIV-negative population and should, therefore, undertake routine screening to avoid late diagnosis. Also, older age (≥50 years) and having opportunistic infections increase the risks of SARS-CoV-2 infection among PLWH.

Keywords: SARS-CoV-2, people living with human immunodeficiency virus (PLWH), IgG, IgM, asymptomatic infectors, symptomatic patient

INTRODUCTION

By 10 December 2021, a total of 268,501,588 confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases and 5,286,843 SARS-CoV-2-related deaths had been reported globally since the COVID-19 pandemic onset in 2019 (1). As living with HIV compromises natural immunity and could translate to more complications in COVID-19-infected patients, persons living with HIV (PLWH) were considered more vulnerable to the SARS-CoV-2 (2). However, research findings from some recent studies showed that the SARS-CoV-2 infection does not increase morbidity in PLWH (3). In addition, asymptomatic infectors are largely overlooked in the existing literature as most previous studies did not consider them (4, 5). Whether knowledge and evidence on the SARS-CoV-2 infection will remain similar or differ from the existing literature after accounting for these two groups of SARS-CoV-2 infections is currently unknown.

This study aimed to investigate further the prevalence of the SARS-CoV-2 infection and determine its associated risk factors among PLWH in Wuhan, China.

MATERIALS AND METHODS

Study Design and Participants' Recruitment

As an extension of our previous work (6, 7), we conducted a cross-sectional study among two cohorts of people that participated in the previous SARS-CoV-2 seroepidemiological survey in the Wuchang district of Wuhan. From 1 May 2020 to 30 May 2020, we recruited PLWH and HIV-negative individuals aged 18 years and above who had lived in the Wuchang district for at least 1 month during the COVID-19 onset (from 1 December 2019 to 8 April 2020).

Participant's Recruitment

All PLWH managed by the Wuchang district Center for Disease Control and Prevention (CDC) were eligible for recruitment. This is because all individuals diagnosed with HIV are reported to the Wuchang CDC through the China National HIV/AIDS Comprehensive Response Information Management System (CRIMS) as required by health protocols in the region.

HIV-negative participants were recruited from the general population in Wuchang. A two-stage cluster random sampling method was employed for this recruitment. First, communities were selected as primary sampling units (PSUs) in the first stage, and families were selected in the second stage. All communities were eligible for certainty PSUs, of which 11 communities were selected with a probability proportional to the sized sampling method. Within each of the 11 communities, 36 households were selected through a systematic random sampling method, and all members of the households received an invitation to participate in the study. To ensure that the age structure of the participants mirrored that of the natural population, we substituted randomly the sample where individuals of an age group were missing.

Data Collection

All participants provided demographic information which included age and gender. All participants self-reported on COVID-19 testing history, which we double-checked by name and identification card number in the recorded COVID-19 patients' records of the CDC information management system. All SARS-CoV-2 infection diagnoses followed the 8th edition of clinical practice guidelines for COVID-19 in China (8). Information from HIV-negative participants was collected using a structured pretested questionnaire. The PLWH participants provided additional information on chronic co-morbidities, HIV infection route, antiretroviral (ARV) regimen, and current opportunistic infections (OIs) if any. To ensure accuracy, the PLWH data on ARV regimens was re-obtained from the CRIMS.

Laboratory Procedures

The PLWH received CD4+ T lymphocyte count (CD4 count) and HIV viral load (HIV-VL) tests. All recruited HIV-negative participants received HIV antibody screening tests to ensure that all individuals in the control group were HIV-negative. All participants were tested for the SARS-CoV-2 infection using a throat swab sample SARS-CoV-2 real-time fluorescence polymerase chain reaction (RT-PCR) test and serum IgM/IgG antibody test. All positive tests (RT-PCR, IgM, or IgG positive) were sent to China CDC for confirmation. In the laboratory, the SARS-CoV-2 infection diagnosis was confirmed by respiratory specimens RT-PCR (Shengxiang Biotechnology Co., LTD), serum SARS-CoV-2 IgM/IgG antibody colloidal gold test, and magnetic particle chemiluminescence (qualitative result) (Guangzhou Wanfu Biotech Co., LTD). All test kits used in the study were approved by the China Food and Drug Administration (FDA).

Definitions

Chronic co-morbidities in this study include hypertension, diabetes, chronic respiratory disease, cancer, and any other clinically diagnosed chronic disease. Our definition of OIs followed the guideline formulated by the United States Department of Health and Human Services (DHHS) (9). All individuals with the SARS-CoV-2 infection were divided into symptomatic patients and asymptomatic infectors. We defined a "symptomatic patient" as a patient diagnosed with clinical manifestations, a positive SARS-CoV-2 nucleic acid test. We divided an asymptomatic infector into nucleic acid-positive asymptomatic infector and serology-positive asymptomatic infector. A "nucleic acid-positive asymptomatic infector" was diagnosed as an infector without clinical manifestations, but had a positive SARS-CoV-2 nucleic acid test. A "serology-positive asymptomatic infector" referred to an infector without clinical manifestations, who had a negative SARS-CoV-2 nucleic acid test, but a positive IgM or IgG antibody examination. Our estimated total SARS-CoV-2 infection rate included the proportions of symptomatic patients, nucleic acid-positive asymptomatic infectors, and serology-positive asymptomatic infectors.

Statistical Analysis

Continuous variables were expressed as median and interquartile ranges (Q) [M(*P*25, *P*75)], and categorical variables were expressed as frequency and percentages. We compared continuous variables using the Wilcoxon rank-sum test and categorical variables using the χ^2 test or the Fisher's exact test. The crude rate of the SARS-CoV-2 infection with a 95% confidence interval (95% CI) was estimated using the exact binomial distribution. A logistic regression model was used to assess the difference in the adjusted rate of the SARS-CoV-2 infection among the PLWH and HIV-negative participants. The regression model was adjusted for age, gender, and chronic co-morbidities. Univariate and multivariable modified Poisson regression methods were used to explore the risk factors associated with the SARS-CoV-2 infection among PLWH. A two-sided p-value of <0.05 was deemed statistically significant. STATA version 13.0 (STATA Corporation, College Station, Texas) and IBM SPSS Statistics Version 26.0 (SPSS Corporation, Chicago) software were used for all statistical analysis.

RESULTS

Overall, 910 PLWH under the management of the Wuchang CDC were eligible for recruitment in the study. A total of two individuals were excluded because they were living abroad during the Wuhan lockdown, and 51 refused to participate in this study. A total of 1,100 HIV-negative individuals selected from the residents living in the Wuchang district were offered participation in the study of which 52 declined. Overall, 857 PLWH and 1,048 HIV-negative individuals were enrolled in this study. The PLWH participants were significantly younger than the HIV-negative participants ($p = 0.001$). Also, the PLWH participants were predominantly males ($p = 0.001$) and had fewer co-morbidities than the HIV-negative participants ($p = 0.001$) (**Table 1**).

SARS-CoV-2 Infection Between PLWH and HIV-Negative Group

The crude SARS-CoV-2 infection rate was 1.63% (14/857) among PLWH and 6.49% (68/1048) in the HIV-negative group. Of the 14 SARS-CoV-2-infected PLWH participants, 6 (42.8%) were symptomatic patients, 4 (28.6%) were nucleic acid-positive asymptomatic infectors, and 4 (28.6%) were serology-positive asymptomatic infectors. Among the 68 HIV-negative participants diagnosed with the SARS-CoV-2 infection, 5 (7.4%) were symptomatic patients, and 63 (92.6%) were serology-positive asymptomatic infectors.

The adjusted rate of the SARS-CoV-2 infection was lower among the PLWH participants (1.96, 95% CI: 0.90–3.01) than among the HIV-negative participants (5.74, 95% CI: 4.31–7.17; $p = 0.001$). Similarly, the adjusted rate of the serology-positive asymptomatic infectors was significantly lower among the PLWH participants (0.54, 95% CI: 0.00–1.07) than in the HIV-negative participants (5.46, 95% CI: 4.02–6.91; $p = 0.001$). But the adjusted rate of symptomatic patients did not significantly differ between the PLWH participants (1.10, 95% CI: 0.11–2.10) and HIV-negative participants (0.37, 95% CI: 0.04–0.69; $p = 0.107$) (**Table 2**). The rate of serology-positive asymptomatic infectors among SARS-CoV-2 infection of PLWH is lower than that in the HIV-negative population (0.4% vs. 6.0%, $p = 0.001$).

Comparison of the Characteristics of SARS-CoV-2-Infected and Non-Infected PLWH

The PLWH infected with SARS-CoV-2 tended to be much older than uninfected PLWH (53.5 years vs. 35.0 years, $p = 0.005$) and had a higher rate of chronic co-morbidities ($p = 0.048$). In addition, the PLWH with OIs had a higher SARS-CoV-2 infection rate (14.3%) compared to PLWH without OIs (0.6%) ($p = 0.005$). There were no significant differences between the two groups in terms of these factors: ARV regimens, gender, HIV transmission routes, CD4 count, and HIV viral load count (**Table 3**).

Risk Factors of SARS-CoV-2 Infection Among PLWH

The univariate regression analysis results showed that older age $\geq$50 years (OR = 8.36, 95% CI: 3.01–23.22, $p = 0.001$), chronic co-morbidities (OR = 4.70, 95% CI: 1.42–15.58, $p = 0.011$), opportunistic infections (OR = 23.05, 95% CI: 5.93-89.57, $p = 0.001$), and CD4 count $<100/\mu l$ (OR = 0.19, 95% CI: 0.05–0.76, $p = 0.019$) were associated with increased odds of SARS-CoV-2 infection among PLWH. In the multivariable regression analysis, only older age $\geq$50 years (aOR = 4.50, 95% CI: 1.34–15.13, $p = 0.015$) and opportunistic infections (aOR = 9.59, 95% CI: 1.54–59.92, $p = 0.016$) were associated with increased risks of SARS-CoV-2 infection among PLWH. The model was adjusted for gender, chronic co-morbidities, the transmission route of HIV, CD4 count, HIV viral load count, and ARV regimens (**Table 4**).

DISCUSSION

This study extends the existing literature by our consideration of all three types of SARS-CoV-2 infection and investigated the risks of total SARS-CoV-2 infection among PLWH. A cross-sectional survey conducted in May 2020 (1 month after the

TABLE 1 | SARS-CoV-2 infection between HIV positive and negative group in Wuchang District, 2020 (*N* = 1905).

	HIV-positive group (*N* = 857)	HIV-negative group (*N* = 1048)	*H/χ² value*	*P*-value
Age, year*	39.7 (29, 50)	47.4 (37, 58)	−12.432	0.001
Gender (%)			459.156	0.001
Male	774 (90.3)	451 (43.0)		
Female	83 (9.7)	597 (57.0)		
Chronic Co-morbidities (%)			118.143	0.001
No	806 (94.1)	793 (75.7)		
Yes	51 (5.9)	255 (24.3)		
Total SARS-CoV-2 infection (%)	14 (1.6)	68 (6.5)	26.978	0.001
Symptomatic patients	6 (0.7)	5 (0.5)	0.408	0.523
Asymptomatic infectors				
nucleic acid positive	4 (0.5)	0 (0.0)	4.902	0.040
serology positive	4 (0.5)	63 (6.0)	42.714	0.001
IgM (+) IgG (-)	1 (0.1)	11 (1.1)		
IgM (-) IgG (+)	2 (0.2)	29 (2.7)		
IgM (+) IgG (+)	1(0.1)	23 (2.2)		

**The data were expressed as median and interquartile ranges (Q) [M (P25, P75)]. Categorical variables were expressed as frequency and percentages Comparisons of continuous variables using the Wilcoxon rank-sum test and categorical variables using the χ^2 test or the Fisher exact test. "Symptomatic patient" as diagnosed patient with clinical manifestations, a positive SARS-CoV-2 nucleic acid test. "nucleic acid positive asymptomatic infector" were diagnosed infector without clinical manifestations, but had positive SARS-CoV-2 nucleic acid test. "serology positive asymptomatic infector" referred to infector without clinical manifestations, who had a negative SARS-CoV-2 nucleic acid test, but a positive IgM or IgG antibody examination.*

TABLE 2 | Comparison of SARS-CoV-2 infection between HIV positive and negative group in Wuchang District (*N* = 1905).

	HIV positive group (*N* = 857)	HIV negative group (*N* = 1,048)	*P*-value
Total SARS-CoV-2 infection			
Crude rate (%, 95% CI)#	1.63 (0.78–2.48)	6.49 (4.99–7.98)	
Adjusted rate (%, 95% CI*	1.96 (0.90–3.01)	5.74 (4.31–7.17)	0.001
Symptomatic patients			
Crude rate (%, 95% CI)#	0.70 (0.14–1.26)	0.48 (0.06–0.90)	
Adjusted rate (%, 95% CI)*	1.10 (0.11–2.10)	0.37 (0.04–0.69)	0.107
nucleic acid positive asymptomatic infectors			
Crude rate (%, 95% CI)#	0.47 (0–0.92)	0	
Adjusted rate (%, 95% CI)*	NA	NA	NA
serology positive asymptomatic infectors			
Crude rate (%, 95% CI)#	0.47 (0–0.92)	6.01 (4.57–7.45)	
Adjusted rate (%, 95% CI)*	0.54 (0.00–1.07)	5.46 (4.02–6.91)	0.001

*#Confidence intervals estimated using exact binomial distribution. *The adjusted rate was obtained after adjusting for age, gender, and chronic comorbidities using logistic regression.*

primary onset of the SARS-CoV-2 epidemic was contained in China), showed that the rate of positive SARS-CoV-2 antibodies among the Wuhan populations was 4.43% (10). This finding is similar to the total rate of SARS-CoV-2 infection observed among the HIV-negative participants in our study (6.5%). Our results also showed that the rate of SARS-CoV-2 infection was lower among PLWH (1.6%) than among the HIV-negative participants. But the infected PLWH participants exhibited more varied forms of SARS-CoV-2 infections than the infected HIV-negative participants. The 0.45% rate of symptomatic SARS-CoV-2 infections reported in Wuhan (3) was similar to the rates observed among both infected HIV-negative participants (0.5%, 5/1,048) and infected PLWH (0.7%, 6/857) in our study. Similarly, findings from another study showed no significant difference in the rate of symptomatic patients between the PLWH and HIV-negative populations (11).

We found that more SARS-CoV-2-infected PLWH tended to be nucleic acid-positive asymptomatic infectors than SARS-CoV-2 infected HIV-negative individuals. Although no nucleic acid-positive asymptomatic infectors were found in HIV-negative participants in this study, we observed that 0.5% (4/857) rate of nucleic acid-positive asymptomatic infectors among SARS-CoV-2-infected PLWH was higher than the previous rates of 0.013% (8/61,437 in Wuchang district) and 0.001% (221/1,58,403

TABLE 3 | Demographic features of enrolled PLWH in Wuhan, China, 2020 ($N = 857$).

Characteristics	Uninfected SARS-CoV-2 ($N = 843$)	Infected SARS-CoV-2 ($N = 14$)	χ^2-value	*P*-value
Age, year*	35.0 (29, 49)	53.5 (42.25, 61)	NA	0.005
Gender (%)			0.105	1.000
Male	761 (90.3)	13 (92.9)		
Female	82 (9.7)	1 (7.1)		
Chronic comorbidities (%)			5.892	0.048
No	794 (94.2)	11 (78.6)		
Yes	49 (5.8)	3 (21.4)		
The transmission route of HIV (%)			0.202	0.904
Heterosexual transmission	196 (23.3)	3 (21.4)		
Homosexual	637 (75.5)	11 (78.6)		
Other	10 (1.2)	0 (0.0)		
OIs (%)			31.871	0.005
Yes	5 (0.6)	2 (14.3)		
No	838 (99.4)	12 (85.7)		
CD4 count (%)			5.467	0.074
$<$100 cells/μL	26 (3.1)	2 (14.3)		
$\geq$100 cells/μL	817 (96.9)	12 (85.7)		
HIV-VL (%)			0.025	1.000
$<$20 cells/μL	618 (73.3)	10 (71.4)		
$\geq$20 cells/μL	225 (26.7)	4 (28.6)		
ARV regimens (%)			4.428	0.219
NRTI+NNRTI	699 (82.9)	13 (92.9)		
PIs-based	78 (9.3)	0 (0.0)		
INIs-based	51 (6.0)	0 (0.0)		
Not on ARV	15 (1.8)	1 (7.1)		

**Data were expressed as median and interquartile ranges (Q) [M (P25, P75)]. Categorical variables were expressed as frequency and percentage. Comparisons of continuous variables were assessed using the Wilcoxon rank-sum test, while categorical variables were assessed using the χ2 test or the Fisher exact test. NRTI, nucleoside reverse transcriptase inhibitors. NNRTI, non-nucleoside reverse transcriptase inhibitors. PIs, protease inhibitors. INIs, integrase inhibitors. OIs, opportunistic infections.*

in Wuhan city) reported by previous Wuhan studies (12, 13). We hypothesize that two potential factors may have contributed to this finding. First, it is possible that immune deficiency causes the body of PLWH to clear the SARS-CoV-2 antibodies more slowly than SARS-CoV-2-infected HIV-negative individuals (14–16). This explanation is possible as a previous study found a median virus shedding time of 19 days in asymptomatic infectors and 14 days in symptomatic patients among SARS-CoV-2 infected HIV-negative individuals (14). On the other hand, another study found an-18 day median time of virus shedding among 68% of the SARS-CoV-2 infected PLWH, but also observed that the virus was still detectable in 32% of the patients 40 days later (17). Second, PLWH may not exhibit typical clinical symptoms of immunodeficiency with a SARS-CoV-2 infection due to their compromised immunity (18, 19). This may have increased their possibility of being nucleic acid-positive asymptomatic infectors at the initial stages of a SARS-CoV-2 infection.

We also found that serology-positive asymptomatic infectors were preponderant among SARS-CoV-2-infected HIV-negative individuals (6.0%, 63/1,048) than SARS-CoV-2-infected PLWH (0.5%, 4/857). This outcome was salient even when multivariable regression models were adjusted for possible confounding factors including age and gender. We speculate that three factors concurrently or individually may have potentially accounted for this finding. First, previous study findings have suggested that B-cell dysfunction appears during an HIV infection and results in impaired antibody responses to vaccines (20). Thus, the compromised immunity of PLWH leads to insufficient antibody production than found in HIV-negative people. Second, it is possible that serum levels of IgG antibody decrease faster in PLWH than in HIV-negative populations. A study in the Chongqing province of China made a similar observation that antibodies decreased by more than 70% in 90% of the SARS-CoV-2-infected HIV-negative populations after 2 months (14). Our previous findings also showed that the positive IgG conversion rate for SARS-CoV-2 infection was relatively lower and quickly lost in PLWH (21). Finally, practicing preventive health behaviors like social distancing could have shielded PLWH from SARS-CoV-2 infection.

Our results showed that PLWH with OIs is at higher risk of SARS-CoV-2 infection than PLWH without OIs. It is a well-known phenomenon that the appearance of OIs means severely impaired immunity, and that means the affected PLWH are prone to getting other infections (22). However,

TABLE 4 | The risk factors of SARS-CoV-2 infection among PLWH from Wuchang district in Wuhan, China ($N = 857$).

Characteristics	Univariate analysis		Multivariable analysis*	
	OR (95%CI)	*P*-value	Adjusted OR (aOR) (95%CI)	*P*-value
Age (years)				
18–49	1.00		1.00	
≥50	8.36 (3.01–23.22)	0.001	4.50 (1.34–15.13)	0.015
Gender				
Male	1.00		1.00	
Female	0.65 (0.12–3.50)	0.616	0.82 (0.07–9.12)	0.872
Chronic Co-morbidities				
No	1.00		1.00	
Yes	4.70 (1.42–15.58)	0.011	2.17 (0.52–9.12)	0.290
The transmission route of HIV				
Non-MSM	1.00		1.00	
MSM	0.36 (0.11–1.19)	0.093	0.53 (0.13–2.11)	0.617
OIs				
No	1.00		1.00	
Yes	23.05 (5.93-89.57)	0.001	9.59 (1.54-59.92)	0.016
CD4 count (cells/μL)				
<100	1.00		1.00	
≥100	0.19 (0.05–0.76)	0.019	0.27 (0.04–1.96)	0.197
HIV-VL (copies/mL)				
<20	1.00		1.00	
≥20	1.38 (0.46–4.17)	0.567	0.98 (0.26–3.79)	0.985
ARV regimens				
Yes	1.00		1.00	
No	0.66 (0.04–11.00)	0.769	1.00 (1.00–1.00)	NA

*MSM, men who have sex with men. *Each association was mutually adjusted for the other characteristics in the table. OIs, opportunistic infections.*

reports about SARS-CoV-2 infection in PLWH with OIs are limited (23). On the other hand, the common OIs among PLWH include tuberculosis, pneumocystis pneumonia, and bacterial pneumonia. All of these diseases could compromise the immunity of the local pulmonary and cause lung damage in severe cases (24). Possibly, the compromised immunity of the local pulmonary could enhance the risk of SARS-CoV-2 infection in theory. Some studies have also suggested that PLWH with tuberculosis infection is more susceptible to SARS-CoV-2 infection (25, 26). However, more studies are needed to ascertain the role of these factors in SARS-CoV-2 infection among PLWH.

At the early onset of the SARS-CoV-2 pandemic outbreak, many scholars speculated that the ARV drugs may have therapeutic and preventive effects on SARS-CoV-2 infection (27, 28). Yet, a study in Spain found that the ARV drugs could not reduce SARS-CoV-2 infection-related morbidity among PLWH (29). Findings from a randomized controlled open-label trial also showed no benefits in the use of lopinavir-ritonavir among the SARS-CoV-2 infection patients (30). Our study findings also suggest that the ARV drugs do not provide prophylaxis for SARS-CoV-2 infection among PLWH. Thus, the speculated protection that ARVs offer to PLWH against SARS-CoV-2 infection is unfounded; hence we recommend that routine SARS-CoV-2 testing interventions should be tailored to include PLWH.

Our study has several limitations. First, this was a cross-sectional study, and hence, may not reflect the conditions at the early onset of the SARS-CoV-2 pandemic outbreak in Wuhan. Second, our study sample size is relatively small, and this limited us from conducting more significant analyses. In addition, differences in the adjusted rate of asymptomatic SARS-CoV-2 infections between the two groups could not be compared since we found no asymptomatic patients among our HIV-negative participants. Finally, although the serological IgM/IgG antibody test had some false positives, each positive specimen was double-tested to reduce the risk of this error.

In conclusion, our study findings show that SARS-CoV-2 infected PLWH are more likely to be nucleic acid-positive asymptomatic infectors, and the seroprevalence of antibodies is lower among SARS-CoV-2-infected PLWH than SARS-CoV-2-infected HIV-negative individuals. Therefore, strategies should be established to enable routine SARS-CoV-2 testing among PLWH and facilitate early diagnosis among the population. We also found that older PLWH and those with OIs are at higher risk of SARS-CoV-2 infection. Therefore, more attention should be given to encouraging the practice of personal protective behaviors (like hand washing and social distancing) by this group of PLWH to reduce exposure to infection.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee Zhongnan Hospital of Wuhan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WT and KL conceived and designed this investigation. FM and XZ helped to design the scheme of the investigation. FM and MW collected the original data. MW and SW analyzed the data. MW, WT, and KL contributed to the interpretation of the data. MW, SW, GM, WT, and KL contributed to the writing of the paper. All authors have read and approved the final manuscript.

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COVID-19 Vaccine Hesitancy in Italy: Predictors of Acceptance, Fence Sitting and Refusal of the COVID-19 Vaccination

Cristina Zarbo [1†], *Valentina Candini* [1*†], *Clarissa Ferrari* [2], *Miriam d'Addazio* [1], *Gemma Calamandrei* [3], *Fabrizio Starace* [4], *Marta Caserotti* [5], *Teresa Gavaruzzi* [5], *Lorella Lotto* [5], *Alessandra Tasso* [6], *Manuel Zamparini* [1‡] and *Giovanni de Girolamo* [1‡]

[1] Unit of Epidemiological Psychiatry and Evaluation, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy, [2] Service of Statistics, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy, [3] Centre for Behavioral Science and Mental Health, Istituto Superiore di Sanità, Roma, Italy, [4] Department of Mental Health and Drug Abuse, Azienda Unitá Sanitaria Locale (AUSL) Modena, Modena, Italy, [5] Department of Developmental Psychology and Socialization, University of Padova, Padova, Italy, [6] Department of Humanities, University of Ferrara, Ferrara, Italy

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Roger Nlandu Ngatu,
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Charles J. Vukotich Jr.,
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***Correspondence:**
Valentina Candini
vcandini@fatebenefratelli.eu

† These authors share first authorship
‡ These authors share last authorship

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Background: The hesitancy in taking the COVID-19 vaccine is a global challenge. The need to identify predictors of COVID-19 vaccine reluctance is critical. Our objectives were to evaluate sociodemographic, psychological, and behavioral factors, as well as attitudes and beliefs that influence COVID-19 vaccination hesitancy in the general population of Italy.

Methods: A total of 2,015 people were assessed in two waves (March, April and May, 2021). Participants were divided into three groups: (1) individuals who accepted the vaccination ("accepters"); (2) individuals who refused the vaccination ("rejecters"); and (3) individuals who were uncertain about their attitudes toward the vaccination ("fence sitters"). Group comparisons were performed using ANOVA, the Kruskal-Wallis test and chi-square tests. The strength of the association between the groups and the participants' characteristics was analyzed using a series of multinomial logistic regression models with bootstrap internal validation (one for each factor).

Results: The "fence sitters" group, when compared to the others, included individuals of younger age, lower educational level, and worsening economic situation in the previous 3 months. After controlling for sociodemographic factors, the following features emerged as the main risk factors for being "fence sitters" (compared with vaccine "accepters"): reporting lower levels of protective behaviors, trust in institutions and informational sources, frequency of use of informational sources, agreement with restrictions and higher conspirative mentality. Higher levels of COVID-19 perceived risk, trust in institutions and informational sources, frequency of use of informational sources, agreement with restrictions and protective behaviors were associated with a higher likelihood of becoming "fence sitters" rather than vaccine "rejecters."

Conclusions: The "fence sitters" profile revealed by this study is intriguing and should be the focus of public programmes aimed at improving adherence to the COVID-19 vaccination campaign.

Keywords: trust, conspiracy, vaccination, perceived risk, restrictions, protective behaviors

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has caused havoc in global healthcare systems and has had a significant impact on different aspects of daily life (1–3), prompting pharmaceutical companies to urgently create vaccines and monoclonal antibodies to combat this public health emergency. The development of safe and effective COVID-19 vaccinations is widely regarded as the first step toward a long-term solution to the pandemic. Indeed, a high vaccination rate would ensure the pandemic's eradication or control. However, as the pandemic has progressed, the number of people willing to get vaccinated has declined (4). Even before the COVID-19 crisis, the World Health Organization (WHO) confirmed vaccine hesitancy as one of the top 10 global health threats for 2019. The SAGE Working Group has defined vaccine hesitancy as "*a delay in acceptance or refusal of vaccines despite availability of vaccination services*" adding that "*vaccine hesitancy is complex and context specific, varying across time, place and vaccines*" (5, 6).

Vaccine hesitancy is influenced by factors such as confidence (do not trust vaccine or provider), complacency (do not recognize a need for a vaccine, do not value vaccination) and convenience (accessibility to vaccines) (7). COVID-19 vaccine hesitancy has been frequently linked to fears that the vaccinations are unsafe, they were developed too quickly, they may induce adverse effects (e.g., infertility, death), they are pointless due to COVID-19's innocuous nature, and they are designed to inject microchips (8–13). Moreover, some conspirative theories suggest that pharmaceutical corporations produced and disseminated the virus in order to sell their medications and vaccines (14, 15).

Therefore, it is critical to identify the predictors of COVID-19 vaccine hesitancy so that specific *ad hoc* public programmes and communication strategies can be implemented to inform governments, increase the positive responses to the COVID-19 vaccination campaign (including the "booster dose" or periodic), and establish guidelines for better managing future pandemics. Previous studies have indicated that the factors affecting vaccine intention and uptake differ substantially depending on the country, culture and socioeconomic conditions. COVID-19 vaccine hesitancy has been associated with younger age (16–21), female gender (12, 16, 18, 19, 22–24), adherence to conspiracy theories (14, 16, 18), belief that the risks related to the COVID-19 pandemic had been exaggerated by the media and that the pandemic would not last much longer (25), low perceived risk (16, 18, 24, 26), lower use of traditional and authoritative information sources (27), poor perception of government measures (20) and low trust/confidence in scientists, healthcare workers, health systems and government (12, 16, 20, 22, 28). Furthermore, a recent Italian study (29) focusing on vaccination hesitancy in case people will be tested positive for COVID-19 (i.e., post-positive reluctance) and those who relied on others to get vaccinated (i.e., free-riding intention) discovered that these two groups had a medium or high frequency of media information use and medium or high levels of conspiracy-mindedness. Various studies have revealed contrasting results for income and education. Specifically, some studies found that vaccine reluctance was associated with lower education (16, 18, 30) and lower income (16, 20, 30), while others discovered that vaccine hesitancy was higher in people with a university/postgraduate education degree (22), college-level education (26) or higher monthly income (12).

Despite their importance, most of these studies have focused on attitudes and intentions toward vaccines, rather than on behavior (acceptance or refusal), mostly when they were not available yet (i.e., until the end of 2020). Furthermore, limited studies have investigated the predictors of COVID-19 vaccine hesitancy in the general Italian population (31–35), and only a few study have looked into the predictors that differentiate individuals who accepted the vaccination ("accepters"), individuals who refused the vaccination ("rejecters") and individuals who were uncertain about getting vaccinated when the vaccine will be available for them ("fence sitters").

Therefore, the present study aimed to determine which sociodemographic, psychological, belief and behavioral factors influence COVID-19 vaccine hesitancy in a representative sample of the Italian general population, with a special focus on "fence sitters" profiles. According to Verger and Dubé (36), "fence sitters" are a primary target for measures aimed at increasing vaccination coverage. In particular, we aimed at: (1) exploring sociodemographic, psychological, belief and behavioral differences between "accepters," "rejecters" and "fence sitters," and (2) identifying the factors that most predict the likelihood of being "accepters" vs. being "fence sitters," and the likelihood of being "rejecters" vs. being "fence sitters."

METHODS

Participants and Procedures

This cross-sectional study is part of a larger project promoted by the WHO Regional Office for Europe called "*Monitoring knowledge, risk perceptions, preventive behavior and trust to inform pandemic outbreak response*" and conducted in 33 countries (see WHO 2021 for the full protocol). The Italian survey *COVID Monitoring in Italy* ("COMIT") (registered ISRCTN on 11/05/2021, ID: ISRCTN 26200758) was conducted in four waves (January–May 2021) with a sample of 10,013 people aged 18–70 years old using an online questionnaire designed *ad hoc* by WHO. In this manuscript, we will discuss specific data on behavior and attitudes toward the COVID-19 vaccine, involving 2,015 participants from the Italian general population and collected in the last two waves (when vaccines become accessible to a large portion of the population): Wave 3 (23rd March-2nd April 2021) and Wave 4 (7th-20th May 2021). **Figure 1** shows the flowchart for sampling selection.

A detailed sampling plan was designed to obtain a representative stratification of the Italian adult population. The following variables were employed to stratify the participants: by gender, by age (18–34, 35–44, 45–54, and 55–70 years); geographical area (Northwest, Northeast, Center, South, and Islands), size of living centers (above and below 100,000 inhabitants), education level (up to lower middle school, beyond lower middle school) and employment (employed, not employed). According to the most recent data from the Italian Statistics Institute (ISTAT, 12/31/2019), a weighting

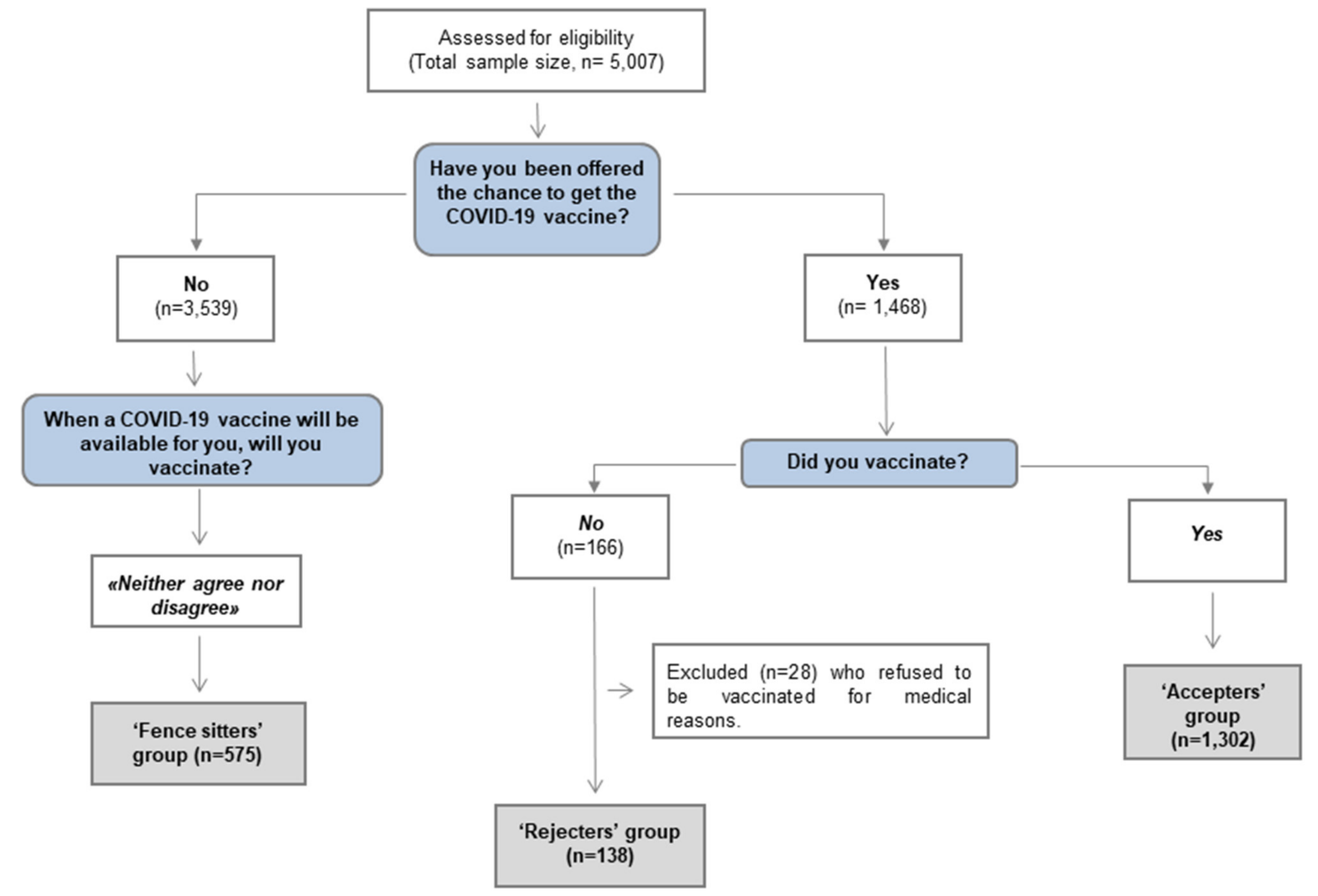

FIGURE 1 | Flow-Chart of groups' stratification.

technique was conducted at the end of each wave to precisely restore the proportionality of the total sample investigated with the reference population. The main socio-demographic and geographic variables were weighted (e.g., sex by age by geographical area, occupation, education, geographical area and size of living centers). The survey study was conducted by Doxa S.p.A. and carried out using an online panel utilizing the computer-aided web interview technique (CAWI) and the Confirmit software platform. All participants, as a representative sample of the target population, received an invitation by e-mail to fill the online interview via a link: first, informed consent was requested and then the questionnaire was accessed. The average administration time was ∼20 min. This study was approved by the Ethics Committee and all participants gave their informed consent.

Measures

The WHO questionnaire covered 21 different subject categories, including knowledge, risk perception, preventive behaviors, and trust. Following the WHO's translation guidelines, the questionnaire was translated into Italian. Forward translation, panel experts, back-translation, pre-test and cognitive interviews and development of the final edition were all part of the process.

In this article, we considered the following domains of the WHO questionnaire: socio-demographic characteristics (i.e., age, sex, education level, occupational status and financial situation), personal direct and indirect experience with COVID-19, COVID-19 perceived risk, trust in healthcare institutions, trust in information provided by media, trust in information provided by institutions, frequency of use of media information sources, frequency of use of health information sources, agreement with restrictions enforced by the Italian government during the pandemic, conspiracy mentality assessed using the Conspiracy Mentality Questionnaire (CMQ) (37), wellbeing assessed through the WHO-5 (38) and three items of the Brief Resilience Scale (39). Detailed information on the items covered in each factor is presented in **Supplementary Table S1**.

The willingness to be vaccinated was evaluated using three questionnaire items (see **Figure 1**). The "rejecters" group was represented by individuals who refused the COVID-19 vaccine (with the exception of those who were unable to get the vaccination because of medical reasons); the "accepters" group included those who accepted the vaccine; finally, the "fence sitters" group included those who had not been offered the vaccine at the time of the survey and who chose the middle point "*neither agree nor disagree*" on the Likert 7-point scale at the item exploring their willingness to get vaccinated in the near future.

Since the three groups matched distinct demographic strata in terms of vaccination time schedules at the time of the survey, *ad-hoc* methodological changes were made as needed (see next section). These adjustments were required due to differing vaccination access: in fact, "accepters" and "rejecters" belonged to a subgroup of the population (e.g., older people, health workers, educational staff and individuals with chronic diseases) who were offered the vaccination first, whereas "fence sitters" belonged to a larger stratum of the general population who were excluded from the initial vaccination schedule and had to wait longer to receive the vaccine as per the government policy.

Statistical Analyses

Descriptive statistics consisted of means and standard deviations (SD) for continuous variables and frequency tables for categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to analyse whether continuous variables were normally distributed. ANOVA (or the related non-parametric Kruskal-Wallis test if the investigated variable was not normally distributed) was used to compare groups in terms of mean scores, and multiple comparisons were adjusted with Bonferroni *post-hoc* technique. The relationships between categorical variables and groups were examined using the chi-square test.

Due to the large number of WHO items, a data reduction approach based on exploratory factor analysis was applied to derive a few key factors (see **Supplementary Table S1**). To assess the strength of the association (expressed in terms of Odds Ratio and Nagelkerke's R^2 [N-R^2] index) between the study groups and the subjects' features, a series of multinomial logistic regression models (one for each factor) were employed with groups ("accepters," "fence sitters" and "rejecters") as dependent variables and behavioral factors as independent variables. To account for possible biases due to the different subpopulations in the three groups, we included the main findings of the descriptive analyses related to these three groups in the multinomial logistic regression model, and the models were adjusted for age, gender, chronic disease, educational level, working (and health-working) status, economic situation in the last 3 months and COVID-19 infection, to manage the potential confounding effect caused by the disparity between the two groups who were offered the vaccination ("accepters" and "rejecters") and the group that was not yet offered the vaccination ("fence sitters") and was assessed on their willingness to get vaccinated in the future. The results were confirmed using the bootstrap method on 500 bootstrap samples to account for the imbalance of the three groups (40). Analyses were performed using R (41) and SPSS version 27.0.

RESULTS

Table 1 and **Figure 2** show the sociodemographic, psychological, belief and behavioral characteristics and differences between the three subgroups. As expected, almost all variables were distributed differently across the three groups. In terms of socio-demographic features, "fence sitters" were younger (M_{Age} = 43.1, SD = 11.9) than "accepters" or "rejecters" (M_{Age} = 50.5 and 49.9, SD = 11.8 and 11.9, respectively) ($p < 0.001$). Significant differences were also found between groups in terms of education, with "fence sitters" and "rejecters" having the lowest level of education and "accepters" having the highest; occupational status, with "fence sitters" showing a higher rate of unemployment; financial situations, which had low rate of improvement in the last 3 months for "fence sitters"; and COVID-19 experience, with "accepters" having more direct (10.3 vs. 7.5% of "fence sitters" and 5.8% of "rejecters," $p < 0.001$) and indirect (79.0 vs. 64.7% of "fence sitters" and 73.2% of "rejecters," $p < 0.001$) experience with the virus (i.e., had personally been infected or knew someone who contracted the virus). "Fence sitters" had the lowest rate of chronic diseases (17.1 vs. 30.4% in "rejecters" and 32.0% in "accepters," $p < 0.001$). These sociodemographic and clinical differences accurately reflect the official vaccination policy during the study period, when people who were first offered the vaccine (here divided into "accepters" and "rejecters") were predominantly older, had chronic diseases, were highly educated (e.g., health workers or teachers), or had priority in the vaccination campaign due to risks of the virus contagion and spread related to their job.

Psychological and behavioral factors and beliefs were distributed very clearly among groups, as shown in **Figure 2**: the CMQ scores range from "accepters" (lowest) to "rejecters" (highest), with "fence sitters" in the middle, while protective behaviors, trust and use of media and Health information sources, trust in Healthcare Institutions, agreement with restrictions and COVID-19 perceived risk have the opposite trend: from "rejecters" (lowest values) to "accepters" (highest values). In *post-hoc* comparisons there were no differences between "fence sitters" and "accepters" in terms of frequency use of media information sources.

The findings of the resilience tests are also intriguing, with "rejecters" scoring the highest value, and "accepters" scoring higher than "fence sitters," who are once again in the most unfavorable position (these differences, however, did not remain in the *post-hoc* comparisons).

The multinomial logistic regression models (**Table 2**) show that for every additional point of COVID-19 perceived risk, the probability of being a "rejecter" rather than a "fence sitter" was about halved (OR = 0.53, $p = 0.002$). There was also a link between trust and use of the media and health information sources, as well as agreement with restrictions, with each additional point lowering the probability of being a "rejecter" rather than a "fence sitter" by ∼30 to 40%. Higher protective behaviors, trust in Healthcare Institutions and agreement with restrictions were also associated to a greater probability of being a "fence sitter" rather than a "rejecter" (OR = 0.76, $p = 0.049$, OR = 0.75, $p = 0.042$ and OR = 0.58, $p = 0.002$, respectively). The CMQ scores was no longer significantly associated with being a "fence sitter" rather than a "rejecter" after covariates adjustment.

Increases in specific psychological and behavioral factors were linked to a higher probability of being an "accepter" rather than a "fence sitter." These factors are: trust in healthcare institutions (OR = 1.75, $p = 0.002$) and trust and frequency of use of health information sources (OR = 1.79, $p = 0.002$ and OR = 1.89, $p = 0.002$, respectively), trust in media information sources (OR

TABLE 1 | Sociodemographic, psychological, belief and behavioral differences between "Rejecters," "Fence sitters" and "Accepters".

	"Rejecters" (*N* = 138, 6.8%*)	"Fence sitters" (*N* = 575, 28.5%*)	"Accepters" (*N* = 1,302, 64.6%*)	*p*-value	*Post hoc*
Socio-demographic information					
Age (years; mean, SD)	49.9 (11.9)	43.1 (11.9)	50.5 (11.8)	**<0.001**	**FS<A/R**
Gender (n, % Male)	69 (50.0%)	272 (47.3%)	645 (49.5%)	0.649	
Education				**<0.001**	
0–8 years (*n*, %)	64 (46.4%)	264 (45.9%)	394 (30.2%)		
9–13 years (*n*, %)	49 (35.5%)	225 (39.1%)	532 (40.9%)		
>13 years (*n*, %)	25 (18.1%)	86 (15.0%)	376 (28.9%)		
Working (*n*, % yes)	81 (58.7%)	285 (49.6%)	713 (54.8%)	0.052	
Being health worker (*n*, % yes)	5 (6.2%)	5 (1.8%)	136 (19.1%)	**<0.001**	
Chronic disease (*n*, % yes)	42 (30.4%)	98 (17.1%)	416 (32.0%)	**<0.001**	
Economic situation in last 3 months				**<0.001**	
Improved (*n*, %)	9 (6.7%)	22 (3.9%)	62 (4.8%)		
Remained the same (*n*, %)	87 (64.4%)	300 (53.5%)	884 (68.6%)		
Worsen (*n*, %)	39 (28.9%)	239 (42.6%)	342 (26.6%)		
Wellbeing status				**0.013**	
Good WB (*n*, %)	61 (44.2%)	215 (37.4%)	597 (45.9%)		
Poor WB (*n*, %)	39 (28.3%)	180 (31.3%)	374 (28.7%)		
Depression (*n*, %)	38 (27.5%)	180 (31.3%)	331 (25.4%)		
COVID-19 experience					
Personal experience (*n*, % yes)	8 (5.8%) [4.3%]**	43 (7.5%) [23.2%]**	134 (10.3%) [72.5%]**	**<0.001**	
Experience of acquaintances (*n*, % yes)	101 (73.2%) [6.7%]**	372 (64.7%) [24.8%]**	1,029 (79.0%) [68.5%]**	**<0.001**	
Conspiracy Mentality Questionnaire score (mean, SD)	25.0 (5.3)	23.7 (4.8)	22.2 (5.5)	**<0.001**	**R>FS>A**
Protective behaviors (mean, SD)	−0.4 (1.2)	−0.1 (1.0)	0.1 (0.8)	**<0.001**	**R<FS<A**
Trust in Media Information sources (mean, SD)	−0.4 (1.2)	−0.1 (0.9)	0.1 (0.9)	**<0.001**	**R<FS<A**
Trust in Health Information sources (mean, SD)	−0.7 (1.2)	−0.3 (0.9)	0.2 (0.9)	**<0.001**	**R<FS<A**
Frequency use media information sources (mean, SD)	−0.3 (0.9)	0 (0.8)	0 (0.9)	**<0.001**	**R<FS/A**
Frequency use Health information sources (mean, SD)	−0.7 (1.0)	−0.3 (0.9)	0.2 (0.9)	**<0.001**	**R<FS<A**
Trust in Healthcare Institutions (mean, sd)	−0.6 (1.2)	−0.3 (0.9)	0.2 (0.9)	**<0.001**	**R<FS<A**
Agreement with restrictions (mean, SD)	−0.5 (1.1)	−0.1 (0.8)	0.1 (0.9)	**<0.001**	**R<FS<A**
COVID-19 Perceived risk (mean, SD)	−0.3 (1.0)	−0.1 (0.8)	0.1 (0.7)	**<0.001**	**R<FS<A**
Resilience (mean, SD)	0.1 (1.1)	−0.1 (0.8)	0 (0.9)	**0.042**	**/**

*Percentages refer to the total sample included in these analyses (N = 2,015).
**Percentages refer to the total of COVID-19 Personal experience (N = 185) and of acquaintances (N = 1,502).
R, "Rejecters"; FS, "Fence sitters"; A, "Accepters".
Bold values refer to p value < 0.05.

= 1.18, $p = 0.044$) and agreement with restrictions (OR = 1.27, $p = 0.006$). The effects of protective behaviors (OR = 1.20, $p = 0.036$) were still significant. On the contrary, a lower Conspiracy Mentality Questionnaire (OR = 0.94, $p = 0.002$) was associated with a higher probability of being an "accepter" rather than a "fence sitter." After covariates adjustment, COVID-19 perceived risk was no longer significantly associated with being a "fence sitter" rather than an "accepter." **Figure 3** shows an overview of the findings of the multinomial logistic regression models.

DISCUSSION

Our study found that several factors have been linked to acceptance, fence sitting, or refusal of the COVID-19 vaccine. These include sociodemographic features (such as age, education, economic situation, having a chronic disease, COVID-19 experience), psychological wellbeing, attitudes and beliefs (such as trust in media sources and institutions, trust in institutions, agreement with restrictions, COVID-19 perception risk, conspirative mentality) and behaviors (i.e., protective behavior against the virus, frequency of use of media or institutional informational sources).

Sociodemographic Factors

Our findings imply that the three identified subgroups have significant differences in some sociodemographic features. Indeed, the majority of "fence sitters" were mainly young people with a low educational level, worsened economic situation in the

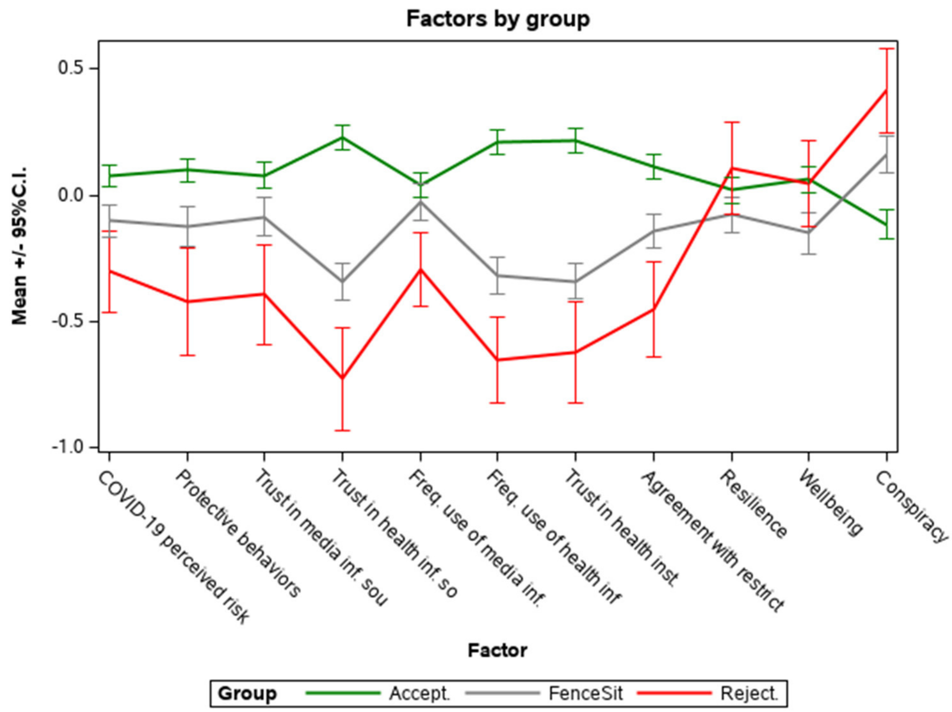

FIGURE 2 | Average scores of factors in the three groups (Accepters, Fence Sitters, and Rejecters)*. *To facilitate visualization and interpretation, Wellbeing and Conspiracy scores were standardized. Error bars represent 95% confidence intervals.

preceding 3 months, lower rates of both employment as health workers and chronic diseases. No differences between the three groups were found for gender and working status. At odds with this finding, other studies suggested that there is an association between female gender and vaccine hesitancy (12, 16, 18, 19, 22–24). Our results were consistent with previous studies that linked COVID-19 vaccine hesitancy to sociodemographic factors such as younger age (16–21), lower education (16, 18, 30) and lower income (16, 20, 30).

Our results highlight the relevance of education in affecting vaccination behavior and attitudes (i.e., only 15.0% of "fence sitters" had an education level > 13 years, *compared with* 28.9% of the "accepters"). Indeed, we suppose that low education may be linked to poor health literacy, which is related to the ability to obtain, process and understand essential health information and services required to make informed health decisions (42). As a result of this shortcoming, there may be misunderstanding and uncertainty, reducing the willingness to get vaccinated.

Furthermore, we found that economic situations may have a significant impact on the decision to get vaccinated. This may be because individuals who did not experience economic difficulties as a result of the pandemic felt "protected" by the government and were more prone to trust and agree with government policies (i.e., including vaccination campaign).

In addition, we found that "accepters" reported higher rates of both direct and indirect experience with COVID-19 infection than vaccination skeptics; closer interaction with the virus may contribute to a greater risk perception and sensitivity to the need of protecting themselves. However, this point should be further investigated because it contradicts previous results that people who believed they had COVID-19 were less likely to report following lockdown measures (43), and people who had COVID-19 with severe symptoms were more hesitant to take the vaccine than people who did not experience the disease at all (44).

Psychological Wellbeing

When compared to the "accepters," the "fence sitters" group reported lower rates of wellbeing status. Individuals with psychological difficulties may vacillate in their decision to get vaccinated due to maladaptive behavior (i.e., reduced medical seeking, lower prevalence of health-protecting behavior, poor self-care and noncompliance with medical prescriptions), which is common among them (45, 46). Individuals with psychological difficulties may be more hesitant to self-protect and follow the vaccination campaign as a result of this predisposition. However, to the best of our knowledge, only a few studies have investigated the relationship between psychological status and COVID-19 vaccination intentions or behavior. Batty et al. (47) discovered that having a pre-pandemic diagnosis of anxiety or depression, or a high score on the distress symptom scale, had no influence on vaccine willingness. Therefore, our findings highlight that "fence sitters" had the highest psychological burden and for these reasons, they require specific attention in light of ongoing vaccination campaigns.

TABLE 2 | Likelihood of being in the "*Rejecters*" or "*Accepters"* respect to "*Fence sitters"* group: output of the multinomial logistic regression models (one for each factor).

Rejecters	OR*	95% C.I.*	*p*-value**	Nagelkerke's R^2
Wellbeing status				0.226
Good WB (*n*, %)	1 (ref)			
Poor WB (*n*, %)	1.17	0.62–2.21	0.653	
Depression (*n*, %)	1.15	0.61–2.18	0.685	
Protective behaviors	0.76	0.59–0.97	**0.049**	0.237
Trust in Media Information sources	0.72	0.55–0.95	**0.040**	0.237
Trust in Health Information sources	0.71	0.55–0.92	**0.024**	0.297
Frequency use media information sources	0.69	0.51–0.94	**0.038**	0.231
Frequency use Health information sources	0.61	0.46–0.81	**0.002**	0.317
Trust in Healthcare Institutions	0.75	0.59–0.97	**0.042**	0.288
Agreement with restrictions	0.58	0.44–0.78	**0.002**	0.255
Conspiracy Mentality Questionnaire	1.02	0.97–1.08	0.415	0.246
COVID-19 Perceived risk	0.53	0.38–0.75	**0.002**	0.240
Resilience	1.17	0.88–1.54	0.333	0.223
Accepters	**OR***	**95% C.I.***	***p*-value****	**Nagelkerke's R^2**
Wellbeing status				0.226
Good WB (*n*, %)	1 (ref)			
Poor WB (*n*, %)	0.92	0.63–1.34	0.693	
Depression (*n*, %)	0.73	0.50–1.06	0.120	
Protective behaviors	1.20	1.02–1.41	**0.036**	0.237
Trust in Media Information sources	1.18	1.00–1.39	**0.044**	0.237
Trust in Health Information sources	1.79	1.51–2.13	**0.002**	0.297
Frequency use media information sources	1.08	0.91–1.29	0.389	0.231
Frequency use Health information sources	1.89	1.59–2.26	**0.002**	0.317
Trust in Healthcare Institutions	1.75	1.47–2.08	**0.002**	0.288
Agreement with restrictions	1.27	1.07–1.51	**0.006**	0.255
Conspiracy Mentality Questionnaire	0.94	0.91–0.97	**0.002**	0.246
COVID-19 Perceived risk	1.09	0.89–1.34	0.361	0.240
Resilience	1.00	0.85–1.17	0.954	0.223

Adjusted for age, chronic disease, educational level, working status, health-working status, economic situation in last 3 months and COVID-19 experience.
**Bootstrap results, based on 500 bootstraps samples.*
Bold values refer to p value < 0.05.

Attitudes and Beliefs

We observed that trust in both media and health information sources and in healthcare institutions, as well as agreement with restrictions, conspirative mentality and COVID-19 perception risk, were all associated with vaccine behavior or attitudes. Lower levels of trust in media and health information sources and in healthcare institutions, as well as agreement with restrictions, and higher levels of conspiracy mentality, were all linked to a higher likelihood of being in the "fence sitters" group rather than the "accepters" group. Additionally, a higher level of trust in both media and health information sources, as well as in healthcare institutions, agreement with restrictions and an increased COVID-19 risk perception were associated with a higher likelihood of being in the "fence sitters" group rather than the "rejecters" group.

Our results are in line with previous studies indicating an association between COVID-19 vaccine hesitancy and adherence to conspiracy theories (14, 16, 18, 29, 48), poor perception of government measures (20) and a lack of trust/confidence in scientists, healthcare personnel, health institutions and/or the government (12, 16, 20, 22, 28). Furthermore, past research has revealed that conspiracy theories can harm trust in authorities and institutions (49, 50), as well as act as barriers to health protective behavior, including unwillingness to vaccinate (14, 48, 50–53).

We found that "rejecters" had lower COVID-19 perceived risk than "fence sitters" and "fence sitters" had lower COVID-19 perceived risk than "accepters." Furthermore, increased COVID-19 perceived risk was linked to a higher likelihood of being in the "fence sitters" group rather than the "rejecters" group, even after adjusting for sociodemographic factors. Interestingly, vaccine "accepters" reported the highest levels of COVID-19 perception risk even if their got vaccinated. We may argument that probably this may be a trait-related perception that led them to choose vaccination as protection. Moreover, it is possible that "rejecters" may not have trusted the available information concerning the severity of the COVID-19 virus and hence perceived a low risk. Indeed, earlier research focusing on groups with significant vaccine hesitancy has reported the belief that risks related to the COVID-19 pandemic had been exaggerated by the media and that the pandemic would not last long (25). Indeed, previous studies on vaccine hesitancy (covering both "rejecters" and "fence sitters") indicated that this group has a low perceived risk (16, 18, 24, 26). Our study may allow a better distinction in risk perception between those who refused and those who were uncertain about their future decision, pointing to a higher perceived risk in those who were unsure about their future decision.

Behavioral Factors

We found that a higher frequency of using health informational sources, and higher rates of protective behavior were linked to a higher likelihood of being a vaccine "accepter" rather than a "fence sitter." This finding is consistent with earlier research that identified a link between vaccine hesitancy and either a lesser use of traditional and authoritative information sources (27) or a higher use of media information sources (29, 54). During a global emergency, the frequency with which different information sources, particularly institutional ones, are used is critical. A low rate of usage of institutional information sources

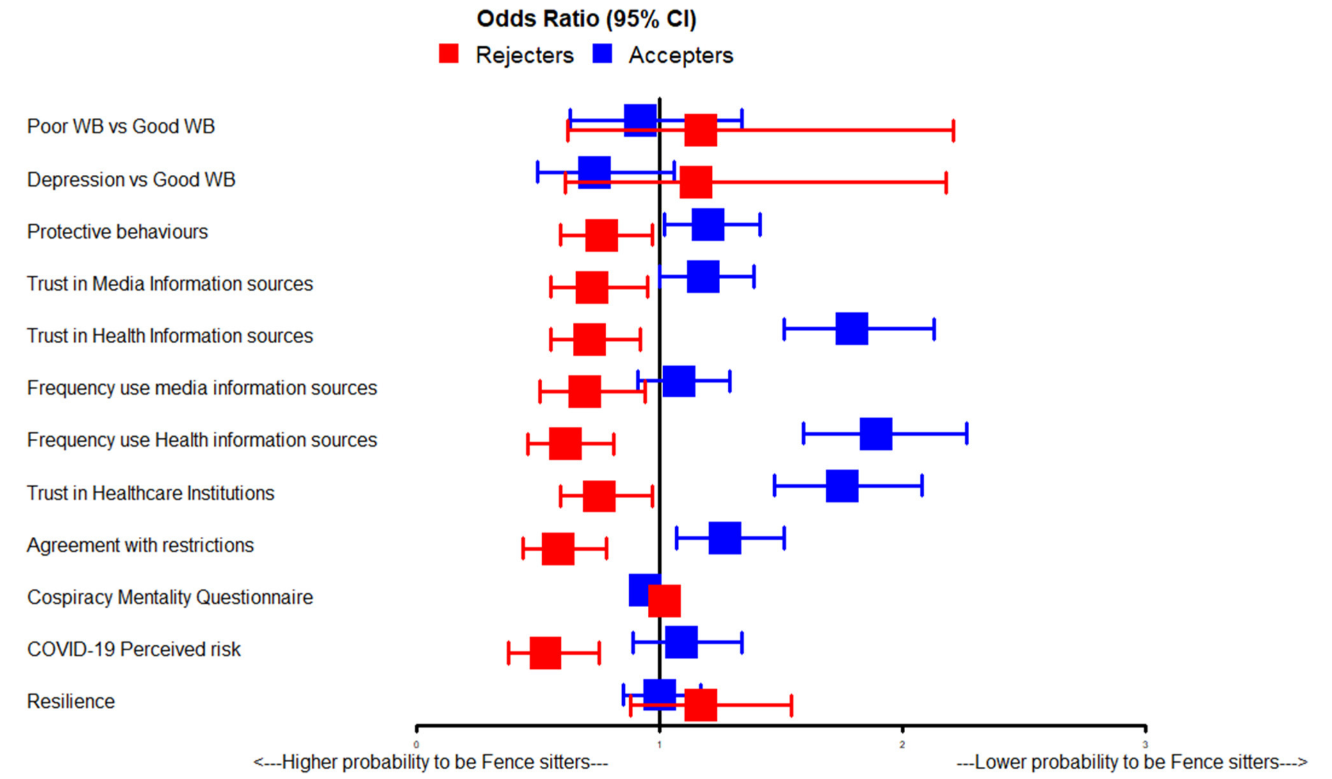

FIGURE 3 | Graphical representation of ORs (and 95%CI) of the multiple logistic regression models.

may be associated with vaccine reluctance because people are misinformed about vaccines and their efficacy, and they regard them as something out of their control.

We also discovered that "fence sitters" reported COVID-19 associated protective behavior that was lower than to vaccine "accepters" but higher than that of vaccine "rejecters," which could be related to the trend of risk perception among three groups. We suppose that protective behaviors are closely linked to the risk perception: indeed, an increased risk perceived may be associated with an higher probability that protective behaviors, including vaccination, are implemented.

Limitations

The length of the survey was the study's principal constraint. Indeed, the COVID-19 vaccine was only offered to specific population groups in Italy in March, April and May 2021 (i.e., healthcare workers, older people, individuals with chronic and disabling diseases and educational staff), as shown by the socio-demographic characteristics of the three groups studied. This limitation may limit the generalizability of these findings to the whole Italian population. To reduce selection bias, we adjusted multinomial logistic regression for all sociodemographic features which were linked to vaccination rates. Therefore, the logistic regression models were adjusted for age, gender, chronic disease, educational level, working (and health-working) status, economic situation in the last 3 months and COVID-19 infection. In this way we were able to manage the potential confounding effect caused by the disparity between the two groups who were offered the vaccination ("accepters" and "rejecters") and those who were not yet offered the vaccination ("fence sitters") and were assessed about their willingness to get vaccinated in the future.

Furthermore, in the case of "fence sitters," we only assessed a snapshot of vaccination views at a single point in time, when vaccination had not yet been proposed to them; thus, we have no way of knowing how vaccine attitudes may evolve in response to circumstantial or individual changes (e.g., COVID-19 spread, economic changes or personal experiences). Finally, the representativeness of the Italian adult population is limited to individuals under the age of 70 who have access to the Internet. Unfortunately, during a pandemic conducting face to face interviews is not recommended since it may favor subjects exposure to the risk of contagion, and for this reason the conduct of an online questionnaire administration was a mandatory choice. The missed involvement of older people and people not acquainted with ITC devices was a necessary limitation to prevent Covid-19 and to promote good health practice.

CONCLUSIONS

The WHO has stated that media messaging about public health issues can have a huge impact on individual behavior. Therefore, the results of this study may be useful in informing governments and addressing specific media communication strategies, particularly for those who are uncertain about getting vaccinated against COVID-19. Specific communication strategies should be developed to improve the frequency of use and trust in health information sources, as well as to alleviate the concerns of vaccine skeptics. The profile of "fence sitters" that emerged from this study is particularly interesting because it highlights a specific profile of a young person, who is poorly educated, has economic difficulties, and is particularly concerned about the pandemic in terms of subjective psychological distress. People in their early 40 s who are poorly educated and have economic difficulties should be the sociodemographic target profile of public programmes aimed at improving vaccine campaign adherence. Given the "fence sitter" group's characteristics, it is likely that this segment of the population is most concerned about the possible side effects of vaccines. From this perspective, targeted information about the vaccinations' potential side effects could persuade a significant number of "fence sitters" to get vaccinated. According to the "five Cs," to combat vaccine hesitancy (55), communication strategies and public programmes should emphasize the following features: Confidence (i.e., vaccines are important, safe and effective); Complacency (i.e., perception of low risk and disease severity); Convenience (i.e. access issues based on the context, time and specific vaccine being offered); Communications (i.e., decreasing misinformation and infodemic); and Context (i.e., sociodemographic characteristics). To address the public's concerns and build confidence, a true transparent communication is essential.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. Datasets and codes are available here: http://doi.org/10.5281/zenodo.5040719.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRCCS San John of God Fatebenefratelli of Brescia (no. 72-2020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GG: funding acquisition, conceptualization, methodology, original draft, and writing—review and editing. CZ, MZ, CF, and VC: conceptualization, methodology, data curation, data analysis, original draft, writing—review, and editing. Md'A: conceptualization, original draft, and writing—review and editing. GC, FS, MC, TG, LL, and AT: writing—review and editing. All authors contributed to the article and approved the submitted version.

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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.2022.873098/full#supplementary-material

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OPINION
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Omicron: A Blessing in Disguise?

Esayas Kebede Gudina[1], Solomon Ali[2] and Guenter Froeschl[3,4]*

[1] Department of Internal Medicine, Jimma University Institute of Health, Jimma, Ethiopia, [2] Department of Microbiology, Immunology and Parasitology, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, [3] Division of Infectious Diseases and Tropical Medicine, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany, [4] Center for International Health, Ludwig-Maximilians-Universität, Munich, Germany

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Two years after the first reported case and a year after the first shot of an effective vaccine, COVID-19 remains a major global threat and source of uncertainties. Although many thought a year ago that 2022 would be the year to return to normalcy, the world welcomed the New Year with record number of daily new cases in most countries. This is happening while we are having 10 vaccines approved for use by the World Health Organization (1) and some 64.5% of the global population has already taken at least a dose of one of the vaccines (2). The success against the pandemic was undermined by an inequitable distribution of the vaccines (3) and evolution of highly transmissible variants of the virus (4). Today while most of the wealthy countries have provided a booster dose vaccination for at least a third of their population (2), only 14% of the population in Africa has received the first shot (5). Paradoxically, there is a relevant proportion of the population, especially in high-income countries, that oppose getting immunized, as part of the no-vax movement (6).

The onset of November 2021 saw many countries relaxing their COVID-19 travel restrictions. However, the announcement of B.1.1.529 (Omicron), a highly mutated variant, by WHO on 26 November 2021 as variant of concern (7) led to an epidemiological situation that the world was not quite prepared for. This soon led to many countries reimposing their restrictions. Although mutations leading to new variants are evolutionary features of the virus (8), such occurrences remain a major setback even in an era where the world disposes of ever more tools to fight infectious diseases. The Delta variant (B.1.617.2) was first discovered in India in late 2020, spread to 179 countries and became the dominant variant globally in less than a year. It caused more infections, hospitalizations, and deaths globally specially among unvaccinated people than previous variants (9). This happened when there were effective vaccines already widely available.

Since its discovery in November 2021, the Omicron variant is spreading at an unprecedented rate, surpassing all previous variants (10). It is now the predominant variant circulating globally, due to its so far milder course of illness, and its potential to escape from vaccine-induced immune-responses (11). Omicron has several sub-lineages of which BA.1 and BA.2 are the most common ones (12). Although BA.1 has been the predominant Omicron sub-lineage until recently, the relative proportion of BA.2 sub-variant is increasing in several countries in the past few months (13). It is thought to be more transmissible and shorter doubling time than BA.1 (14). Existing evidence also shows that the BA.2 sub-variant has an even more pronounced immune escape capacity and higher resistance to existing treatments (15). Despite these facts, Omicron in general is associated with lower risk of severe disease, hospitalization (16), and death than the previous variants such as Delta (17).

Controlling the spread of Omicron has been found to be more challenging due to the diverse nature of the subvariants. Most infected people have milder symptoms and therefore may continue their social interactions, infecting many others in the process. The proportion of infected individuals ending up in hospitals and ICU as well as dying of COVID-19 may be lower than the previous circulating variants, but the absolute number may be much higher due to the sheer incidence of infections. Thus, the Omicron variant may ultimately result in a much higher pressure

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Roger Nlandu Ngatu, Kagawa University, Japan

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Amin Talebi Bezmin Abadi, Tarbiat Modares University, Iran

****Correspondence:***
Esayas Kebede Gudina
esakgd@gmail.com

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on public health systems than previous variants especially in resource limited settings. The surge of the new sub-lineages such as BA.2 may even prolong and aggravate the current Omicron wave (14).

On the other hand, the fact that this variant has milder symptoms may result in more people (vaccinated or unvaccinated) getting the infection with relatively lower health impact as per case. This may ultimately lead to widespread immunity in a faster way. Although the degree of protective immunity conveyed by natural infections from previous variants is not clear yet, recurrent infections and break-through infections in vaccinated people may lead to more robust immune responses (18).

The full picture of the upcoming months may reveal a high rate of transmission and at the same time a low proportion of severe disease and death. Hence, in a few months we may be able to approach some form of global herd immunity that would at least prevent severe diseases and death downstream, realizing the initial assumption that 2022 may become a year of return to normalcy, and SARS-CoV-2 becoming a member of the group of globally endemic flu-like infections (19).

GLOBAL SURGE OF BA. 2 SUBVARIANT AND THE LOOMING UNCERTAINTIES

Although close to two third of the world population and over 80% of the population in the high-income countries have received at least one dose of COVID-19 vaccine (2), more daily new cases of COVID-19 are being reported globally than in the pre-vaccine era (20). The BA.2 subvariant, known to cause widespread infection even among vaccinated and previously infected individuals, is deriving the current wave (21). One of the features of this variant is the difficulty to track it with the current common tests and hence known as "Stealth Omicron". Even though the standard real time PCR is able to detect BA.2, it may not be able distinguish it from the Delta variant (22). Thus, it may be underreported in settings where genomic sequencing is not performed routinely to track the variants.

While the full virological characteristics and epidemiology of the of BA.2 is still unfolding, it is spreading at an overwhelming rate than the previous variants (14). It is now the predominant variant globally and a cause of new peaks in countries with high vaccination coverage in Europe and Asia (20, 21). The lifting of COVID-19 restrictions in many countries has led to this recent surge due to BA.2.

Despite the unprecedented surge, this subvariant is not associated with more severe disease, hospitalization, and death than BA.1 and previous variants (16, 17). However, due to the waning immunity from vaccination and previous infections, and relaxation of most of the restrictions globally, it is possible to have another wave of the outbreak among unvaccinated population. Nevertheless, major health system crisis due to the outbreak is less likely to happen because of some form of immunity from vaccinations and previous infections (23).

Regardless of this optimism, the global action against the pandemic remains fragile as ever and mired with uncertainties. As we have seen in the past several months, new variants are evolving more frequently and BA.2 will not be the last one. As a result, SARS-CoV-2 remains a serious global public health issue and the world should remain vigilant to deal with the most likely new variants in the future. Boosting immunity against the virus through vaccination (24) and cutting its spread through non-pharmacological methods such as mask use (25) remain the most powerful and proven means to deal with the evolutionary adaptability of the virus.

The fight against the virus thus needs concerted global action through equitable distribution of vaccines, dealing with vaccine hesitancy, and optimizing non-pharmacological preventive interventions until the pandemic is under control at least to a degree that is not detrimental to health systems. The global community will benefit more from ensuring that as many people as possible are immunized globally, rather than from nation-states cocooning and stockpiling vaccines for their defined populations. This is true both from an ethical as well as from an epidemiological point of view. Countries should also put in place strategies to closely monitor and track SARS-CoV-2 emerging variants.

AUTHOR CONTRIBUTIONS

EG wrote the first draft. SA and GF reviewed the manuscript for intellectual contents. All authors have approved the manuscript in the current version.

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Social Contacts and Transmission of COVID-19 in British Columbia, Canada

Notice Ringa[1,2]*, *Sarafa A. Iyaniwura*[1,3], *Samara David*[1], *Mike A. Irvine*[1,4], *Prince Adu*[1,2], *Michelle Spencer*[1], *Naveed Z. Janjua*[1,2] and *Michael C. Otterstatter*[1,2]

[1] Data and Analytic Services, British Columbia Centre for Disease Control, Vancouver, BC, Canada, [2] School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada, [3] Department of Mathematics, Institute of Applied Mathematics, University of British Columbia, Vancouver, BC, Canada, [4] Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada

Background: Close-contact rates are thought to be a driving force behind the transmission of many infectious respiratory diseases. Yet, contact rates and their relation to transmission and the impact of control measures, are seldom quantified. We quantify the response of contact rates, reported cases and transmission of COVID-19, to public health contact-restriction orders, and examine the associations among these three variables in the province of British Columbia, Canada.

Methods: We derived time series data for contact rates, daily cases and transmission of COVID-19 from a social contacts survey, reported case counts and by fitting a transmission model to reported cases, respectively. We used segmented regression to investigate impacts of public health orders; Pearson correlation to determine associations between contact rates and transmission; and vector autoregressive modeling to quantify lagged associations between contacts rates, daily cases, and transmission.

Results: Declines in contact rates and transmission occurred concurrently with the announcement of public health orders, whereas declines in cases showed a reporting delay of about 2 weeks. Contact rates were a significant driver of COVID-19 and explained roughly 19 and 20% of the variation in new cases and transmission, respectively. Interestingly, increases in COVID-19 transmission and cases were followed by reduced contact rates: overall, daily cases explained about 10% of the variation in subsequent contact rates.

Conclusion: We showed that close-contact rates were a significant time-series driver of transmission and ultimately of reported cases of COVID-19 in British Columbia, Canada and that they varied in response to public health orders. Our results also suggest possible behavioral feedback, by which increased reported cases lead to reduced subsequent contact rates. Our findings help to explain and validate the commonly assumed, but rarely measured, response of close contact rates to public health guidelines and their impact on the dynamics of infectious diseases.

Keywords: social contacts, COVID-19, transmission control, correlation, regression

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Roger Nlandu Ngatu,
Kagawa University, Japan

Reviewed by:
Ross Gore,
Old Dominion University, United States
Biswaranjan Paital,
Orissa University of Agriculture and Technology, India

****Correspondence:***
Notice Ringa
notice.ringa@bccdc.ca

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INTRODUCTION

A wide variety of infectious respiratory diseases, including influenza, measles, plague, tuberculosis and the new and ongoing Coronavirus Disease 2019 (COVID-19), are transmitted largely through close-contact and spread based on the social contacts and mixing patterns of the host population (1–3). Effective contacts (interactions that allow pathogen transfer between individuals) typically involve inhalation of infectious secretions from coughing, sneezing, laughing, singing or talking, but may also include touching contaminated body parts or surfaces followed by ingestion of the pathogen (4). Control strategies against such infections are based on contact avoidance measures, including isolation of those who are ill, use of personal protective equipment such as gloves and face masks, and physical distancing (5, 6). In this study, we examine the relations between self-reported social contact patterns, public health control measures, and the dynamics of COVID-19 in the province of British Columbia (BC), Canada. The history and epidemiological features of COVID-19 have been documented by several studies including in (7–14), and we present a summary of these as well as conventional COVID-19 transmission control measures in **Appendix 1**.

A small number of studies, including in (15–18), have analyzed population patterns of social contacts, and their connection to the dynamics of close-contact infectious diseases. Overall, the studies show that disease incidence and effective reproduction number (average number of newly infected individuals per case) increase with contact rates. However, contact rates and their effects on infection dynamics may vary over time and with factors such as geographical location, sex, age, household size, occupation and other socio-economic factors.

In our study, we explore and quantify associations between social contact patterns, public health orders, transmission, and reported cases of COVID-19, in BC and in the two most populous BC regional health authorities: Fraser Health Authority (FHA) and Vancouver Coastal Health Authority (VCHA) (19). We make use of detailed contact survey data and estimate transmission using a model-based metric of the time-varying reproductive number, *Rt*. We specifically consider data from autumn of 2020 onward, during which a series of regional and provincial public health orders were introduced to reduce the number of close contacts and curb transmission.

METHODS

We studied the association between close-contact rates [based on the BC Mix COVID-19 Survey data, which is summarized in **Appendix 2** and described in detail in (20)], daily new confirmed COVID-19 cases [obtained from BC COVID-19 data, which is provided by the BC Centre for Disease Control (21), and also available at (22)] and R_t [derived by fitting the *covidseir* transmission model of (7), where R_t was computed using the Next-Generation matrix method (23, 24), to the reported case data] in BC, from September 13, 2020 to February 19, 2021, a period in which three public health contact-restriction orders were introduced (October 26, November 7 and November 19). Further details of the public health orders are provided in **Appendix 3**. For each successive four-day period, we calculated (i) population rates of contact as the average number of self-reported close-contacts made by an individual in a day (average daily contacts); (ii) the average number of newly reported COVID-19 cases per day (average daily cases or new cases); and (iii) transmission rate of COVID-19 as the average daily value of our model-based estimate of R_t. We used segmented linear regression [described in **Appendix 4** and (25–27)] to investigate the impact of public health orders on the three variables. We used Pearson correlation [summarized in **Appendix 5** and described in detail in (28–31)] to assess the instantaneous relationship between contact rates and R_t. Finally, we used vector autoregressive (VAR) models [described in **Appendix 6** and in (32–35)] to quantify lagged associations between contact rates, new cases and R_t. All analysis was performed using R version 3.6.3. We use $\alpha = 0.05$ for all statistical tests.

RESULTS

Effects of Public Health Orders on Average Daily Contacts, Average Daily Cases and Transmission

Provincially, rising contact rates and transmission (R_t) reversed shortly after the first health order on October 26, 2020 (**Figures 1A,G**); for contacts, this declining trend lasted only until the second public health order (13 days later, on November 7), whereas for R_t, the decline continued to at least the third order (25 days later, on November 19).

Both contact rates and R_t were relatively stable after the third order until the end of our study period (February 19, 2021). As expected, the trend in new cases mirrored that of our transmission indicator but was shifted about 2 weeks later, corresponding to the delay between transmission to symptom onset followed by diagnosis, and case reporting (**Figures 1D–G**). The same patterns were generally apparent in both of the regional health authorities we studied, although declines in contact rates and R_t appeared to start roughly 1 week before the first public health order in FHA, and roughly 1 week after the first order in VCHA (**Figures 1B–I**). Simple comparison of overall contact rates and R_t before and after the introduction of public health orders indicated that in BC, FHA and VCHA, contact rates declined by 30.1, 29.2, and 29.9%, while R_t declined by 17.9, 25.0, and 5.4%, respectively, following the first public health order onwards.

Our segmented linear regression models showed that in BC, FHA and VCHA, the slope of the contact rate regression line was positive before the first public health order, turned substantially negative thereafter and slightly increased, but remained negative or close to zero through all other health orders (**Table 1**).

The changes in contact rate slope after the first public health order (i.e., $\Pi_1 \leq t \leq \Pi_2$) were statistically significant in the province and in VCHA ($p < 0.05$), but not in FHA. Provincially and in the two regional health authorities, the changes in contact rate slope following the second and the third health orders (i.e., $\Pi_2 \leq t \leq \Pi_3$ and $t \geq \Pi_3$) were not statistically significant (*p*

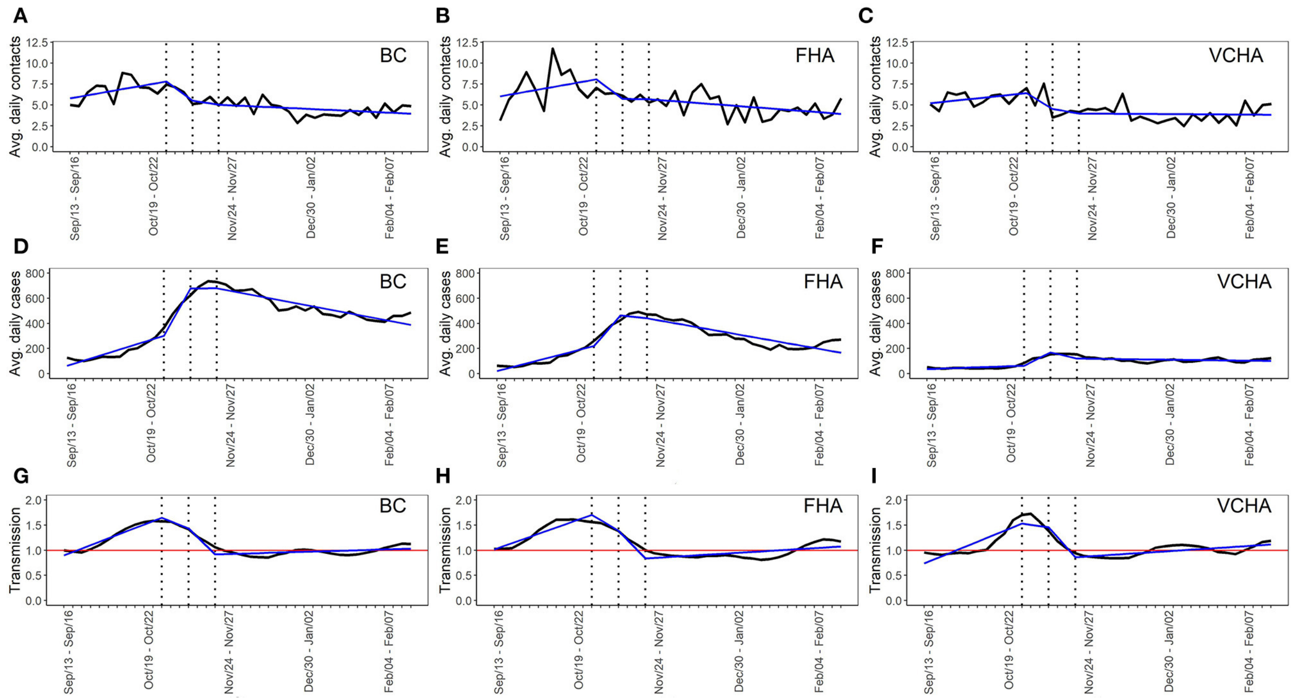

FIGURE 1 | Time series of average daily contacts (contact rates), average daily cases (new cases) and transmission (R_t) of COVID-19 in BC **(A,D,G),** FHA **(B,E,H)** and VCHA **(C,F,I)** from September 13, 2020 to February 19, 2021. The vertical dotted lines indicate dates of announcement of public health contact-restriction orders on October 26, 2020, November 07, 2020 and November 19, 2020. Each plot contains derived segmented linear regression lines with three knots at the dates of introduction of the public health orders. Horizontal lines in the plots for transmission indicate the transmission threshold $R_t = 1$.

TABLE 1 | Slopes of regression lines of average daily contacts and transmission in the province and in FHA and VCHA, within the four time intervals separated by the three dates (Π_1, Π_2 and Π_3) of announcement of public health orders, based on associated model estimates β_1, β_2, β_3 and β_4 presented in **Supplementary Tables S3, S5** in **Appendix 4**.

	$t \le \Pi_1$	$\Pi_1 \le t \le \Pi_2$	$\Pi_2 \le t \le \Pi_3$	$t \ge \Pi_3$
Slope of BC average daily contacts	0.184**	−0.768***	−0.159	−0.048
Slope of FHA average daily contacts	0.185	−0.779*	−0.013	−0.079
Slope of VCHA average daily contacts	0.111	−0.634**	−0.182	−0.007
Slope of BC transmission	0.068***	−0.071***	−0.173***	0.005***
Slope of FHA transmission	0.063***	−0.105***	−0.184	0.011***
Slope of VCHA transmission	0.072***	−0.025***	−0.199***	0.011***

*$p < 0.1$; **$p < 0.05$; ***$p < 0.01$.

> 0.05). Provincially and in the two regional health authorities, the slope for transmission (R_t) was positive before the first public health order, turned negative after this order, decreased further following the second public health order, and stabilized after the third health order (**Table 1**). Changes in transmission slope following all public health orders were statistically significant ($p < 0.05$), except after the second health order in FHA.

Pearson Correlation of Average Daily Contacts and Transmission

Our correlation analysis showed that high contact rates and high transmission tended to occur at the same time. Provincially, and in both regional health authorities, transmission (average daily R_t) was significantly positively correlated with average daily contacts ($r^{BC} = 0.64$, p < 0.001); $r^{FHA} = 0.53$, p < 0.001; $r^{VCHA} = 0.34$, $p = 0.033$). Based on these values, the magnitude of the correlation was about 50% stronger in FHA compared to VCHA ($r^{FHA} = 1.56\times{}^{VCHA}$).

VAR Models of Average Daily Contacts and Average Daily Cases, and Average Daily Contacts and Transmission

The notations $BC_{contacts\_t}$, BC_{casest} and $BC_{transmission\_t}$ represent the (stationary) time series of average daily contacts, cases, and transmission, respectively, in BC. The corresponding notations for FHA and VCHA are similarly defined. Our

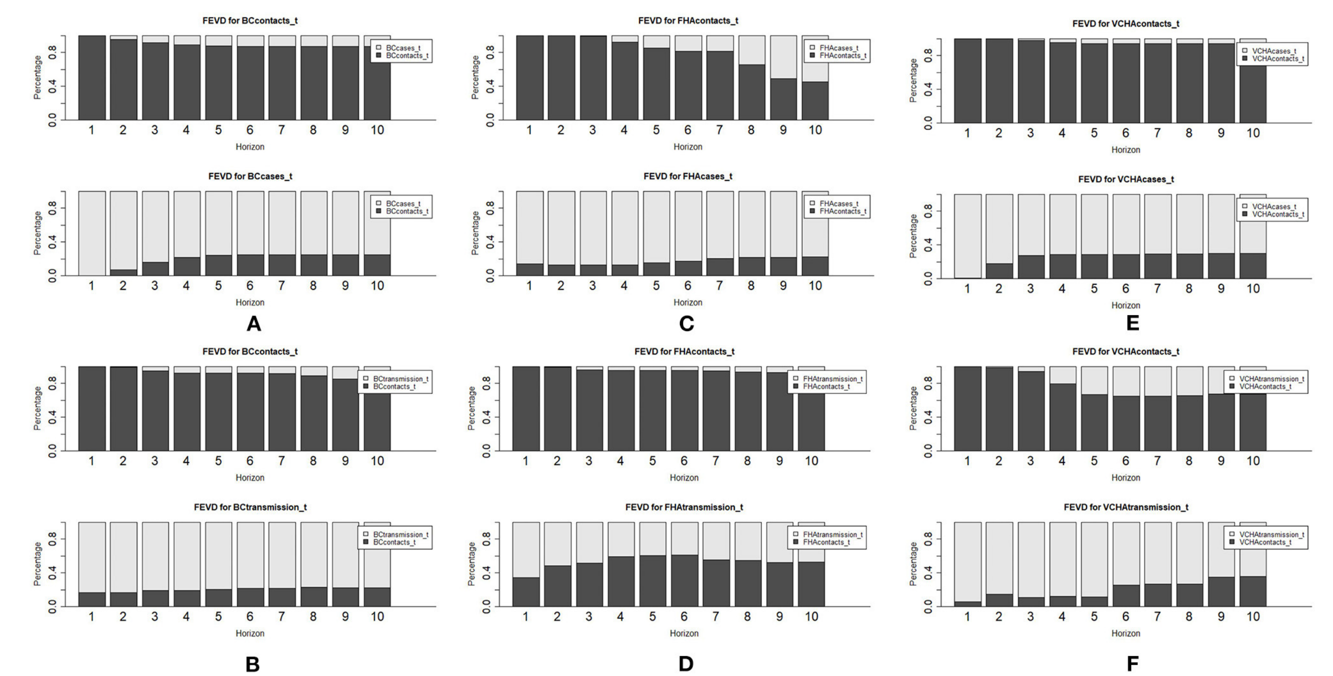

FIGURE 2 | Forecast error variance decomposition (FEVD) results for VAR models of average daily contacts and cases and average daily contacts and transmission in BC **(A,B),** FHA **(C,D)**, and VCHA **(E,F)**.

TABLE 2 | Granger causality test results for average daily contacts and average daily cases and average daily contacts and transmission, in BC and two health regions, FHA and VCHA.

$BC_{contacts\_t}$ G-causes BC_{cases_t} ($p = 0.006$)	$BC_{contacts\_t}$ does not G-cause $BC_{transmission_t}$ ($p = 0.945$)
BC_{cases_t} G-causes $BC_{contacts\_t}$ ($p = 0.049$)	$BC_{transmission_t}$ does not G-cause $BC_{contacts\_t}$ ($p = 0.544$)
$FHA_{contacts\_t}$ does not G-cause FHA_{cases_t} ($p = 0.519$)	$FHA_{contacts\_t}$ does not G-cause $FHA_{transmission_t}$ ($p = 0.574$)
FHA_{cases_t} G-causes $FHA_{contacts\_t}$ ($p = 0.001$)	$FHA_{transmission_t}$ does not G-cause $FHA_{contacts\_t}$ ($p = 0.582$)
$VCHA_{contacts\_t}$ G-causes $VCHA_{cases_t}$ ($p = 0.011$)	$VCHA_{contacts\_t}$ G-causes $VCHA_{transmission_t}$ ($p = 0.017$)
$VCHA_{cases_t}$ does not G-cause $VCHA_{contacts\_t}$ ($p = 0.537$)	$VCHA_{transmission_t}$ G-causes $VCHA_{contacts\_t}$ ($p = 0.023$)

time series models showed that variation in new cases and transmission of COVID-19 were significantly attributable to past values of average daily contacts, whereas variation in average daily contacts was explained largely by its own past values (**Figure 2**).

Each panel of the FEVD plots shown in **Figure 2** illustrates the proportion of variation in cases, contacts or transmission that is explained by that variable's own past values vs. the past values of other variables.

Provincially, on average, about 19% of the variation in average daily cases, and about 20% of the variation in COVID-19 transmission, was explained by previous rates of daily contact (**Figures 2A,B**). In FHA, previous average daily contacts contributed up to 22% of the variation in average daily cases (**Figure 2C**) and up to 61% of the variation in transmission (**Figure 2D**). In VCHA, up to 30% of the variation in average daily cases was explained by average daily contacts, whereas contact rates explained up to 36% of the variation in transmission (**Figures 2E,F**). **Supplementary Table S13** in **Appendix 6.5** shows numerical representations of all FEVD plots in **Figure 2**.

Granger causality testing confirmed that provincially and for VCHA, previous daily contacts were a significant time series driver of average daily cases (BC: $p = 0.006$, VCHA: $p = 0.011$), but the same did not hold for FHA (see **Table 2**). **Supplementary Figure S4** in **Appendix 6.5** provides a visual description of the Granger causality testing results in **Table 2**.

Our time series models also showed that some variation in average daily contacts was explained by previous average daily cases and transmission of COVID-19. Provincially, average daily cases and transmission explained up to 13% (or 10% on average) and up to 18%, respectively, of the variation in average daily contacts (**Figures 2A,B**). In FHA, past average daily cases contributed up to 55% of the variation in the contact rates (**Figure 2C**), whereas previous transmission rates contributed up to 7% to the variation in average daily contacts in (**Figure 2D**). In VCHA, the reverse was true with previous average daily cases explaining little (up to 6%) variation in average daily contacts, but transmission explaining up to 35% of the variation in average daily contacts (**Figures 2E,F**).

The impact of previous case counts on average daily contacts was significant at the provincial level and in FHA (BC: $p = 0.049$; FHA: $p = 0.001$), but not significant for VCHA. Past values of average daily contacts did not significantly impact transmission provincially or in FHA; however, these two variables were significantly associated in VCHA.

DISCUSSION

The primary approach to prevent the spread of many infectious diseases transmissible through close person-to-person contact is reduction or avoidance of such contacts altogether. Yet, few studies have quantified the impact that such contact-restrictions have on rates of "effective" contact (those actually involved in transmission) and on transmission itself. In our study, we explored time series relationships between close contact patterns and the dynamics of the ongoing COVID-19 pandemic in British Columbia, Canada and in its two most populous regional health authorities, FHA and VCHA, from mid-September, 2020 to mid-February, 2021. During this period, three public health contact-restriction measures were introduced (on October 26, November 7 and November 19) to control rising numbers of cases. We used data from the BC Mix Survey, which specifically captures rates of close contacts that are likely to underlie transmission. We analyzed contact rates in relation to the timing of contact-restriction measures and assessed their impact on COVID-19 transmission (average daily number of new infections generated per case, R_t) and reported new cases.

We found that in BC, FHA and VCHA, all three public health orders reduced contact rates and transmission, or helped to maintain lowered rates. Overall, declines in contact rates and transmission occurred concurrently with the announcement of public health orders, whereas declines in newly reported cases were, as expected due to reporting delays, lagged by roughly 2 weeks. The decline we observed in contact rates in FHA about 1 week prior to the public health orders could have resulted from public anticipation and early media reporting of the upcoming restriction orders and/or from reports of rising numbers of new cases of COVID-19. Contact rates declined by roughly 30% overall after the first public health order. Transmission similarly declined in response to these orders, although this effect varied by region (R_t reduced by 17.9, 25.0, and 5.40% in BC, FHA and VCHA, respectively). This observation suggests that compliance to public health orders by limiting the frequency of person-to-person contacts played an important role in reducing the transmission of COVID-19. In all regions, transmission curves mirrored, and were highly correlated with those of contact rates, suggesting that these self-reported rates of close contact were directly and concurrently related to spread of COVID-19. Through time series analysis, we showed that lagged daily contacts significantly predicted, and explained roughly 19% of the variation in subsequent new cases at the provincial level. Interestingly, we also found evidence of behavioral feedback at the population level, whereby increased reported cases led to reduced subsequent rates of contact: overall, previous daily cases explained about 10% of the variation in subsequent daily contacts in the province. The interdependence of previous contact rates, new cases and transmission of COVID-19 varied by region.

It is important to note that our time series analysis only assesses the impact of previous or lagged contacts on transmission and new cases, i.e., it does not include the impact of concurrent contacts. Hence, we find that previous contacts primarily impact numbers of new cases, where there is naturally a delay due to reporting, rather than rates of transmission (where the impact is expected to largely occur concurrently). However, we show through our correlation analysis that contacts and transmission are significantly concurrently related.

A few studies have quantified variation in transmission or cases of an infectious disease as a function of contact rates. For instance, in (16), the authors analyzed United Kingdom contact survey data during periods before and after the March 2020 lockdown due to the COVID-19 pandemic, and found that a model-derived effective reproduction number declined by 75% as a response to a 74% reduction in average daily contacts. In (15), the authors studied contact survey data from Belgium during different stages of intervention against COVID-19 and found that an 80% decline in the average number of contacts during the first lockdown period resulted in a decline of the effective reproduction number to below one, resulting in fewer reported new cases. In (36), the authors studied United Kingdom population mixing patterns during the 2009 H1N1 virus influenza epidemic and found that a 40% reduction in contacts among school children during school holidays resulted in about 35% decline in the reproduction number of influenza. These studies confirm a relation between self-reported contact rates and infectious disease transmission, but also show variation that may be due to epidemiological factors such as difference in the transmission environment (e.g., use of personal protective equipment) and the types of contacts being measured. Other studies that have explored the control of COVID-19 by management of social contacts include (37, 38), which indicated that the relatively low transmission rate of COVID-19 in India in early 2020, was attributable to public compliance to a strict government-imposed lockdown on social gatherings.

The possibility of a feedback mechanism in which contacts rates decrease as a result of increasing transmission and new cases, has been documented in some previous studies. For instance, during the 2014 Ebola outbreak in Sierra Leone, self-reported prevention practices such as avoidance of contacts with corpses, were found to have increased with rising disease prevalence (39). During the early stages of the COVID-19 pandemic, the practice of cautious social contacts by the Singaporean population, increased with rising rates of infection due to behavioral drivers such as fear and perceived risk of infection (40). Similarly, the decline of close contacts in Hong Kong during the first quarter of 2020 is thought to have resulted from increasing messaging and spread of information about the prevalence of COVID-19 (41). Thus, wide-spread public awareness of increasing numbers of new cases, through public health and various information media, may help to explain population reductions in contact rates.

In our study, we found that contact patterns and the related dynamics of COVID-19 varied with the geographies considered. A number of previous studies have also identified variation in contact rates by geography, and by factors that themselves vary geographically. In (17), the authors analyzed and compared social contact survey data for eight European countries in 2005 and 2006, and found that contact rates varied by geographical location, but also by sex, age and household size. In (42), the authors reviewed contact survey data across several countries from varying economic brackets and found that, in general, high contact rates were associated with densely populated settings and large household sizes, which characterized most low to middle-income countries. This is consistent with the general expectation that close-contact infectious diseases are more likely to impact densely populated regions and settings with large household sizes. Geographic variation in our results, particularly the higher contact rates, transmission and numbers of new cases in FHA compared to VCHA, may reflect the generally higher population density and larger household sizes in FHA (19). Related to the above factor is the evidence that the geographic spread of COVID-19 cases is connected to the local economic structure of a location relative to neighboring regions–in Italy, COVID-19 hit economic core locations (which were also characterized by higher populations densities) harder than regions with lower economic activities (43). Variations in close contact, case counts and transmission of COVID-19 can offer guidance for shaping or relaxing public health restrictions (44). For instance, a more rapid deployment of control measures can be applied in densely populated regions reporting high contact rates and cases than in sparsely distributed populations; and control measures can be tailored to capture population heterogeneity and other infection risk factors such as age groups.

Our analysis has several important limitations. We relied on case surveillance data to determine the number of new cases and the transmission indicator of COVID-19 over time. This means we did not account for asymptomatic infection, which may be a strong driver of COVID-19 transmission, and could have impacted the conclusions of our study. Relying on case surveillance data may also underestimate the actual number of new cases in settings where symptomatic individuals did not seek testing or where testing capacity is constrained by inaccessibility or shortage of resources. Three regional health authorities were not included in the assessment of regional associations of contact rates to COVID-19 dynamics - the Northern, Interior and Vancouver Island Health Authorities. These health authorities have relatively smaller population sizes, are more sparsely populated and have many rural communities (19). In these health authorities, self-reported contact rate data were too sparse for us to explore relations with reported cases and transmission. As a result, this study may not be representative of patterns in more rural populations. Limitations of the self-reported contact rates that may affect our analysis are provided in (20). For instance, some population groups including the economically marginalized, the under-housed, and those in immigration detention or incarceration, are likely underrepresented in the survey. In this study, we compared time series of means (averages) of daily contacts, cases and transmission of COVID-19, and did not consider other measures of central tendency, which may be crucial when analyzing skewed data. For instance, in the early stages of the COVID-19 pandemic contact rates were possibly higher during social gatherings over holidays, while more cases of COVID-19 tended to be reported on days after weekends and on days following holidays (45). Our conclusions may also be impacted by the choice of the time series analysis methods employed-in (46), the authors showed how the choice of the best times series analysis method can depend on factors such as the stage of an outbreak and the granularity of the geographic level explored.

This is the first study analyzing extensive and novel data on person-to-person contacts collected continuously throughout the province of British Columbia, Canada to understand the role of close contacts in transmission and control of infectious diseases. The study provides a quantitative approach to measuring the temporal associations among self-reported close contact rates, public health contact-restriction orders, and transmission dynamics of COVID-19. The observed impacts of person-to-person contacts on COVID-19 dynamics, as well as the capability of public health measures to modify these contact rates, are likely to prevail, although with varying magnitudes, in other jurisdictions and for other infectious diseases with similar modes of transmission. These findings support the quantitative study of population contact rates, which can inform infectious disease control strategies.

DATA AVAILABILITY STATEMENT

The raw COVID-19 case data used in this article was extracted from a line list generated by BCCDC Public Health Reporting Data Warehouse (PHRDW). The contact rate data used in this study was retrieved from the BC Mix COVID-19 survey and may be available upon reasonable request.

ETHICS STATEMENT

The study was approved by the University of British Columbia Behavioral Research Ethics Board (No: H20-01785).

AUTHOR CONTRIBUTIONS

NR and MO developed this concept along with NJ. All authors reviewed and agreed on the final submission.

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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.2022.867425/full#supplementary-material

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Discourse on COVID-19 Mass Testing vs. Rapid Testing Processing

Ali Cheshmehzangi[1,2]* *and Tong Zou*[2]

[1] *Network for Education and Research on Peace and Sustainability (NERPS), Hiroshima University, Hiroshima, Japan,*
[2] *Faculty of Science and Engineering, University of Nottingham Ningbo China, Ningbo, China*

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INTRODUCTION

COVID-19 "mass testing" and "rapid processing" are often mistaken as one process. While the two are correlated and partly overlapping each other, they are different in terms of processing and implementation. Mass testing is related to the size factor, while rapid processing is mainly related to the time factors. The former is mainly based on testing coverage of a larger population when and where infected clusters are found. At the same time, the latter must be understood as the rapid process of testing and verifying the situation for the suspects of potential positive cases. The two differ in how the pandemic could be contained at smaller or even larger scales. In this opinion article, we delve into this discourse to discuss the differences between the two.

COVID-19 MASS TESTING AND WHAT IT ENTAILS

As discussed by many scholars (1–4), mass testing is an effective way of identifying infected cases and clusters or hotspots. It helps initiate larger-scale processes such as contact tracing, isolation, and breaking chains of transmission. For example, the combination of mass testing and lockdown can significantly reduce the infected cases by 60% and COVID-19 mortality by 0.41% compared to employing a lockdown strategy alone (5, 6). The belief is that mass testing facilities could end the epidemic rapidly (7). It has been effective for rapid detection and isolation procedures in mini outbreaks of the ongoing COVID-19 pandemic across China (8), UK (9), India (10), and Italy (11).

The governmental function and institutional efficiency in responding to pandemic outbreaks are effective. However, large-scale pandemic control and prevention strategies vary differently across the world. They could depend on the countries' unique contextual factors. Those institutional and political constraints with deteriorating insufficient administrative capacity and weak executive ability can impair the effectiveness of restrictions significantly. Hence, they can cause additional disruptions to other areas like social stability. For instance, a systematic review and meta-analysis (12) found no significant difference in the effect of lockdowns on COVID-19 mortality, with the mortality reduction in Europe and the United States being only about 0.2% for lockdowns and 2.9% for shelter-in-place despite their huge economic and social drawbacks.

While mass testing is not necessarily used to avoid the spread of COVID-19 between different countries and cities, the method was proven to effectively enhance control of the disease spread using intensive contact tracing in a South Korean case study (13). Mass testing processes have enabled countries and cities to work with existing public health infrastructures or propose new facilities to support larger-scale testing. Thus, it is beneficial to public health (14) and effective in tracking close contacts, identifying infected cases in clusters, and finding ways of closing or restricting infected areas. Despite the claims that mass testing is related to rapid finding (15), we argue this is not entirely true.

The main differences between mass testing and the rapid testing process are their focuses. Mass testing is named after the extensiveness and wide coverage of the testing process, while rapid

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Roger Nlandu Ngatu,
Kagawa University, Japan

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Frank Orlando,
University of Florida, United States

Correspondence:
Ali Cheshmehzangi
Ali.Cheshmehzangi@nottingham.edu.cn

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testing process is named for its merits on the speed and efficiency of the entire process. Some rapid testing processes are voluntary, not only useful for people who need to provide a negative report to enter certain public places or transportations, but also essential for patients who need an urgent hospitalization to clear any suspicion of COVID-19 infection. On the other hand, for most circumstances, mass testing processes are mandatory and usually designated by local governments for contamination detection and control. Mass testing is related to scale and is affected by time. Rapid processes and technologies are essential to ensure the effectiveness of mass testing, which are still widely missing. As highlighted by Peto et al. (16), there are indeed unnecessary obstacles to COVID-19 mass testing, which must be looked at from a combination of scientific, governance, and management perspectives. More importantly, mass testing processes are generally costly and time-consuming. Some countries have implemented other methods of pooled testing (17), data collection fin a mass-testing setting (18), mass screening (6), and leading to digital contact tracing (19) and other processes. In earlier days, such an approach was effective after a single suspected or confirmed case was found (20) or in places where border closures and high-level restrictions are still in place.

Because the newer COVID-19 variants Delta and Omicron have faster infection rates, it has become even more important for mass testing to employ rapid processes to be effective. To date, comparative studies of mass testing with tracing and other processes in the UK have identified low-level – yet promising – evidence concerning the effectiveness of mass testing and contract tracing processes (21). Nonetheless, the key arguments are that mass testing alone is ineffective and becomes more effective when combined with other processes or practices, such as contact tracing and lockdown (5, 6). Sold as a rapid testing process, examples such as the UK's Operation Moonshot mass testing programme (22) was not necessarily compelling despite the efforts of weekly testing and creating the so-called "vital loop" to control the disease spread. In this programme, despite the high expenditures, the performance of tests was not effective enough. Poor detection rates and lack of other measures remain questionable factors that show the limitations of such mass testing processes. The process has been different in places where large-scale lockdown and closures are immediately implemented when hotspots are found. For instance, in December 2021, a northern district of the City of Ningbo, East China, was entirely amputated from regular city operations and connections to other parts (of the city). Back then, the city managed to only succeed with mass testing practice just because of the immediate closure of the whole Zhenhai district, after the first case was found on the 6th of December 2021. After reaching the peak in about 2 weeks and the gradual process of smaller-scale containment, the lockdown restrictions were eventually lifted, and mass testing was gradually stopped. To put this in another perspective, we could imagine the ineffectiveness of mass testing if the district was not immediately closed.

Accordingly, existing evidence is not sufficient to prove the effectiveness of mass testing alone in preventing the spreading of COVID-19 disease. But perceptions like "mass testing cannot prevent the disease from spreading" should be avoided. In fact, mass testing could lead to the development of illogical processes and/or redundant routines just to follow governmental regulations and policies, eventually turning into a pointless act of formalism of normalizing pandemic control and prevention. We have seen from many global examples that regular weekly or biweekly mass testing processes have not avoided disease spread but are just used to detect infected cases. Therefore, we argue that mass testing alone cannot be used for containment and ending the pandemic.

There are many limitations, barriers, and constraints regarding mass testing and public health strategy implementation, varying from social, cultural, institutional, technical factors. As a public health strategy, conducting mass testing may encounter social and cultural obstacles like lack of knowledge about the virus, poor understanding of the need for pandemic prevention/poor safety culture, the culture of denial, and/or public stigmatization (23, 24). Other systematic and institutional constraints may involve an underdeveloped healthcare system (23), poor communication between governmental health institutions and the public, lack of administrative commitment and support at the community level, lack of strict enforcement of regulations, and lack of resources and funds (24). Furthermore, one crucial factor that needs careful attention in mass testing practices is the quantity and quality of testing kits and technologies. In most places, facilities cannot necessarily handle mass testing. With higher demand, we often see difficulties following the safety and control measures and protocols meant to keep people safe. In mass testing procedures, large-scale groups of people are lined up in clusters where the risk of getting infected is even higher. Some innovative methods, such as the use of biosensors (25), are proposed to change the landscape of mass testing procedures, but are yet not implemented or are still experimental. Some have questioned the accuracy of rapid testing; however, mass spectrometry-based detection of COVID-19 host response has a reported sensitivity and specificity of 100 and 93% respectively in a diverse population including those who are asymptomatic, have been vaccinated for COVID-19, and who have any COVID-19 variant (26). This emphasizes another missing factor in mass testing processes: time.

The temporal aspect plays a significant part in the effectiveness of mass testing, making the argument of mass testing vs. rapid testing processing valid for future research directions. What we see globally are mass testing procedures or mass testing combined with restricted measures. The latter has been more effective but lacks rapid identification and containment. Thus, we urge to consider what has been discussed beyond just the scaling up testing capacity (27) and toward genuine rapid testing processes and/or practices. In this regard, the use of more advanced technologies cannot be disregarded, meaning that we have not yet explored other effective alternatives (28–30). Thus, mass testing could only cover testing a larger population. Without closure restrictions, the approach is merely costly to governments and fatiguing for our already overexploited public health facilities and services. An example is that if a person involved in mass testing or regular testing could travel from A to B without a problem, then there are obvious flaws in this process. If the test results are not out before the person's departure to another location, then the testing was not done to avoid the spread of the disease but to detect if the person is infected or is contacted with an infected person. Hence, mini outbreaks keep reoccurring just because the test results are delayed for several hours and sometimes up to a whole 24 h cycle. This lack of rapid processing leads to the development of absurd formal processes of regular testing without understanding the importance of rapid test results. This fact puts a critical question on mass testing effectiveness if rapid processing is not considered or embedded in such practices.

DISCUSSION: MASS TESTING VS. RAPID PROCESSING OF TESTING

Since mobility causes the rapid spread of the disease (31, 32), we cannot just rely on current mass testing methods to end the pandemic. Without suitable frequency, speedy efficiency, and effective protocols to ensure and confirm all the positive suspects within the least time frame regarding the transmissibility timeline, most efforts of mass testing are very likely to be wasted. For instance, undetected active infections can be developed into mini outbreaks (33) or even larger very quickly through a contaminated airplane (34, 35). Ongoing research studies on rapid processing of testing highlight the urgent need for novel testing techniques beyond just scale and more related to the faster processing of tests (27). While testing strategies differ from country to country, we have yet to see which testing model has been more effective in the long run. The wide-scale regular community testing processes could only be effective if rapid processing is embedded in their processes. Otherwise, breaking chains of transmissions becomes a mission impossible, and this pandemic could be further prolonged. An example is to have rapid and accurate testing processing on departure or arrival points, to ensure test results are out before people's departure or entry to different locations (e.g., cities, countries, etc.). It is already evidenced that even a 72 h test result with several weeks of restricted isolation and quarantine does not solve the problem of disease spread (36, 37). Yet, rapid testing remains challenging (38), or else they could curb COVID-19 much earlier. Despite their current challenges, rapid antigen tests have shown to be promising in smaller scales (39), meaning that regular processes are not the only way of keeping communities safe.

Lastly, we note that COVID-19 mass testing protocols are still weak. They only provide support to rapid response in the cases of detection and isolation but are not helping to avoid the spread of the disease. For example, to deal with the potential risks of false negatives, protocols for repeated testing and isolations of patients with a single negative result but COVID-19 symptoms are suggested (40). Therefore, frequent mass testing without rapid processing of the results is a costly process by all means. The current and future research should focus on the deployment and utilization of faster and more accurate technologies to ensure test results are processed rapidly. It is only then that mass testing could save us from the ongoing pandemic, as we would be able to detect, isolate, and treat the infected person in his/her original location of A, and not when he/she has already arrived at point B. This pandemic has proven that "time" is a crucial factor should we wish to reach an end to this prolonging adversity any time soon.

AUTHOR CONTRIBUTIONS

AC drafted and wrote the paper. TZ worked on literature review and revisions. Both authors contributed to the article and approved the submitted version.

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Obesity and Impaired Metabolic Health Increase Risk of COVID-19-Related Mortality in Young and Middle-Aged Adults to the Level Observed in Older People: The LEOSS Registry

Norbert Stefan[1,2,3*†], Katrin Sippel[1,2,3†], Martin Heni[1,2,3], Andreas Fritsche[1,2,3], Robert Wagner[1,2,3], Carolin E. M. Jakob[4,5], Hubert Preißl[1,3], Alexander von Werder[5,6], Yascha Khodamoradi[7], Stefan Borgmann[8], Maria Madeleine Rüthrich[9], Frank Hanses[10], Martina Haselberger[11], Christiane Piepel[12], Martin Hower[13], Jürgen vom Dahl[14], Kai Wille[15], Christoph Römmele[16], Janne Vehreschild[3,4,17], Melanie Stecher[4,5], Michele Solimena[3,18], Michael Roden[3,19,20], Annette Schürmann[3,21], Baptist Gallwitz[2], Martin Hrabe de Angelis[3,22,23], David S. Ludwig[24,25,26], Matthias B. Schulze[3,27], Bjoern Erik Ole Jensen[28†] and Andreas L. Birkenfeld[1,2,3†] on behalf of the LEOSS Study Group

[1] Institute of Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center Munich, Tübingen, Germany, [2] Department of Internal Medicine IV, University Hospital of Tübingen, Tübingen, Germany, [3] German Center for Diabetes Research (DZD), Munich, Germany, [4] Department of Internal Medicine I, Faculty of Medicine, University Hospital Cologne, Cologne, University of Cologne, Cologne, Germany, [5] German Center for Infection Research (DZIF), Partner-Site Bonn-Cologne, Cologne, Germany, [6] Department of Internal Medicine II, School of Medicine, University Hospital Rechts der Isar, Technical University of Munich, Munich, Germany, [7] Department of Internal Medicine, Infectious Diseases, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt am Main, Germany, [8] Department of Infectious Diseases and Infection Control, Ingolstadt Hospital, Ingolstadt, Germany, [9] Department of Internal Medicine II, University Hospital Jena, Jena, Germany, [10] Emergency Department, University Hospital Regensburg, Regensburg, Germany, [11] Department of Internal Medicine I, Passau Hospital, Passau, Germany, [12] Department of Internal Medicine I, Hospital Bremen-Center, Bremen, Germany, [13] Department for Pneumology, Infectiology, Internal Medicine and Intensive Care, gGmbH, Dortmund, Germany, [14] Division of Cardiology, Hospital Maria Hilf Mönchengladbach, Mönchengladbach, Germany, [15] University Clinic for Hematology, Oncology, Hemostaseology and Palliative Care, University of Bochum, Minden, Germany, [16] Internal Medicine III - Gastroenterology and Infectious Diseases, University Hospital of Augsburg, Augsburg, Germany, [17] Department of Internal Medicine, Hematology and Oncology, University Hospital Cologne, Goethe University Frankfurt, Frankfurt am Main, Germany, [18] Helmholtz Center Munich, Faculty of Medicine, Paul Langerhans Institute Dresden, University Hospital, Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, [19] Department of Endocrinology and Diabetology, Medical Faculty and University Hospital, Heinrich-Heine University, Düsseldorf, Germany, [20] Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich- Heine University, Düsseldorf, Germany, [21] Department of Experimental Diabetology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany, [22] Institute of Experimental Genetics, Helmholtz Zentrum München, Oberschleißheim, Germany, [23] TUM School of Life Sciences (SoLS), Chair of Experimental Genetics, Technische Universität München, Freising, Germany, [24] New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, Boston, MA, United States, [25] Department of Pediatrics, Harvard Medical School, Boston, MA, United States, [26] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [27] Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany, [28] Department of Gastroenterology, Hepatology and Infectious Diseases, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

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***Correspondence:**
Norbert Stefan
norbert.stefan@med.uni-tuebingen.de

†*These authors have contributed equally to this work*

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Advanced age, followed by male sex, by far poses the greatest risk for severe COVID-19. An unresolved question is the extent to which modifiable comorbidities increase the risk of COVID-19-related mortality among younger patients, in whom COVID-19-related hospitalization strongly increased in 2021. A total of 3,163 patients with SARS-COV-2 diagnosis in the Lean European Open Survey on SARS-CoV-2-Infected Patients (LEOSS) cohort were studied. LEOSS is a European non-interventional multi-center cohort study established in March 2020 to investigate the epidemiology and clinical course of SARS-CoV-2 infection. Data from hospitalized patients and those who received ambulatory care, with a positive SARS-CoV-2 test, were included in the study. An additive effect of obesity, diabetes and hypertension on the risk of mortality was observed, which was particularly strong in young and middle-aged patients. Compared to young and middle-aged (18–55 years) patients without obesity, diabetes and hypertension (non-obese and metabolically healthy; $n = 593$), young and middle-aged adult patients with all three risk parameters (obese and metabolically unhealthy; $n = 31$) had a similar adjusted increased risk of mortality [OR 7.42 (95% CI 1.55–27.3)] as older (56–75 years) non-obese and metabolically healthy patients [$n = 339$; OR 8.21 (95% CI 4.10–18.3)]. Furthermore, increased CRP levels explained part of the elevated risk of COVID-19-related mortality with age, specifically in the absence of obesity and impaired metabolic health. In conclusion, the modifiable risk factors obesity, diabetes and hypertension increase the risk of COVID-19-related mortality in young and middle-aged patients to the level of risk observed in advanced age.

Keywords: obesity, diabetes, hypertension, impaired metabolic health, mortality, COVID-19

INTRODUCTION

As of 14 February 2022, more than 404 million people worldwide have been infected with SARS-CoV-2, resulting in more than 5.7 million deaths (1). Early in the SARS-CoV-2 pandemic, older age was identified as the strongest risk factor for COVID-19-related mortality. Furthermore, male sex and several comorbidities were found to be associated with an increased risk of mortality in patients with COVID-19 (2–4). Obesity and hyperglycemia in the non-diabetic range were additionally identified as potential risk factors for COVID-19 morbidity and mortality (5–9). Of note, these relationships were independent of age, sex and other comorbidities (10–14). Consequently, obesity and impaired metabolic health are now viewed as important modifiable risk factors for disease severity (15–17).

However, recently, in a large, international, multicenter study from 18 sites in 11 countries, of 7,244 patients hospitalized with COVID-19, obesity and diabetes were found to associate with increased adjusted odds of supplemental oxygen/non-invasive ventilatory support, yet, not with mortality (18). Furthermore, in a very large community-based cohort study from the United Kingdom that evaluated data from 6,910,695 patients with a positive SARS-CoV-2 test result, obesity strongly associated with mortality in the younger and middle-aged adults, but not in the older patients (19). Unfortunately, in that study no adjustment for comorbidities could be done. Thus, it is important to clarify whether obesity and other metabolic comorbidities may increase the risk of COVID-19-related mortality, independently of other diseases, specifically in younger and middle-aged patients.

These patients with COVID-19 are generally considered to have substantially lower risk of COVID-19-related mortality, than those older than 65 years. However, risk in younger age groups has become increasingly relevant, with initially selective vaccination of older individuals and rapidly rising incidence of infection and hospitalization among children, adolescents, and young adults (20). Data from the US Centers for Disease Control and Prevention (CDC) suggests that a 35-year-old with diabetes mellitus, hypertension, cardiovascular disease, obesity, or other chronic conditions had a similar risk of COVID-19-related death as a 65-year-old with none of these conditions (21). Furthermore, in an analysis of data from an US Premier Healthcare Database of hospital-based patients with COVID-19, younger patients (age 18–34 years) with morbid obesity, hypertension, and diabetes faced similar risk of death or need for mechanical ventilation, as that observed in middle-aged (age 35–64 years) adults (22). However, these did not consider potential confounding, and in the CDC report no information about comorbidities was available in 22% of the patients (21). Adjustment for sex and other comorbidities, such as cardiovascular, renal and liver disease, is essential, as these comorbidities are strongly related to impaired metabolic health.

To clarify the potential impact of obesity and impaired metabolic health on COVID-19 related mortality in younger adults, we have studied the determinants of COVID-19-related mortality in 3,163 patients with COVID-19 of the Lean European Open Survey on SARS-CoV-2-Infected Patients (LEOSS) cohort study.

RESEARCH DESIGN AND METHODS

Study Design and Patient Cohort

A total of 6,457 consecutive patients, who were included in the LEOSS registry between March 2020 and February 2021, were evaluated. LEOSS is a European non-interventional multi-center cohort study established in March 2020 to address the lack of information on the epidemiology and clinical course of SARS-CoV-2 infection (23, 24). The registry collects data on hospitalized patients of all ages and patients who receive ambulatory medical consultation. As of July 2020, more than 125 sites from 7 different countries have been registered to LEOSS. Daily statistics are provided on the LEOSS website (https://leoss.net). To facilitate the rapid data acquisition needed during a pandemic, LEOSS involves autonomous, self-managed study sites that collect data in an anonymous form. To achieve this, no directly identifying data are stored in the registry and demographic data as well as timestamps are only collected in a rough form. Furthermore, data were documented categorically. Patient privacy was additional protected using the anonymization procedures described by Jakob et al. (24). Data collection is performed once per case, retrospectively after treatment has finished or the patient has died. Although this method precludes longitudinal data collection and follow-up of discharged patients, it has the advantage that no informed consent is necessary. Furthermore, this method provides for the inclusion of data on children and unconscious or deceased patients and avoids problems that could arise from language barriers. All patients had a diagnosis confirmed by positive results of PCR testing. Approval for LEOSS was obtained by the applicable local ethics committees of all participating centers and registered at the German Clinical Trails Register (DRKS, No. S00021145).

Clinical Data and Outcomes

Data were recorded in an electronic case report form operated using the online cohort platform ClinicalSurveys.net, which was developed by the University Hospital of Cologne (UHC), Germany. ClinicalSurveys.net was hosted by QuestBack, Oslo, Norway on servers of UHC, Cologne, as part of a software-as-a-service agreement. Baseline data closest to the first positive SARS-CoV-2 test were analyzed. Demographic, clinical, laboratory and outcome data were extracted from the in-hospital medical records. Operational definitions of the co-morbidities studied are based on the medical diagnosis guidelines that were applied by the treating physicians in the hospital. Diagnosis were either pre-known or newly made by the treating physicians based on the clinical in-hospital evaluation and/or laboratory results. Analyzed laboratory data were collected within 48 h of a positive SARS-CoV-2 PCR result, irrespective of the patient's status. Among the 6,457 patients evaluated only adult (age ≥18 years) patients who had complete information about sex, age, BMI and the comorbidities diabetes, hypertension, coronary artery disease, chronic kidney disease and chronic liver disease ($N =$ 3,517) were considered eligible for the analyses. Among them, a total of 354 patients with missing information on survival were excluded, yielding a sample of 3,163 for the main analyses (**Supplementary Figure 1**).

Comorbidities were dichotomized (e.g., diabetes present/absent, coronary artery disease present/absent). Comorbidities were set to unknown/missing when all specific comorbidities of one group were unknown or missing. Values documented as unknown were defined as missing. Besides sex, age, BMI and the above-mentioned comorbidities, the following clinical parameters related to metabolic risk, which were not available in all patients, were evaluated: hemoglobin A1c (HbA1c), serum creatinine, serum C-reactive protein (CRP), serum interleukin-6 (IL-6), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum gamma-glutamyl transferase (GGT), as well as urine ketone bodies. Clinical parameters were set to unknown/missing if not available. The primary outcome was COVID-19-related mortality. In an exploratory approach disease severity, which is not a hard endpoint, was also studied (uncomplicated phase: patients were either asymptomatic, and had symptoms of upper respiratory tract infection, fever or nausea, emesis, or diarrhea; complicated phase: patients had at least one of the characteristics new need for oxygen supplementation or clinically relevant increase of prior oxygen home therapy, PaO2 at room air < 70 mmHg, SO2 at room air < 90%, increase of AST or ALT > 5 × upper limit of normal, new cardiac arrythmia, new pericardial effusion > 1 cm or new heart failure with pulmonary edema, congestive hepatopathy, or peripheral edema; critical phase patients were dependent on catecholamines, experienced life-threatening cardiac arrhythmia, had mechanical ventilation (invasive or non-invasive), or need for unplanned mechanical ventilation prolongation (> 24 h) of planned mechanical ventilation, liver failure with an INR > 3.5 (quick < 50%), a qSOFA score of > = 2, or acute renal failure with need of dialysis).

Statistical Analyses

We calculated and report patient characteristics as absolute numbers and percentages. For comparison of percentages between groups the χ^2-test was used. The odds ratios of baseline characteristics, comorbidities and laboratory parameters, with mortality were assessed in univariate and in multivariable logistic regression models. Univariate and multivariable relationships of baseline characteristics with mortality were also assessed after patients were stratified in young and middle aged (18–55 years; $n = 1{,}068$), older age (56–75 years; $n = 1{,}220$) and old age (>75 years; $n = 875$) groups. Then patients in each age group were further categorized by the presence or absence of obesity, of obesity+diabetes and of obesity+diabetes+hypertension. For the main analyses, patients in the three age groups were subdivided into those (i) without obesity (BMI<30 kg·m^{-2}) and without impaired metabolic health (no diabetes and no hypertension, $n = 1{,}098$) and in those (ii) having all three risk factors (BMI ≥30 kg·m^{-2}, diabetes and hypertension, $n = 259$). Kaplan-Meier analyses were used to compare the survival of the patients among these six subgroups. A $p < 0.05$ was considered to indicate statistical significance. Data management, statistical analysis, and computation of figures were conducted using R (R Development Core Team, Vienna, Austria, Version 3.5.2., 2019). Additional information about the LEOSS questionnaire can be found under https://leoss.net/.

RESULTS

Among the 3,163 patients included in the analyses, data were collected primarily from Germany ($N = 95\%$), as well as from Turkey, Belgium, Switzerland, Spain, Austria, Italy, Bosnia and

TABLE 1 | Multivariable relationships of selected anthropometrics, comorbidities and laboratory parameters with COVID-19-related mortality.

Characteristics	Recovered/died	OR	Lower 95%CI	Upper 95%CI	*p*
Age 18–25 (years)	71/0	0.00	0.000	0.00	0.97
Age 26–35 (years) (ref)	199/3				
Age 36–45 (years)	290/4	0.82	0.18	4.22	0.80
Age 46–55 (years)	475/26	2.89	0.10	12.3	0.09
Age 56–65 (years)	578/83	7.14	2.60	29.5	0.001
Age 66–75 (years)	446/113	11.9	4.35	49.2	<0.0001
Age 76–85 (years)	478/196	17.4	6.37	71.7	<0.0001
Age >85 (years)	124/104	44.8	15.9	187	<0.0001
Sex female (ref)	1,059/171				
Sex male	1,602/331	1.62	1.30	2.04	<0.0001
BMI 18.5–24.9 ($kg·m^{-2}$) (ref)	873/167				
BMI 25–29.9 ($kg·m^{-2}$)	977/178	0.99	0.78	1.29	0.99
BMI 30–34.9 ($kg·m^{-2}$)	534/94	1.04	0.76	1.40	0.81
BMI ≥35 ($kg·m^{-2}$)	277/63	1.77	1.22	2.56	0.003
No diabetes (ref)	2,119/333				
Diabetes	542/169	1.44	1.09	1.89	0.009
HbA1c <6.4% (ref)	48/6				
HbA1c 6.4–8 %	118/27	2.04	0.82	5.88	0.15
HbA1c 8.1–10%	61/14	2.65	0.95	8.16	0.07
HbA1c >10%	30/12	6.37	2.13	20.8	0.001
HbA1c not available	2,404/443	3.96	1.73	10.8	0.003
No hypertension (ref)	1,416/138				
Hypertension	1,245/364	1.27	0.99	1.61	0.056
No coronary artery disease (ref)	2,340/376				
Coronary artery disease	321/126	1.14	0.88	1.48	0.31
No chronic kidney disease (ref)	2,322/359				
Chronic kidney disease	339/143	1.42	1.10	1.82	0.007
No liver cirrhosis (ref)	2,643/493				
Liver cirrhosis	18/9	2.41	0.97	5.70	0.048

OR, odds ratio; CI, confidence interval.

Herzegovina, United Kingdom and Latvia. A total of 2,989 from 3,144 patients (19 patients with missing information) had an inpatient stay. Disease course was classified as uncomplicated ($N = 1,284$) complicated ($N = 1,130$) and critical ($N = 749$) (24). From the 3,163 patients studied, 2,661 patients recovered from the disease while 502 patients died (**Supplementary Table 1**).

Univariable and Multivariable Relationships of Patient Characteristics With Mortality

In univariable analyses, among the parameters age, sex, BMI, comorbidities and selected laboratory variables, determined at the day of SARS-COV-2 diagnosis, higher age, male sex, diabetes, hypertension, HbA1c >10%, coronary artery disease, chronic liver disease and liver cirrhosis were associated with an increased risk of mortality (**Supplementary Table 2**). In a multivariable regression model including all studied parameters, higher age, male sex, BMI ≥35 $kg·m^{-2}$, diabetes, HbA1c >8.1%, CRP ≥30 mg/L and GGT >10 upper limit of normal were independently associated with an increased risk of mortality (**Supplementary Table 3**).

To avoid over-adjustment in the statistical models by including variables that are highly related to each other, e.g., the diagnosis of liver cirrhosis and elevated transaminases or chronic kidney disease and elevated serum creatinine, we further focused in the multivariate regression models on the parameters reported in the **Table 1**. In that parsimonious multivariable regression model higher age, male sex, BMI ≥ 35 $kg·m^{-2}$, HbA1c >10%, chronic kidney disease and liver cirrhosis were independently associated with an increased risk of mortality. The association with hypertension was borderline, with an adjusted *p*-value of 0.056 (**Table 1**, **Supplementary Figure 2**).

Risk of Mortality in Young/Middle-Aged, Older and Old Patients

To investigate the relationships of obesity and impaired metabolic health with the risk of mortality in different age groups, patients were divided into three age groups (**Supplementary Table 4**), with 1,068 young and middle-aged, 1,220 older age and 875 old age groups. Based on the similar sample sizes these three groups were equally strong powered for

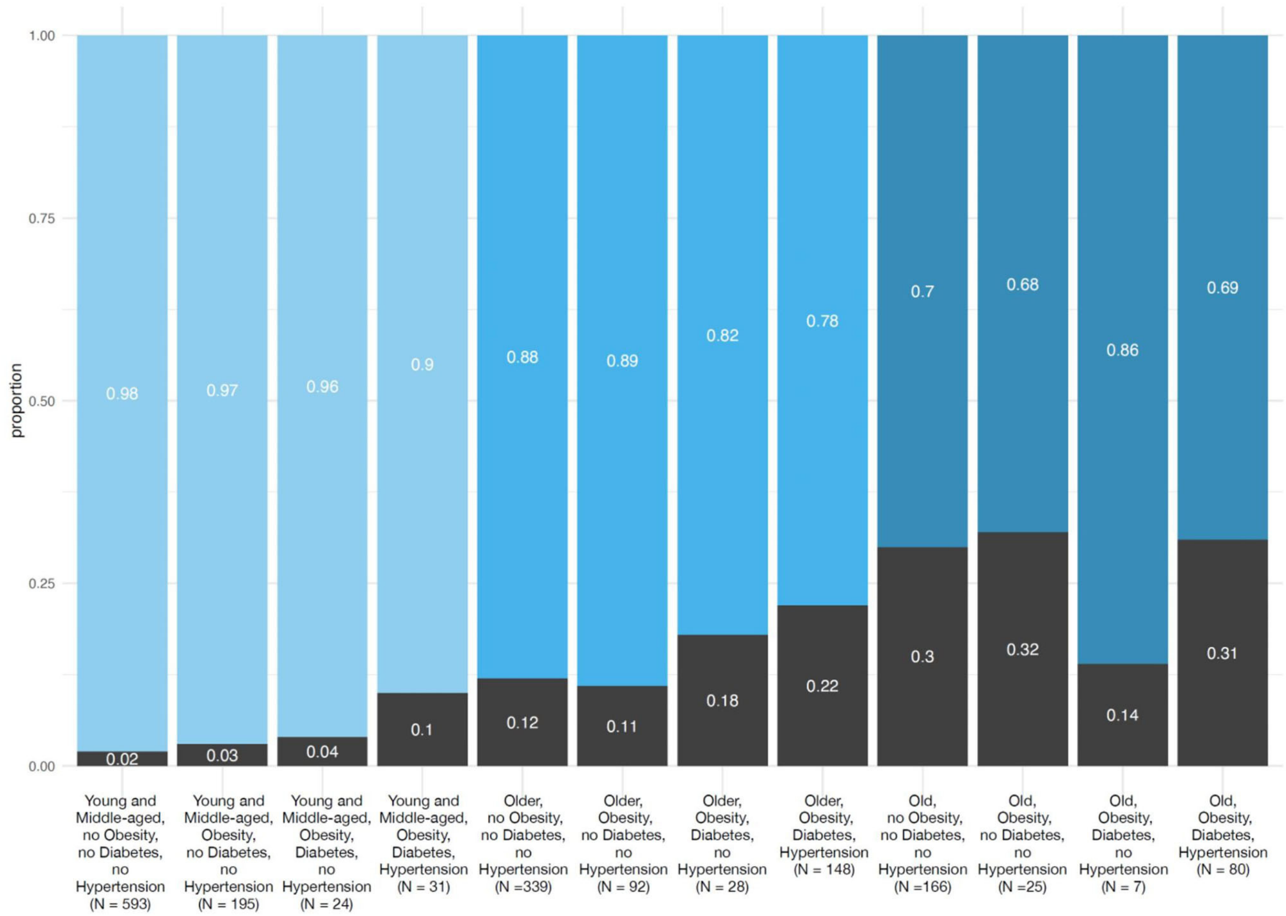

FIGURE 1 | Proportion of COVID-19 patients who recovered and died divided in three age groups based on the presence or absence of obesity, diabetes and hypertension. All COVID-19 patients who recovered and died (n = 3,163) were first divided in three age groups (young and middle aged, 18–55 years, n = 1,068; older age, 56–75 years; n = 1,220 and old age, >75 years; n = 875) and subsequently divided in four groups based on the presence or absence of obesity (BMI ≥ 30 kg·m^{-2}), and impaired metabolic health (diabetes and hypertension).

the investigation of the patient's characteristics with mortality in the statistical analyses. In multivariable regression analyses male sex was associated with a higher risk of mortality in the young/middle-aged and in the old age groups, but not in the older age group. BMI ≥35 kg·m^{-2} was associated with increased mortality in the young/middle-aged and in the older age groups, but not in the old age group. Diabetes was associated with increased mortality only in the old age group (**Supplementary Table 5**).

Risk of Mortality in Subjects Stratified by Age and Obesity/Metabolic Health

To compare the contributions of advanced age vs. obesity and impaired metabolic health (diabetes and hypertension) to the mortality risk, we divided the patients into 12 subgroups based upon age and presence or absence of obesity, diabetes and hypertension. First, to investigate an additive effect of these parameters on the mortality risk, we divided the subjects in the three age groups based on the presence or absence of obesity, obesity + diabetes and obesity + diabetes + hypertension. Second, to investigate the impact of obesity + impaired metabolic health (diabetes and hypertension) on the risk of mortality more in detail, we compared the following 6 groups: (1) young and middle-aged without obesity, diabetes and hypertension (N = 593), (2) young and middle-aged with obesity, diabetes and hypertension (N = 31), (3) older age without obesity, diabetes and hypertension (N = 339), (4) older age with obesity, diabetes and hypertension (N = 148), (5) old age without obesity, diabetes and hypertension (N = 166) and (6) old age with obesity, diabetes and hypertension (N = 80).

When the age groups were stratified by the presence or absence of obesity and impaired metabolic health, both, older age and the presence of obesity and impaired metabolic health associated with increased risk of mortality (**Figure 1**). In the multivariable statistical model (**Table 2**, Model 1) moderately higher adjusted risks of mortality were observed in the young and middle-aged patients with obesity [N = 195; OR 1.75 (95% CI 0.53–5.13)] and obesity + diabetes [N = 24; OR 2.96

TABLE 2 | Multivariable relationships of three age groups based on the presence (unhealthy) or absence (healthy) of obesity, diabetes and hypertension and selected anthropometrics, comorbidities and laboratory parameters with COVID-19-related mortality.

Characteristics	**Model 1**				**Model 2**			
	OR	**Lower 95%CI**	**Upper 95%CI**	***p***	**OR**	**Lower 95%CI**	**Upper 95%CI**	***p***
Young/middle-aged–no obesity, no diabetes, no hypertension (ref.) (*N* = 593)								
Young/middle-age–obesity, no diabetes, no hypertension (*N* = 195)	1.75	0.53	5.13	0.32	1.55	0.47	4.60	0.45
Young/middle-aged–obesity, diabetes, no hypertension (*N* = 24)	2.96	0.16	17.3	0.32	2.81	0.14	17.1	0.35
Young/middle-aged–obesity, diabetes, hypertension (*N* = 31)	6.95	1.45	25.6	0.006	5.99	1.23	23.0	0.014
Older–no obesity, no diabetes, no hypertension (*N* = 339)	8.24	4.12	18.4	<0.0001	6.88	3.40	155	<0.0001
Older–obesity, no diabetes, no hypertension (*N* = 92)	7.70	3.01	20.0	<0.0001	5.88	2.25	15.5	0.0003
Older–obesity, diabetes, no hypertension (*N* = 28)	13.4	3.61	44.9	<0.0001	13.6	3.53	48.2	0.0001
Older–obesity, diabetes, hypertension (*N* = 148)	18.0	8.16	43.0	<0.0001	14.7	6.55	35.9	<0.0001
Old–no obesity, no diabetes, no hypertension (*N* = 166)	24.4	12.1	54.9	<0.0001	21.6	10.5	49.5	<0.0001
Old–obesity, no diabetes, no hypertension (*N* = 25)	29.6	9.88	88.8	<0.0000	24.6	7.94	75.6	<0.0001
Old–obesity, diabetes, no hypertension (*N* = 7)	7.47	0.37	52.4	0.08	6.62	0.32	48.5	0.10
Old–obesity, diabetes, hypertension (*N* = 80)	28.4	12.1	71.5	<0.0001	27.1	11.3	69.6	<0.0001
Sex male	1.38	0.98	1.95	0.07	1.28	0.90	1.83	0.18
HbA1c 6.4–8%	1.40	0.38	6.78	0.64	1.45	0.38	7.23	0.61
HbA1c 8.1–10%	1.99	0.50	10.1	0.36	2.78	0.67	14.6	0.19
HbA1c >10%	3.47	0.67	20.7	0.14	2.98	0.55	18.8	0.22
HbA1c unknown	2.34	0.72	10.6	0.20	2.48	0.74	11.5	0.18
Coronary artery disease	1.13	0.70	1.78	0.61	1.08	0.66	1.74	0.74
Chronic kidney disease	1.75	1.14	2.66	0.009	1.76	1.13	2.73	0.012
Liver cirrhosis	1.55	0.32	5.63	0.53	2.76	0.54	10.7	0.17
CRP 3–29 mg/L	-	-	-	-	1.77	0.58	7.71	0.37
CRP 30–69 mg/L	-	-	-	-	4.95	1.66	21.4	0.011
CRP 70–119 mg/L	-	-	-	-	5.32	1.74	23.3	0.009
CRP 120–179 mg/L	-	-	-	-	6.54	2.05	29.2	0.004
CRP 180–249 mg/L	-	-	-	-	17.4	5.01	81.8	<0.0001
CRP >249 mg/L	-	-	-	-	23.4	6.43	113	<0.0001
CRP unknown	-	-	-	-	6.56	2.31	27.6	0.002

OR, odds ratio; CI, confidence interval; Model 1, adjusted for sex, HbA1c, coronary artery disease, chronic kidney disease and liver cirrhosis; Model 2, adjusted for sex, HbA1c, coronary artery disease, chronic kidney disease, liver cirrhosis and CRP.

(95% CI 0.16–17.3)], which were statistically not significant, when compared to the young and middle-aged patients without obesity, diabetes or hypertension. However, when compared to the latter group, the adjusted risk of mortality was strongly increased in the young and middle-aged patients with obesity+impaired metabolic health [diabetes + hypertension; $N = 31$; OR 6.95 (95% CI 1.45–25.6)]. This group had a nearly 7-fold higher risk of mortality, compared to the young and middle-aged patients without obesity, diabetes or hypertension (**Table 2**, Model 1 and **Figure 2**).

Older patients without obesity, diabetes or hypertension had a higher adjusted risk of mortality [$N = 339$; OR 8.24 (95% CI 4.12–18.4)], compared to young and middle-aged patients without obesity, diabetes or hypertension. This risk increased in the presence of obesity, diabetes and hypertension and older patients having all three risk factors ($N = 148$) had an adjusted OR for mortality of 18.0 (95% CI 8.16–43.0), compared to young and middle-aged patients without obesity, diabetes or hypertension. Interestingly, this risk was merely 2.2-fold higher than the risk of older patients without obesity, diabetes and hypertension (**Table 2**, Model 1 and **Figure 2**).

Old patients without obesity, diabetes and hypertension had a very high adjusted risk of mortality [$N = 166$; OR 24.4 (95% CI 12.1–54.9)], compared to young and middle-aged patients without obesity, diabetes or hypertension. However, in the old patients, obesity, diabetes or hypertension only weakly increased this risk [1.2-fold higher; $N = 80$; OR 28.4 (95% CI 12.1–71.5)] (**Table 2**, Model 1 and **Figure 2**).

Similar relationships were observed when patients were stratified in those with an uncomplicated and a severe

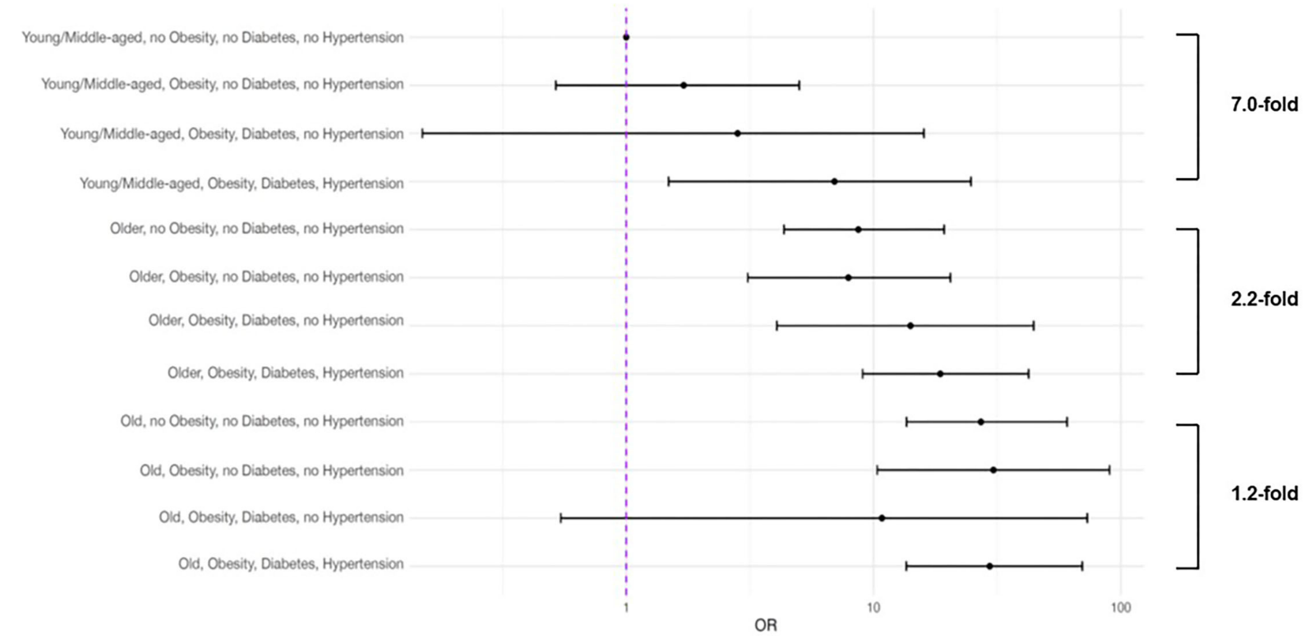

FIGURE 2 | Multivariable relationships of selected anthropometrics, comorbidities and laboratory parameters with COVID-19-related mortality in three age groups based on the presence (unhealthy) or absence (healthy) of obesity, diabetes and hypertension. All COVID-19 patients who recovered and died (n = 3,163) were first divided in three age groups (young and middle aged, 18–55 years, n = 1,068; older age, 56–75 years; n = 1,220 and old age, >75 years; n = 875) and subsequently divided in two groups (n = 1,357) based on the presence (unhealthy) or absence (healthy) of obesity (BMI ≥ 30 kg·m^{-2}), and impaired metabolic health (diabetes and hypertension). All parameters shown were included in the multivariable regression analysis.

(complicated phase and critical phase) course of the disease. For example, when compared to the young and middle-aged patients without obesity, diabetes or hypertension, the adjusted risk of severe COVID-19 was increased in the young and middle-aged patients with obesity + impaired metabolic health [diabetes + hypertension; N = 31; OR 2.60 (95% CI 1.87–3.64)]. Furthermore, this risk was comparable to the risk observed in older non-obese and metabolically healthy patients [n = 339; OR 2.66 (95% CI 2.01–3.52)] (**Supplementary Table 6**).

Among the patients who died, most deaths occurred within the first 2 weeks of follow-up. In Kaplan-Meier survival analyses young and middle-aged patients with obesity and impaired metabolic (diabetes + hypertension) health had a similar time-to-death to those in the older age group without obesity and impaired metabolic health (**Figure 3**). Compared to young and middle-aged patients without obesity and impaired metabolic health (group 1), the adjusted OR of mortality was 6.95 (95% CI 1.45–25.6) in the young and middle-aged group with obesity and impaired metabolic health (group 2), which was not statistically different from the risk in the older age group without obesity and impaired metabolic health [OR 8.24 (95% CI 4.12–18.4)] (**Table 2**, Model 1 and **Figure 2**).

We then explored parameters that may explain the elevated risk of COVID-19-related mortality with age, specifically in the absence of obesity and impaired metabolic health. We additionally adjusted our multivariable regression model for CRP levels (**Table 2**, Model 2). This resulted in an attenuation of the elevated risk of mortality observed in older and old patients without obesity and impaired metabolic health, when compared to young and middle-aged patients without obesity and impaired metabolic health, by 17 and 11%, respectively.

To address, whether the increased risk of mortality that associated with obesity and impaired metabolic health and that was very high, particularly in the group of young and middle-aged patients, may be predominantly driven by the risk in middle-aged patients, we also divided the patients in a younger (age 18–35 years) group and a middle-aged (age 36–55 years) group. Although the sample size was very low, only allowing an exploratory evaluation, we found that young patients with obesity and impaired metabolic health had a 4.2-fold higher risk of mortality, compared to the young patients without obesity and impaired metabolic health. A similarly increased risk (3.5-fold) was observed in the middle-aged patients with obesity and impaired metabolic health, compared to the middle-aged patients without obesity and impaired metabolic health (**Supplementary Table 7**).

DISCUSSION

Both, high BMI and adverse cardiometabolic status, are now established risk factors for severe COVID-19 (25). However, the risk attributed to these factors is considered to be lower than that of advanced age and perhaps also male sex. Nevertheless, the relative importance of these risk factors has not been well-studied. This knowledge gap may have direct public health

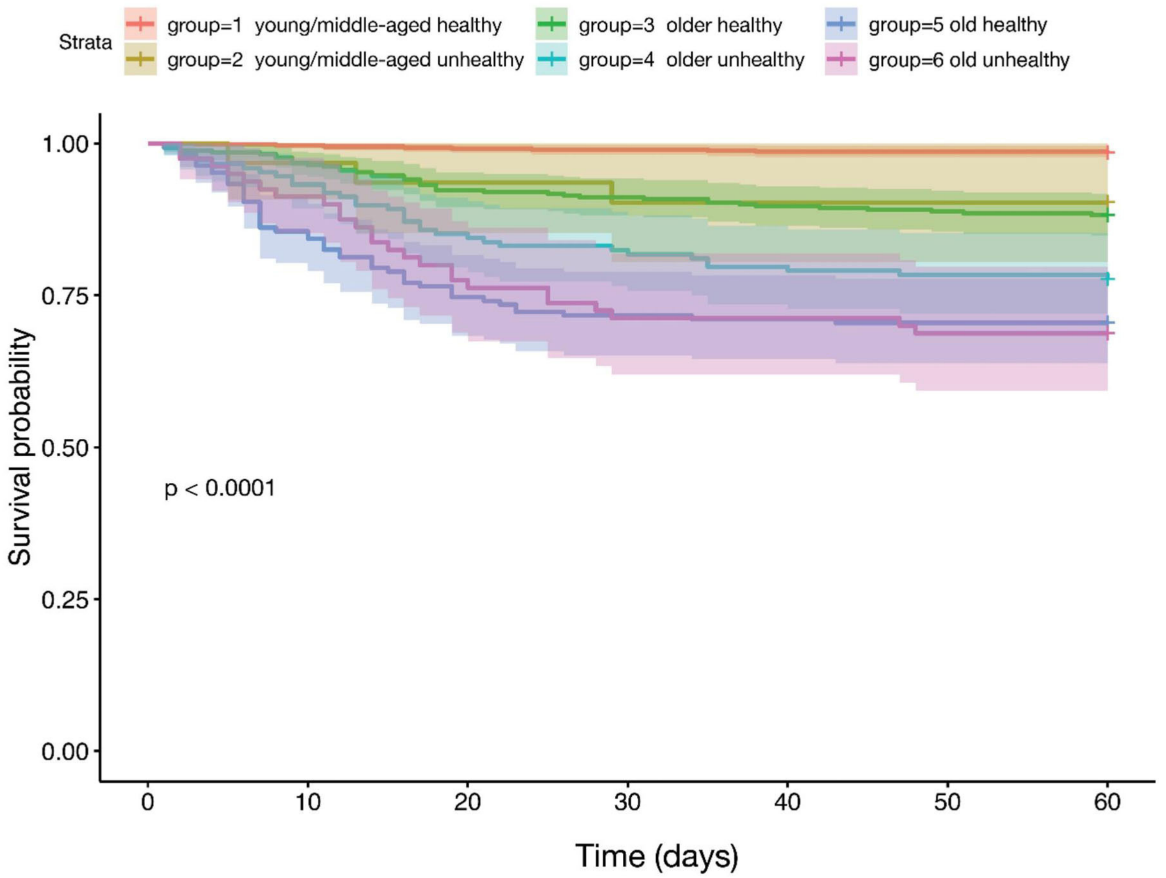

FIGURE 3 | Kaplan-Meier survival comparing three age groups based on the presence (unhealthy) or absence (healthy) of obesity, diabetes and hypertension. All COVID-19 patients who recovered and died ($n = 3,163$) were first divided in three age groups (young and middle aged, 18–55 years, $n = 1,068$; older age, 56–75 years; $n = 1,220$ and old age, >75 years; $n = 875$) and subsequently divided in two groups ($n = 1,357$) based on the presence (unhealthy) or absence (healthy) of obesity (BMI $\geq$ 30 kg·m^{-2}), and impaired metabolic health (diabetes and hypertension).

implications, as metabolic risk factors–unlike age and sex–are modifiable (15–17). In this multi-national study, mostly including hospitalized patients with COVID-19, we found similar relationships of metabolic risk factors and adiposity, with COVID-19-related mortality, as were reported by previous studies (2–14). This allowed us to address an important question: to what extent does obesity, diabetes and hypertension, which were recently found to account for almost 60% of the COVID-19 hospitalizations in the United States (26), increase the risk of COVID-19-related mortality in younger patients, when compared to older patients. We found that an additive effect of obesity, diabetes and hypertension on the risk of COVID-19-related mortality exists. Compared to the respective older and old groups without these risk factors, the adjusted risk of mortality increased particularly strong in the young and middle-aged groups with these risk factors. In this respect, compared to young and middle-aged patients without obesity, patients merely having obesity only had a moderately increased adjusted mortality risk. This risk increased considerably in young and middle-aged patients with obesity and diabetes. Such an increase in risk was not observed in the older and old patients. Importantly, the presence of all three risk factors, obesity diabetes and hypertension, independently of other comorbidities and of sex, increased the risk of COVID-19-related mortality in younger and middle-aged patients to the risk level that we observed in older patients without these diseases. This finding is potentially of major public health relevance, as younger age is considered to protect from severe COVID-19.

Studies including COVID-19 patients from the United Kingdom reported that diabetes most strongly increased the risk of COVID-19-related mortality in younger patients (27, 28). Furthermore, data from the US CDC and the US Premier Healthcare Database of hospital-based patients with COVID-19 previously suggested that younger patients with obesity, diabetes or other comorbidities, have an increased risk of COVID-19-related death, that amounted to the risk often observed in older patients (21, 22). However, in those studies no adjustment for sex and comorbidities was done. In our study, diabetes was associated with an increased risk of COVID-19-related mortality in younger and in middle-aged patients, but this relationship was attenuated with adjustment for sex, BMI and other comorbidities. Thus, our findings indicate that obesity, diabetes and hypertension comprise a phenotype strongly associated with increased risk of COVID-19-related mortality in young and middle-aged patients, independently of other important determinants of severe COVID-19.

These findings may have several clinical implications. First, they support the recommendations of international medical societies, that obesity, diabetes and hypertension are important risk factors that should be critically considered by health care providers, when COVID-19 is being diagnosed in a patient. Intense clinical surveillance of these patients, particularly during the early stages of the disease, should be ensured. This approach is also supported by our findings of an increased mortality of obese and metabolically unhealthy COVID-19 patients during the first 2 weeks after diagnosis, independently of age.

Second, in view of the changing demographics of hospitalizations–with a substantial increase among patients <55 years relative to older people (21)–health care providers should not assume that younger individuals generally are at lower risk for severity of COVID-19. Consequently, younger people with these common risk factors should also be prioritized in vaccination strategies.

Third, there is increasing concern that SARS-CoV-2 will not only become an endemic virus and that an emergent coronavirus may cause severe disease in children (29–31), but that new variants of SARS-CoV-2 may evade the body's immune response, both in vaccinated and in not yet vaccinated people (29–35). Particularly the second year of the COVID-19 pandemic has been dominated by variants of concern (36, 37). Among them, mutations of the SARS-CoV-2 spike protein, the primary antigen, may be problematic, as most recently suggested for the Omicron (B.1.1.529) SARS-CoV-2 variant of concern[1]. In this respect obesity and diabetes may become even more important risk factors than currently considered. Obesity and impaired metabolic health may adversely influence the efficacy of SARS-CoV-2 vaccines (38, 39). In this respect, most recently some preliminary data indicate that obesity, diabetes and CVD may predispose for vaccine breakthrough COVID-19 infections (40–42). Premature immunesenescence, accelerated aging of the immune system, particularly of the CD4+ and CD8+ T cell compartments, has been found in people with obesity or type 2 diabetes (43–45). Intriguingly, as a mechanism explaining this observation, intact insulin signaling was observed to play an important role in modulating the body's immune response. Insulin receptor signaling has an impact on T cell glucose metabolism and amino acid handling. In rodents, insulin receptor-deficient T cells were found to have reduced inflammatory potential and poor protective immunity against H1N1 influenza infection (46). Considering that obesity, especially central adiposity, and impaired metabolic health, strongly associate with insulin resistance (47–49), and a healthy diet and exercise (50), as well as new dietary concepts to improve the gut microbiome (51) are very helpful to improve metabolic health, reduction of fat mass and a healthy diet may be critical for the coming months of the SARS-CoV-2 pandemic.

Fourth, most recently it was shown that, beyond the acute illness, substantial burden of health loss, including disorders of lipid metabolism, diabetes and obesity, is observed in COVID-19 survivors (52, 53). Although, this has not been investigated, yet, the presence of obesity and impaired metabolic health prior to the SARS-CoV-2 infection may particularly increase the burden of health loss in COVID-19 survivors. This may be problematic especially for younger patients, who may, thereby, experience a larger amount of years of life lost, than older patients.

A strength of our study is that the multi-center LEOSS registry prospectively collects epidemiological and clinical data based on a pre-specified protocol. Furthermore, the hospitals have the capacity to also monitor patients with asymptomatic or mild SARS-CoV-2 infections. However, there are several limitations. This study analyzed factors associated with disease course at initial presentation, not treatment, and cannot assess causality. We cannot rule out the presence of confounding from socioeconomic status, health insurance issues and access to health services and country specific testing capacities, among other factors. Some of these factors could be correlated with delayed diagnosis and therefore a more complicated clinical stage at initial presentation. Furthermore, the highest documentation rates were performed by University hospitals in larger cities; consequently, rural areas might be underrepresented. Finally, the sample size in the younger age groups was relatively small, most probably resulting from the fact that younger people generally are less often hospitalized with COVID-19 compared to middle-aged and older people. The small sample size in some of the groups may result in that a statistical error may occur from skewed group comparisons.

In conclusion, we found that obesity, diabetes and hypertension have an additive effect on COVID-19-related mortality and that this effect is particularly strong in young and middle-aged patients. Furthermore, we found that obesity, diabetes and hypertension increased the risk of COVID-19-related mortality in young and middle-aged patients to the risk level that we observed in older but metabolically healthy patients. Importantly, this increased risk was independent of other comorbidities and of sex. Awareness of health care providers about this strong impact of obesity and impaired metabolic health on the risk of COVID-19-related mortality may be critical to intensify surveillance of younger patients infected with SARS-CoV-2 and to motivate subjects at risk to lose weight and improve their metabolic health.

DATA AVAILABILITY STATEMENT

Patient data from the LEOSS registry are subject to the LEOSS governance, data use, and access policy (policy text available on https://leoss.net). Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committees of all participating centers

[1]https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern

and registered at the German Clinical Trails Register (DRKS, No. S00021145). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NS and KS analyzed the data and wrote the manuscript. NS, KS, MHe, and AB designed the study. CJ, AW, YK, SB, MMR, FH, MHa, CP, MHo, JD, KW, CR, JV, MSt, and BJ collected the data and contributed to the discussion. MHe, AF, RW, HP, MSo, MRo, AS, BG, MA, DL, MSc, and AB critically reviewed the manuscript and contributed to the discussion. NS is the guarantor of this study. All authors contributed to the article and approved the submitted version.

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LEOSS STUDY GROUP

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The LEOSS study infrastructure group: Jörg Janne Vehreschild (Goethe University Frankfurt), Carolin E. M. Jakob (University Hospital of Cologne), Lisa Pilgram (Goethe University Frankfurt), Melanie Stecher (University Hospital of Cologne), Max Schons (University Hospital of Cologne), Susana Nunes de Miranda (University Hospital of Cologne), Clara Bruenn (University Hospital of Cologne), Nick Schulze (University Hospital of Cologne), Sandra Fuhrmann (University Hospital of Cologne), Annika Claßen (University Hospital of Cologne), Bernd Franke (University Hospital of Cologne), Fabian Praßer (Charité, Universitätsmedizin Berlin) und Martin Lablans (University Medical Center Mannheim).

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Early and Subsequent Epidemic Characteristics of COVID-19 and Their Impact on the Epidemic Size in Ethiopia

Abebe Feyissa Amhare [1,2]*, *Yusha Tao* [3], *Rui Li* [1] and *Lei Zhang* [1,3,4,5]*

[1] Department of Epidemiology and Health Statistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, China, [2] Department of Public Health, College of Health Science, Salale University, Fitche, Ethiopia, [3] China-Australia Joint Research Center for Infectious Diseases, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, China, [4] Melbourne Sexual Health Centre, Alfred Health, Melbourne, VIC, Australia, [5] Faculty of Medicine, Nursing and Health Sciences, Central Clinical School, Monash University, Melbourne, VIC, Australia

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Roger Nlandu Ngatu,
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***Correspondence:**
Abebe Feyissa Amhare
abebefeyissa21@gmail.com
Lei Zhang
lei.zhang1@xjtu.edu.cn

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In Ethiopia, multiple waves of the COVID-19 epidemic have been observed. So far, no studies have investigated the characteristics of the waves of epidemic waves in the country. Identifying the epidemic trend in Ethiopia will inform future prevention and control of COVID-19. This study aims to identify the early indicators and the characteristics of multiple waves of the COVID-19 epidemics and their impact on the overall epidemic size in Ethiopia. We employed the Jointpoint software to identify key epidemic characteristics in the early phase of the COVID-19 epidemic and a simple logistic growth model to identify epidemic characteristics of its subsequent waves. Among the first 100 reported cases in Ethiopia, we identified a slow-growing phase (0.37 [CI: 0.10–0.78] cases/day), which was followed by a fast-growing phase (1.18 [0.50–2.00] cases/day). The average turning point from slow to fast-growing phase was at 18 days after first reported. We identified two subsequent waves of COVID-19 in Ethiopia during 03/2020-04/2021. We estimated the number of COVID-19 cases that occurred during the second wave (157,064 cases) was >2 times more than the first (60,016 cases). The second wave's duration was longer than the first (116 vs. 96 days). As of April 30th, 2021, the overall epidemic size in Ethiopia was 794/100,000, ranging from 1,669/100,000 in the Harari region to 40/100,000 in the Somali region. The epidemic size was significantly and positively correlated with the day of the phase turning point ($r = 0.750$, $P = 0.008$), the estimated number of cases in wave one ($r = 0.854$, $P < 0.001$), and wave two ($r = 0.880$, $P < 0.001$). The second wave of COVID-19 in Ethiopia is far greater, and its duration is longer than the first. Early phase turning point and case numbers in the subsequent waves predict its overall epidemic size.

Keywords: COVID-19, epidemic size, early epidemic indicators, early characteristics of COVID-19, Ethiopia

INTRODUCTION

In late December 2019, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) was first reported in Wuhan City, China (1–3). The disease was later named coronavirus disease COVID-19 by the World Health Organization (WHO) (4, 5). The COVID-19 epidemic has since spread at an alarming rate worldwide. As of September 21st, 2021, the total number of confirmed

COVID-19 cases exceeded 206 million, and the death toll passed 4.7 million. Countries have implemented orchestrated efforts to confine the COVID-19 epidemic (6–8). Non-pharmaceutical interventions, including social distancing, face mask use and vaccination, have been shown to be effective in slowing the spread of COVID-19 (9–12).

Ethiopia confirmed its first case of COVID-19 on March 13th, 2020 (13). Since then, the Ethiopian government has adopted various strategies to prevent the spread of COVID 19. With the increase in the number of new cases, the Ethiopian government declared a five-month national emergency on April 8th, 2020, after the number of confirmed cases reached 55, but allowed economic activities to continue (14). After declaring a national emergency, the government and the Ethiopian Ministry of Health implemented strict public health measures. These measures included closing schools, restricting large gatherings, including religious gatherings in churches and mosques. Although public transportation is highly transmissible channel for COVID-19, it was only partially limited in Ethiopia. A face mask was mandatory in crowded places and public service places. Social distancing and handwashing with soap were the main control measures and were widely broadcast on the media (15). However, the lockdown was not strictly implemented due to the fragility in the country's economy and people's socio-economic conditions. This endemic disrupts the economy and increases the healthcare system's burden (16–19). Economic activities, especially agricultural and industrial activities, were necessary to continue to maintain food security. During the lockdown, the number of new cases reported daily increased dramatically. As of April 30th, the total number of confirmed SARS-COV-2 cases passed 257,442 and 3,688 deaths were reported in Ethiopia. Since February 2021, the number of new confirmed cases and death cases have been dramatically increasing (20). Stronger public health measures needed to be in place to prevent the further spread of the virus.

In Ethiopia, multiple waves of the COVID-19 epidemic has been observed. However, no studies investigated epidemic indicators of COVID-19 during the early phase of the epidemic and its subsequent waves in Ethiopia. Identifying the epidemic trend in Ethiopia will help inform future prevention and control of the epidemic. Modeling studies have been widely used to investigate the trend of the COVID-19 epidemic and evaluate relevant interventions (21–27). Previous studies demonstrated that the epidemic's early characteristics are useful in projecting the subsequent epidemics (28, 29). The research aims to identify the epidemic characteristics of COVID-19 in its early stage and multiple subsequent waves and their association with Ethiopia's overall epidemic size.

MATERIALS AND METHODS

Source of Data

We collected publicly available data related to COVID-19, such as daily confirmed cases, cumulative cases, recovery, and deaths cases from 10 regions and two administrative cities in Ethiopia from March 13th, 2020, to April 30th, 2021.

Determining the Early Characteristics of the First Wave of COVID-19

Early epidemic indicators, such as the turning point time, the number of cases at the turning point, the slow growth phase and the rapid growth phase, the number of days required to increase from 30 to 100 cases, and the case fatality rate (CFR-100) of the first 100 confirmed cases were estimated by using the Joinpoint software (30) based on the first 100 confirmed cases (28). All of turning points occurred below 30 cases (**Figure 1**). Due to this, we used 30 cases as the threshold to indicate that the epidemic has changed from a slow-growing phase to a rapid-growing phase.

Determining the Characteristics of Multiple Waves of COVID-19

Based on the cumulative confirmed COVID-19 cases, the epidemic's key characteristics were identified using the bi-logistic growth model (https://logletlab.com) among 10 regions and two administrative cities in Ethiopia. The methods of simple logistic function have been documented in previous studies (31, 32). Like the previous study conducted in Australia (29), we used the logistic growth method to know the current status of COVID-19 in Ethiopia and predict its characteristics for the upcoming months. We model the epidemic patterns by identifying one to two growth waves of the COVID-19 epidemic. By this model, the level at which epidemic saturate (K), the midpoint of each epidemic growth (t_m), the lengths of time intervals (Δt) required for the epidemic to grow from 10 to 90% of the saturation level in both waves were identified.

Determining the Overall Epidemic Size of COVID-19

The epidemic size is defined as the total number of confirmed cases as of April 30th, 2021, divided by the population size of each region and administrative city and then multiplied by 100,000 individuals.

Statistically Analysis

Spearman's correlation test was conducted to determine the correlation between epidemic size and bi-logistic parameters. In addition, the correlation between epidemic size and early-stage epidemic indicators was performed. We compared the differences between K_1 and K_2 parameters by using nonparametric Mann-Whitney tests.

RESULTS

Early Characteristics of the COVID-19 Epidemic

This study demonstrated two-phase linear fits to the first 100 confirmed cases of COVID-19 during the early phase of the epidemic in the ten regions and two administrative cities of Ethiopia. **Table 1** illustrates the early-stage epidemic characteristics in Ethiopia. We have identified the slow and fast-growing phases in the early phase of the 100 confirmed cases. The average day that the slow-growing phase turned to the fast-growing phase was 18.09 (12.36–24.82) days. The growth rate

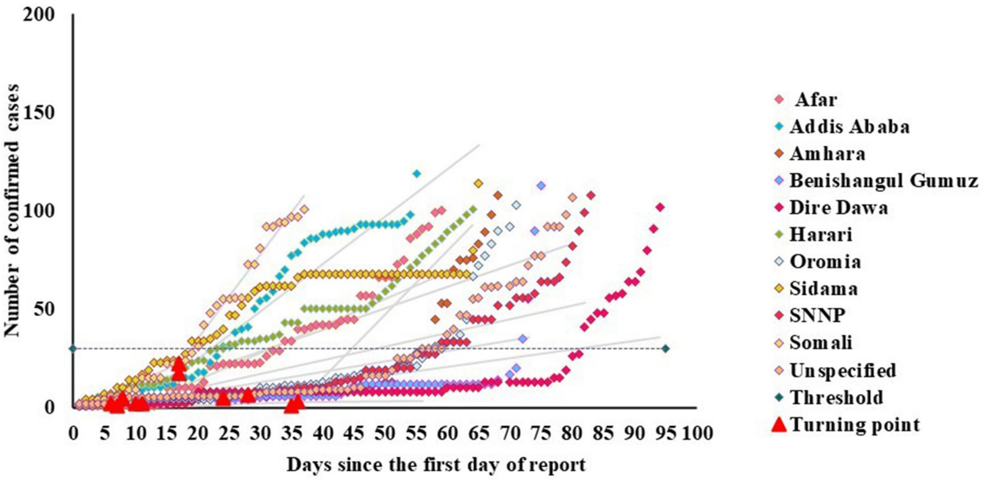

FIGURE 1 | Joinpoint two-phase fitting for Ethiopia regional states, showing the transition point below a threshold of 30 cases.

in the slow-growing phase was 0.37 (CI: 0.10–0.78) cases/day, whereas, in the fast-growing phase, it was 1.18 (CI: 0.50–2.00) cases/day. This indicated that the fast-growing phase was 0.81 times higher than the slow-growing phase. Based on a previous study, the 30 confirmed cases as a critical threshold where the COVID-19 epidemic started to increase rapidly (28). About 82% of the regional states of Ethiopia transited from slow-growing phase to fast-growing phase at a level below 30 cases, as described in **Figure 1**. Besides, the average number of days required to increase from 30 to 100 cases was 22 (CI: 14.91–24.64). The average number of cases at the phase transition point in Ethiopia was 11(CI: 4.55–19.08). The average case-fatality rate in the first 100 confirmed cases across all regional states was 1.93 (CI: 0.79–3.05).

Characteristics of Subsequent COVID-19 Outbreaks

In addition to early-stage of epidemic characteristics, this study used a bi-logistic model to investigate the characteristics of subsequent waves in 10 regions and two administrative cities. According to this investigation, all regions and administrative cities experienced two waves of COVID-19 growth, as described in **Figure 2**. This model estimated the saturation level of the cumulative number of confirmed COVID-19 cases (K) in Ethiopia in both waves. The average saturation level of the second outbreak was estimated to reach a saturation level of 22,788 cases, while the average value of the first outbreak was 10,217 cases. Also, the length of time intervals (t) required for the epidemics to grow from 10% to 90% of the saturation level was described. The average duration from 10 to 90% of the second outbreak epidemic growth was about 116 days, while the average duration of the first epidemic growth was about 95 days. In addition, the midpoint of each epidemic growth (t_m) of the first outbreak was 179 days, while the average midpoint growth for the second outbreak was 412 days (**Figure 3**).

Among all regions and cities of Ethiopia, confirmed COVID-19 cases in Addis Ababa capital city were quite high compared with other regions and cities. As of April 30th, about 166,571 confirmed cases of COVID-19 were reported, which was 64.7 % of confirmed COVID-19 cases reported in Ethiopia. The bi-logistic growth model indicated that the estimated saturation cases for the cumulative number of confirmed COVID-19 cases of both waves were 60,016 and 157,064, respectively, in Addis Ababa (**Table 2**, **Figure 2A**).

COVID-19 Epidemic Size in Various Ethiopian Regions

Epidemic size per 100,000 individuals was performed in all regions and administrative cities of Ethiopia. The epidemic size per 100,000 individuals of Addis Ababa city was 4,851, which is the highest compared with the rest of the country. This was followed by the Harari region of 1,669 per 100,000 individuals. Nationwide, the average epidemic size per 100,000 individuals was 794 with a confidence interval (CI) 159-1668 (**Table 1**).

Association Between Epidemic Characteristics and Current Size

We correlated the early stages of the epidemic characteristics and subsequent wave characteristics with the epidemic size as of the end of April 2021. **Figure 4** indicated the correlation of epidemic size with the early stage of epidemic indicators and characteristics of subsequent waves. The epidemic size per 100,000 individuals was significantly positively correlated with the day of the phase turning point ($r = 0.75$, $P = 0.008$). Also, among characteristics of subsequent waves, epidemic size per 100,000 individuals was significantly positive correlated with saturation level of wave one (K_1: $r = 0.854$, $P < 0.001$), wave two (K_2: $r = 0.880$, $P < 0.001$), and average of saturation level (K_{av}: $r = 0.877$, $P < 0.001$). Furthermore, bi-logistic parameters were significantly correlated with early-stage epidemic indicators. Among them, the midpoint of the second wave of epidemic growth was moderately and

TABLE 1 | Early indicators in the early-stage of the epidemic in each regional state of Ethiopia.

Region	Number of confirmed cases at the date the 100th cases were reported	Number of deaths at the date the 100th cases were reported	Time from 30-to-100 cases	Case fatality rate in the first 100 confirmed cases	Day of the phase turning point	Number of cases at turning point	Slow growing phase (cases/day)	Fast growing phase (cases/day)	Epidemic size/100,000
Addis Ababa	119	4	31	3.36%	36	3	0.01	0.11	4,851
Afar	100	0	25	0.00%	11	1	0.05	1.4	142
Amhara	108	0	11	0.00%	6	2	0.01	0.2	49
Benishangul Gumuz	113	0	4	0.00%	10	2	0.01	0.17	322
Dire Dawa	102	4	12	3.92%	28	8	0.25	0.3	1,056
Harari	101	4	40	3.96%	35	43	0.03	2.63	1,669
Oromia	103	3	12	2.91%	24	5	0.15	0.6	101
Sidama	114	6	46	5.26%	17	24	1.7	2.22	254
SNNP	108	2	22	1.85%	7	5	0.2	0.61	49
Somali	101	0	17	0.00%	17	23	1.5	4.26	40
Unspecified	107	0	23	0.00%	8	5	0.2	0.5	199
Mean (Confidence intervals)	106.9 (103.45–110.63)	2.10 (0.90–3.45)	22 (14.91–24.64)	1.93 (0.79–3.05)	18.09 (12.36–24.82)	11 (4.55–19.08)	0.37 (0.10–0.78)	1.18 (0.50–2.00)	794 (159–1,668)

SNNP; Southern Nations Nationalities and People. Unspecified: refers to areas where we cannot obtain public data. It is obtained by subtracting the data of 9 regions and 2 cities which have publicly available data from the national data.

negatively correlated with the case fatality rate in the first 100 confirmed cases (r = 0.54). The fast-growing phase was also moderately and negatively correlated with the lengths of time intervals ($\Delta t1$) required for the epidemics to grow from 10 to 90% of the saturation level (r = 0.51).

This study also identified the differences between fitted parameters. According to this finding, the average value of the second outbreak (Mean of K_2) is significantly greater than the average value of the first outbreak (Mean of K_1). In addition, the midpoint growth of the second outbreak (412 days) was significantly greater than the midpoint growth of the first outbreak (179 days), as shown in **Figure 3**.

DISCUSSION

Our study has several important findings. First, we investigated the early characteristics of the epidemic in the first 100 confirmed COVID-19 cases in Ethiopia. In the early epidemic indicators, the average number of days from the slow-growing phase turning to the fast-growing phase was determined. The average number of days of slow-growing phase turning to fast-growing phase was 18.09 days. This indicates that the duration of the slow-growing phase was about 18 days, which is a long duration compared with a previous study conducted in China which was about 6 days. Further, we identified that the growth rate of the fast-growing phase (1.18 cases/day) was higher than the growth rate of the slow-growing phase (0.37 cases/day). Most of the regional states of Ethiopia transited from a slow-growing phase to a fast-growing phase at a level below thirty cases. Hence thirty cases can be indicators for the fast-growing phase. This finding is consistent with a previous study (28).

Like the fast-growing phase, the case fatality rate also indicates the early diagnosis and management of the spread of COVID-19. The fast-growing phase and high case fatality rate indicate inadequate diagnosis and prevention of epidemic spread (28). Our research found that the case fatality rate is different between ten regions and two administrative cities in Ethiopia. For example, the case fatality rate is higher in the Sidama regional state compared with Addis Ababa. However, the number of confirmed cases in Addis Ababa is higher than in Sidama. This may suggest a lack of unified early diagnosis and management between regions and cities. In addition, the differences in the case fatality rates in various regions are due to lack of public health infrastructure, geographical differences, and inadequate preventive interventions. The spreading of COVID-19 is associated with geographic location (33). This finding alert health policymakers not to generalize the case fatality rate in one region to other regions in Ethiopia. In addition, the average time required to increase from 30 to 100 cases was 22 days, which is longer than the duration reported in the previous study (28). This difference may be due to the delay in the diagnosis of the epidemic or the uncontrolled spread of COVID-19. The short duration indicates a rapid spread of COVID-19.

We used the bi-logistic model to investigate the characteristics of subsequent waves. All regions and administrative cities in Ethiopia have experienced two waves of COVID-19 growth.

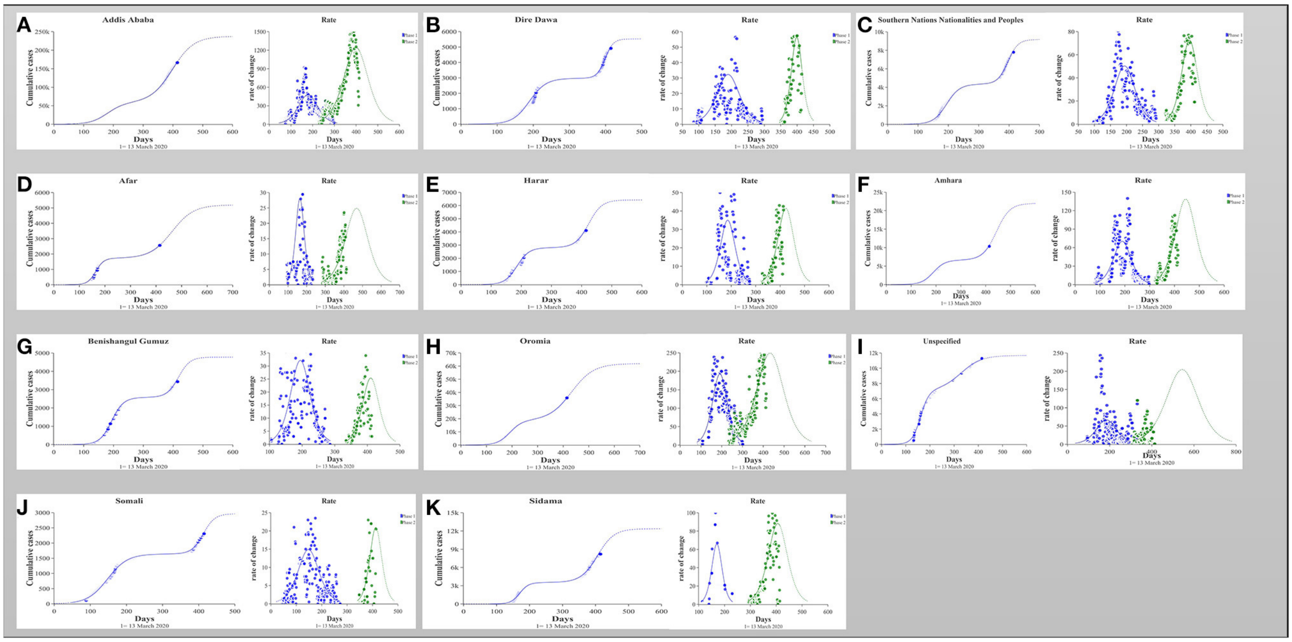

FIGURE 2 | (A–K) The number of cumulative cases was calibrated to a simple bi-logistic function, which was used to model biologic patterns with two growth waves. The parameters *K* represent the asymptotic value that bound the function and therefore specify the level at which the cases saturate; t_m represents the midpoint of the epidemic growth and hence the peak of the outbreak; Δt are the lengths of time intervals required for the epidemic to grow from 10 to 90% of the saturation level.

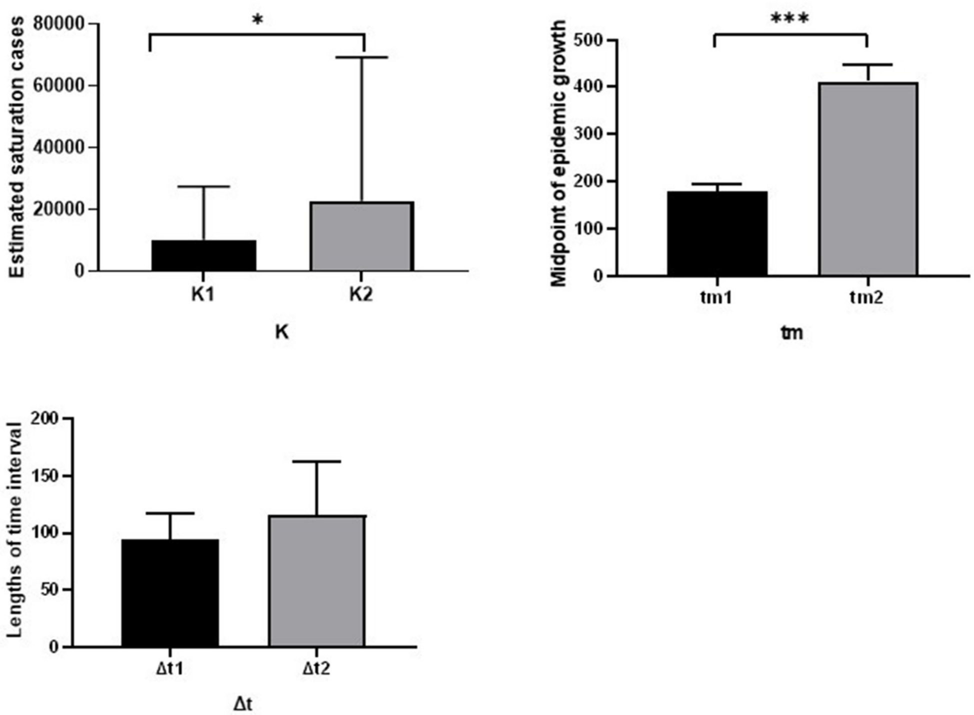

FIGURE 3 | Comparison of the fitted parameters for the bi-logistic approximation of 10 regions and 2 administrative cities of Ethiopia. * indicate $P < 0.05$, *** indicate $P < 0.001$.

TABLE 2 | The fitted parameters for the bi-logistic approximation for the dynamics of the cumulative incidence in each region and city administration of Ethiopia.

Regions	Phase	K_1	Δt_1	tm_1	K_2	Δt_2	tm_2	RMS	Mean of parameters		
									K	Δt	tm
Addis Ababa	2	54,740	127	178	236,568	184	414	1,818	145,654	155.5	296
Afar	2	1,709	67.2	163	3,509	196	467	56.9	2,609	131.6	315
Amhara	2	6,728	104	191	9,686	102	424	141	8,207	103	307.5
Benishangul Gumuz	2	2,564	83.9	194	3,041	98.6	431	37.8	2,802.5	91.25	312.5
Dire Dawa	2	2,980	103	191	2,314	45.7	396	91.5	2,647	74.35	293.5
Harar	2	2,798	86.6	186	3,569	102	425	85.5	3,183.5	94.3	305.5
Oromia	2	19,129	106	193	51,717	188	445	396	35,423	147	319
Sidama	2	3,521	62.2	171	7,078	100	395	171	5,299.5	81.1	283
Somali	2	1,663	124	149	1,451	63	415	35.8	1,557	93.5	282
SNNP	2	4,304	87.6	192	8,029	103	417	117	6,166.5	95.3	304.5
Unspecified	2	8,685	142	184	41,986	225	544	501	25,335.5	183.5	364

SNNP: Southern Nations Nationalities and People. Unspecified: refers to areas where we cannot obtain public data. It is obtained by subtracting the data of 9 regions and 2 cities which have publicly available data from the national data.

The parameters K1, K2, and K represent the asymptotic values that bound the function and therefore specify the level at which the epidemic saturates; tm1 and tm2 represent the midpoint of each epidemic growth and hence the peak of each outbreak; Δt1 and Δt2 are the lengths of time intervals required for the epidemics to grow from 10 to 90% of the saturation level, as defined by the bi-logarithmic function.

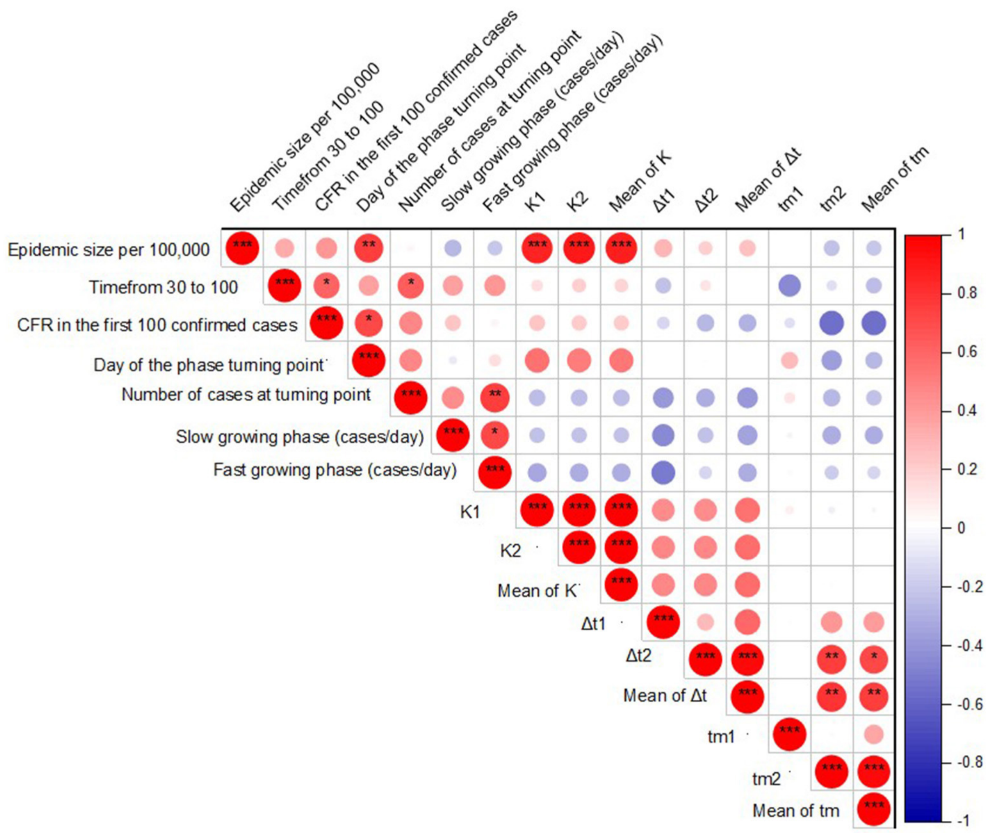

FIGURE 4 | Correlation between epidemic size, early stage of epidemic indicators, and bi-logistic parameters by Spearman's correlation test. *$p \le 0.05$, **$p \le 0.01$, ***$p \le 0.001$.

These findings indicate that the transmission period from the first confirmed case to 100 days (nearly 3 months and 1 week) is very short in all regions of Ethiopia. Since then, the spread of COVID-19 across the country has increased rapidly. The duration of the epidemics from 10 to 90% of the second outbreak (116 days) was higher than that of the first outbreak (96 days). However, there is no significant difference between them. There is no duration gap between both waves. This indicates that the waves are dependent on each other.

We further identified significant correlations between epidemic characteristics and epidemic size. The epidemic size was significantly correlated with the day of the epidemic turning point phase, which may reflect the potential ability of the healthcare system to react to control the spread of COVID-19. Understanding the characteristics of the early epidemic and the size of the epidemic may help to predict its impact on health. In addition, epidemic size per 100,000 individuals was positively correlated with the saturation level of both epidemic waves, suggesting the size of individual waves would predict the eventual epidemic size in the population.

Our research has identified important features of the epidemic in Ethiopia, and these findings may inform the health authorities to determine their gaps in controlling the spread of COVID-19. Therefore, to control the high spread of COVID-19, the government should formulate a new road map by considering the living conditions of Ethiopian citizens. Until enough vaccines are available for the population, Governments should provide minimum protection and safety for health care workers and patients at the health facility and national level, according to local conditions (34–36). Governments should guide the use of personal protective equipment and masks by increasing supplies.

The analysis also provides an early warning to the government of the *potential trajectory* of the COVID-19 epidemic in the coming months. As the rapid spread of COVID-19 continues, it is important to take preventive measures based on local conditions to reduce the spread of the pandemic. Therefore, we recommend the following measures that are very important to the government of Ethiopia and public health agencies to reduce the spread of the SARS-COV-2 pandemic until enough vaccine is available for all populations. First, persistent use of face masks across the country where it is impossible to keep social distancing. The government should enforce face masks use in public spaces. Currently, in Ethiopia, the mandatory wearing of masks is limited to the capital (Addis Ababa), whereas face mask use is low in the rest of the country. Numerous studies have demonstrated the protective effectiveness of face masks (25, 37–41). Second, frequent handwashing with soap or using hand sanitizer with moisturizers after every single activity. People have frequently used hand sanitizer or disinfectants in various parts of the country in the past few months. However, the adherence level of COVID-19 preventive measures was low (42). We recommend using a hand sanitizer with a moisturizer as running water is lacking in most parts of Ethiopia. Also, as a previous study reports, hand sanitizers with moisturizers have minimal allergies and irritation (43). Third, cultural values, owing to different customs, socioeconomic status, and education levels of Ethiopians, may affect social distancing (44). Ethiopians have a culture of sharing food and drinking coffee with their neighbors, which facilitate easy transmission of COVID-19 in the community. It is important to maintain social distancing as much as possible, especially in the field of public services. Finally, we recommend health professionals and public health institutions to work together to increase community awareness of the severity of COVID-19 and discover innovative ways to prevent it. Frequently health education for communities would be necessary.

This study has several limitations. First, we used publicly available data, which may contain underreported values that affect the results of the study. Second, there are differences in the reporting of COVID-19 status in various regions and cities in Ethiopia. Such differences might affect the quality of data. Third, since the control strategies implemented in various parts of Ethiopia are different from those of other countries, our research results may not be representative of other countries. Fourth, interventions such as COVID-19 testing may also impact on the epidemic size, but were not investigated in this study. Finally, the results of this study cannot be compared with findings in neighboring countries due to the lack of comparable studies in neighboring countries. We recommend further investigation to identify corresponding early characteristics and epidemic indicators for COVID-19 in these countries. This will enhance the control and prevention of COVID-19 in the region as a whole.

CONCLUSIONS

The second wave of COVID-19 in Ethiopia is far greater, and its duration is longer than the first. Early phase turning point and case numbers in the subsequent waves predict its overall epidemic size. Understanding the characteristics of the epidemic and the epidemic size of COVID-19 in Ethiopia will inform authorities' decisions on the prevention and control of the epidemic.

DATA AVAILABILITY STATEMENT

We used publicly available data related to COVID-19, and details of the sources are included in the article.

AUTHOR CONTRIBUTIONS

AA and LZ: designed the study. AA, YT, and RL: performed the study and analyzed the data. AA and YT: wrote the manuscript. LZ: provided expert consultations. All authors participated in its design and coordination. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Prevalence and Outcomes of Pancreatic Enzymes Elevation in Patients With COVID-19: A Meta-Analysis and Systematic Review

You Zhou[1,2,3†], Yu-Tong Ge[2,4†], Xiao-Xi Yang[1,2], Qian Cai[1], Yan-Bing Ding[1,2], Liang-Hao Hu[5] and Guo-Tao Lu[1,2*]*

[1] Pancreatic Center, Department of Gastroenterology, Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China, [2] Yangzhou Key Laboratory of Pancreatic Disease, Institute of Digestive Diseases, Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China, [3] Department of Nursing, Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China, [4] Department of Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China, [5] Department of Gastroenterology, Changhai Hospital, The Second Military Medical University, Shanghai, China

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Roger Nlandu Ngatu, Kagawa University, Japan

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Fatemeh Tajik, Iran University of Medical Sciences, Iran

Correspondence:
Guo-Tao Lu
pkulgt@163.com
Liang-Hao Hu
lianghao-hu@hotmail.com

[†] These authors have contributed equally to this work

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Background: Although coronavirus disease 2019 (COVID-19) is considered to be a disease that mainly involves the respiratory system, an increasing number of studies have reported that COVID-19 patients had pancreatic enzymes (PE) elevation and even pancreatic injury. The study aims to determine the prevalence of PE elevation, and the relationship between elevated PE and prognosis in COVID-19 patients.

Methods: A comprehensive literature search was conducted according to the PRISMA guideline in PubMed, Embase, Scopus, Web of Science, and Google Scholar for studies reporting PE elevation in patients with COVID-19 from 1st January 2020 to 24th November 2021.

Results: A total of 13 studies (24,353 participants) were included in our review. The pooled prevalence of PE elevation in COVID-19 patients was 24% (18%–31%), the pooled odds ratio (OR) of mortality was 2.5 (1.7–3.6), the pooled OR of ICU admission was 4.4 (2.8–6.8), and the pooled OR of kidney injury, respiratory failure and liver injury were 3.5 (1.6–7.4), 2.0 (0.5–8.7), and 2.3 (1.4–3.9) respectively. In addition, the subgroup analysis revealed that although PE elevated to $> 3\times$ upper normal limit (ULN) was significantly related to the mortality (OR = 4.4, 2.1–9.4), it seemed that mild elevation of PE to 1–3 ULN also had a considerable risk of mortality (OR = 2.3, 1.5–3.5).

Conclusions: PE elevation was a common phenomenon in patients with COVID-19, and was associated with poor clinical outcomes. However, due to the limited numbers of included studies, the result of our study still needed to be validated.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=295630, identifier: CRD42021295630.

Keywords: COVID-19, pancreatic enzymes, elevation, outcome, meta-analysis, review

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel severe respiratory infectious disease caused by severe respiratory syndrome coronavirus-2 (SARS-CoV-2). Since the first case was officially reported in Wuhan, China in December 2019, COVID-19 has experienced a widespread outbreak and epidemic worldwide, which has caused tremendous impact and pressure on the medical and health systems around the world (1). On March 11, 2020, the World Health Organization announced it as a global pandemic disease. As of November 28, 2021, over 260 million confirmed cases have been reported globally, of which nearly 5.2 million died (2). COVID-19 has now developed into a global health crisis.

Although SARS-CoV-2 was believed to mainly invade the respiratory system of patients, with clinical manifestations as fever, cough, shortness of breath, and extensive lung consolidation, it cannot be ignored that some patients simultaneously had digestive symptoms as nausea, vomiting, and diarrhea (3–6). Consistent with SARS-CoV, SARS-CoV-2 invades cells through combining its spike protein with the angiotensin-converting enzyme II (ACE II) receptors (7, 8). Existing studies suggested that, in addition to type II alveolar epithelial cells, ACE II receptors are also highly expressed in esophagus, small intestine, colon and pancreas (9–11), and show a high affinity for SARS-CoV-2. Therefore, the pancreas may also be a potential target of SARS-CoV-2, which can lead to undetectable pancreatic injury (11).

Wang et al. (12) first reported pancreatic enzymes (PE) elevation in COVID-19 patients in a study involving infected people in the early stage of the epidemic. Subsequently, an increasing number of studies reported the similar findings. Since the critically ill COVID-19 patients often experience severe systemic inflammatory, shock, microcirculatory disturbance and renal failure, some scholars believed that PE elevation might be associated with pancreatic ischemic injury (13–15), and the elevated PE can serve as a surrogate marker for poor prognosis of COVID-19 patients. However, in different studies, due to the different sample sizes and definition of PE elevation, the prevalence of PE elevation varied greatly, and the clinical significance of it was still controversial (14, 16). In a previous meta-analysis by Goyal et al. (17), hyperlipasemia was found to be associated with the severity of COVID-19. However, in their study, severe COVID-19 was defined as death, intensive care unit (ICU) admission and need for mechanical ventilation, which was not rigorous because the elevated PE may have different impacts on different clinical outcomes. In addition, the included studies in their meta-analysis included letter to editor and correspondence, lacking enough case-control and cohort studies covering large samples and multi-centers. We believed that the result of their study was open to question.

Therefore, we performed this meta-analysis and systematic review in order to 1) determine the prevalence of PE elevation in COVID-19 patients, and 2) summarize the impact of PE elevation on the clinical outcomes in patients with COVID-19.

METHODS

Protocol Registration

This meta-analysis and systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (18), and this study was part of the registered protocol on the International Prospective Register of Systematic Reviews (CRD42021295630).

Search Strategy

With the assistance of a professional librarian, we determined the search terms and conducted a literature search in five online databases (PubMed, Embase, Scopus, Web of Science, and Google Scholar) from 1st January 2020 to 24th November 2021 for studies reporting PE elevation in COVID-19 patients. The literature search was limited to English publications. Search terms in PubMed included: [("COVID-19"[MeSH] OR "COVID-19" OR "COVID 19" OR "COVID-19 Virus Disease*" OR "COVID-19 Virus Infection*") OR ("SARS-CoV-2"[MeSH]" OR "SARS-CoV-2" OR "SARS-CoV-2 Virus*" OR "2019-nCoV" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ("Coronavirus"[Mesh] OR "Coronavirus" OR "Coronaviruses")] AND [("Amylases"[Mesh] OR "Amylases" OR "Amylase" OR "hyperamylasemia") OR ("Lipase"[MeSH] OR "Lipase" OR "Hyperlipasemia") OR ("pancreatic enzymes")] AND ("elevat*"). Two reviewers (YZ and YTG) also screened the references of the key articles to include additional studies left out in the initial search.

Eligibility Criteria

Based on the PICOS (Population, Intervention/Exposure, Comparison, Outcome, and Study design) strategy, the inclusion criteria were as follows:

Population: participants included in studies were clearly diagnosed with COVID-19.

- Exposure: PE elevation.
- Comparison: normal level of PE.
- Outcome: COVID-19 clinical outcomes (mortality or hospitalization or complications).
- Study design: Observational studies.

The exclusion criteria were as follows:

- Non-adult studies.
- Studies with unavailable full-text.
- Studies with unclear criteria for PE elevation.
- Studies not providing specific prevalence or outcomes of PE elevation.
- Protocols, review articles, abstracts, letters to editor, correspondence, case reports, and pre-prints.

Study Selection

All identified articles were first imported into the Endnote X9 software to remove duplicates manually, then the titles and abstracts of studies were screened by two reviewers (XXY and QC) blindly in accordance with the inclusion and exclusion criteria to exclude irrelevant articles. The articles meeting the eligibility criteria were next screened on full text by the same two reviewers. Any disagreements were resolved by consulting another reviewer (YZ).

Data Extraction

Data were extracted by two reviewers (YZ and XXY) using a designed Excel sheet. Any disagreements were solved by another reviewer (LHH). The following information was recorded: 1) author, 2) year of publication, 3) country, 4) study type, 5) samples size, 6) type of elevated PE, 7) definition for PE elevation, 8) proportion of patients with PE elevation among all patients, 9) proportion of patients with acute pancreatitis (AP) among patients with PE elevation, 10) clinical outcomes of COVID-19 patients with PE elevation.

Quality Assessment

The Quality in Prognostic Studies tool was used to assess the quality of the included studies, which includes six items: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis (19). Each article was assessed by two reviewers (YZ and QC) independently using a consistent standard. Any disagreements were resolved by consulting another reviewer (GTL).

Statistical Analysis

The statistical analysis was performed using the Stata SE Version 16 software. We conservatively used a random-effects model to analyze the impact of PE elevation on mortality, ICU admission, and complications. A forest plot was used to visualized the data. The heterogeneity of included studies was estimated using the Cochran's Q-test and I^2 statistics, and the value of I^2 between 0 and 25%, 25–75%, and >75% was considered mild, moderate, and high heterogeneity, respectively (20). Prespecified subgroup analyses based on the definition of PE elevation and data source were performed to explore the heterogeneity of clinical outcomes between studies. Sensitivity analyses were preformed to explore the impact of each study by removing studies one by one.

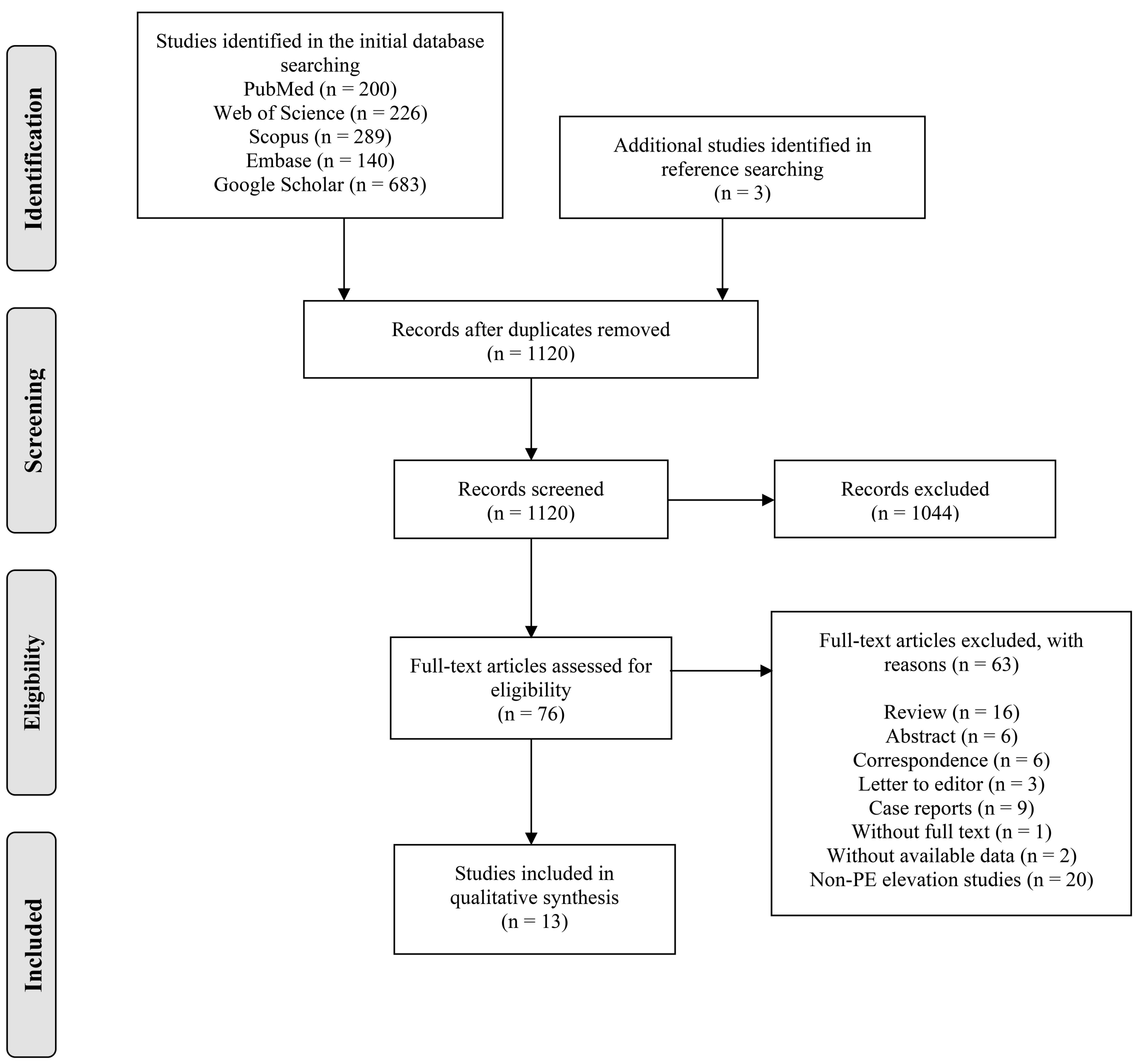

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Egger's test and visual inspection of funnel plot were used to examine the publication bias. A *P*-value <0.05 was considered statistically significant.

RESULTS

Search Results

The PRISAM flow diagram showed the process of article selection (**Figure 1**). A total of 1,538 records were extracted from the initial search, and three additional studies were identified through the reference searching. After removing the duplicates ($n = 421$), we screened 1,120 studies with titles and abstracts, of which 76 studies meeting the eligibility criteria were reviewed with full text. Thirteen studies (12–14, 16, 21–29) were finally included for qualitative and quantitative analysis in this review.

Study Characteristics

Table 1 summarized the characteristic of the included studies. Thirteen studies were from the USA ($n = 5$), China ($n = 3$), Italy ($n = 2$), Turkey ($n = 2$), and Germany ($n = 1$), of which, 12 were retrospective, one (24) was prospective, and five studies (14, 16, 23, 25, 29) were multicenter. The sample size ranged from 38–17225, and the proportion of male participants varied from 44.6–78.9%. Each study had a clear definition of PE elevation, however, it lacked a unified standard and there was an obvious heterogeneity in the definition of upper normal limit (ULN). Ten studies (12–14, 16, 21–23, 26, 27, 29) defined PE elevation as > ULN, and three studies (24, 25, 28) defined PE elevation as > 3× ULN. The results of quality assessment were shown in **Supplementary Table 1**.

Prevalence of PE and AP

Thirteen studies reported the prevalence of PE elevation in COVID-19 patients, covering 2,4353 participants, of which 3,180 participants had elevated PE. The prevalence of PE elevation ranged from 8.2 to 58.2%. The pooled prevalence of PE elevation in COVID-19 patients was 24% (95% CI: 18%−31%), with a high degree of heterogeneity ($I^2 = 98.9\%$) (**Figure 2**).

Six studies (13, 14, 21, 22, 25, 26) with samples more than ten patients reported AP diagnosis according to the revised Atlanta classification of acute pancreatitis 2012 (30), covering 1,705 patients with elevated PE > 3× ULN, of which 182 developed AP. The prevalence of AP ranged from 1.3 to 18.8%. The pooled prevalence of AP in patients with elevated PE > 3× ULN was

TABLE 1 | Characteristic of studies reporting pancreatic enzymes elevation in COVID-19 patients.

Study	Year	Country	Study type	Male, *n* (%)	Age (mean ± SD)	Sample size, n	PE	Definition of PE elevation
Ahmed et al. (14)	2021	USA	Retrospective	606 (61.1)	64 ± 17	992	Lipase	≥ ULN (Center 1: 78 IU/L, Center 2: 60 IU/L)
Bacaksiz et al. (13)	2021	Turkey	Retrospective	700 (51.8)	NP	1378	Amylase and lipase	≥ ULN (Amylase: 105 U/L, lipase: 65 U/L
Benias et al. (29)	2021	USA	Retrospective	680(46.2%)	NP	1471	Lipase	≥ ULN
Caruso et al. (21)	2021	Italy	Retrospective	692 (63.4)	64 (IQR: 52–77)	1092	Lipase	≥ ULN (45 U/L)
Ding et al. (22)	2021	China	Retrospective	37(67.3)	63 (Range: 29-79)	55	Amylase and lipase	≥ ULN (Amylase: 135 U/L, lipase: 78 U/L
Li et al. (23)	2021	China	Retrospective	737 (48.6)	61 (IQR: 49–69)	1515	Amylase	≥ ULN (115 U/L)
Rasch et al. (24)	2021	Germany	Prospective	30(78.9)	68.5 (Range: 26–85)	38	Lipase	≥ 3 ULN (60 U/L)
Singh et al. (25)	2021	USA	Retrospective	8349 (52.7)	NP	17225	Lipase	≥ 3× ULN or 180 U/L
Troncone et al. (26)	2021	Italy	Retrospective	148 (58.3)	67 (IQR: 53–81)	254	Amylase and lipase	≥ ULN (Amylase: 125 U/L for patients <70 years old, 160 U/L for patients >70 years old; lipase: 78 U/L)
Akkus et al. (27)	2020	Turkey	Retrospective	73(57.5)	NP	127	Lipase	≥ ULN (60 U/L)
Baltar et al. (16)	2020	USA	Retrospective	33(46.5)	69.4 ± 15.8	71	Lipase	≥ ULN (60 U/L)
Barlass et al. (28)	2020	USA	Retrospective	37(44.6)	NP	83	Lipase	≥ 3× ULN (52 U/L)
Wang et al. (12)	2020	China	Retrospective	24(46.2)	NP	52	Amylase and lipase	≥ ULN (Amylase: 90 U/L, lipase: 70 U/L)

NP, not reported; PE, pancreatic enzymes, ULN: upper normal limit.

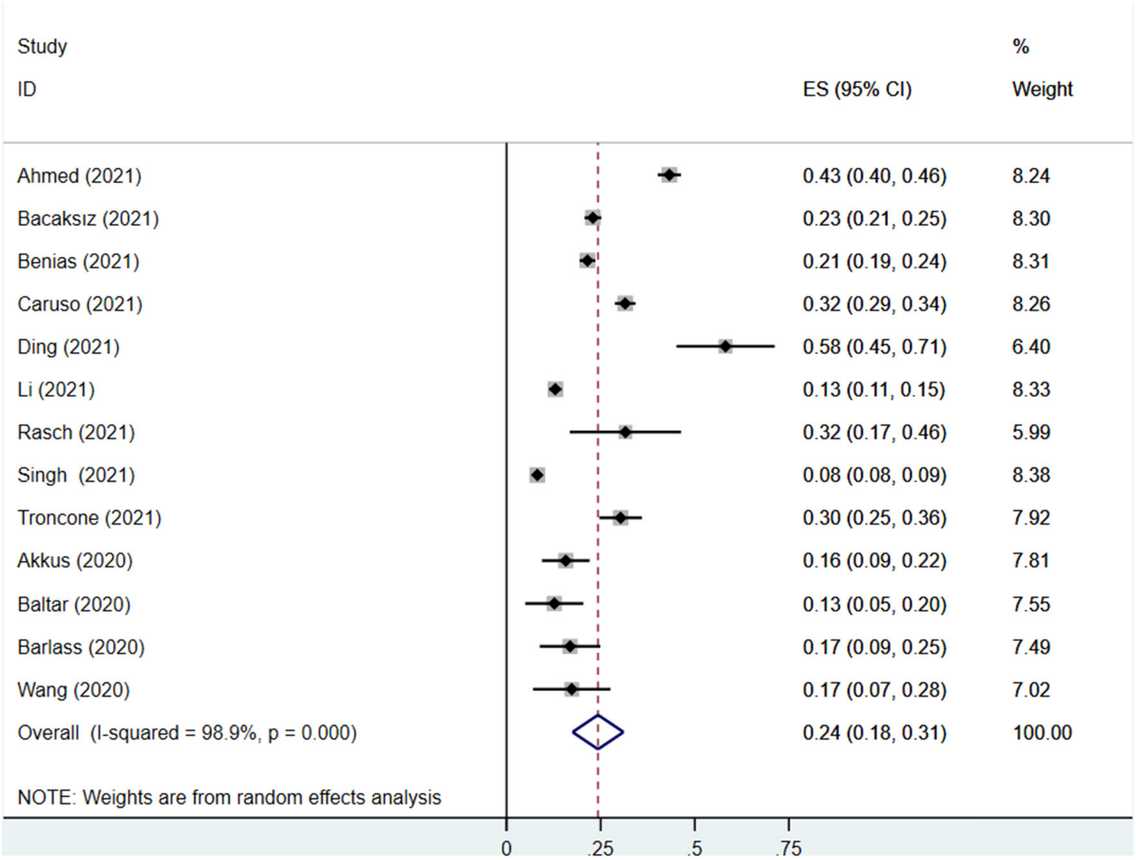

FIGURE 2 | Effect size analysis for the prevalence of PE elevation in COVID-19 patients.

9% (95% CI: 2%-15%), with a high degree of heterogeneity (I^2 = 93.2%) (**Supplementary Figure 1**).

Analysis of PE Elevation and Mortality

Ten studies (13, 14, 16, 21–23, 25–27, 29) reported the mortality associated with elevated PE. A total of 2,4207 participants including 3,142 participants in the elevated PE group, of which 760 participants died, and 2,1065 participants in the normal PE group, of which 2,033 participants died were included in the analysis. The mortality ranged from 10.0 to 79.3%. PE elevation was significantly related to the mortality of COVID-19 patients (OR = 2.5, 95% CI: 1.7–3.6), with substantial heterogeneity (I^2 = 89.5%) (**Figure 3**).

Since the heterogeneity was significant, we performed a sensitivity analysis to explore the impact of each study. The result showed that two studies (13, 23) affected the pooled OR (odds ratio) of mortality (**Supplementary Figure 2**). After removing any one of the two studies, the I^2 did not decrease significantly (78.6–87.7%). After removing both studies simultaneously, the heterogeneity became acceptable (I^2 = 13.3%), and the pooled OR was 1.7 (95% CI: 1.5–1.9) (**Supplementary Figure 3**).

Subsequently, we performed a subgroup analysis based on the definition of PE elevation and data sources. Ten studies were divided into the 1–3 ULN group (13, 14, 21, 23, 26, 29) and the >3× ULN group (13, 14, 21, 23, 25, 26, 29) (six studies (13, 14, 21, 23, 26, 29) reported the two conditions). The 1–3 ULN group involved 1,330 participants, of which 424 died, and the >3× ULN group involved 1,754 participants, of which 308 died. The result of subgroup analysis showed that PE elevated to both 1–3 ULN (OR= 2.3, 95% CI: 1.5–3.5) and >3× ULN (OR = 4.4, 95% CI: 2.1–9.4) were significantly related to mortality, and the pooled OR of the 1–3 ULN group was similar to that before grouping (OR = 2.5, 95% CI: 1.7–3.6) (**Supplementary Figure 4**). Considering two studies with obvious heterogeneity, we also performed subgroup analysis after removing these two studies (**Table 2**) (**Supplementary Figure 4**). Consistent with the previous result, after removing the heterogeneous studies, the pooled OR of the 1–3ULN group (OR = 1.7, 95% CI: 1.3–2.1) was basically the same as that of all eight studies (OR = 1.7, 95% CI: 1.5–1.9).

Based on the different sources of data and removing the heterogeneous studies, we categorized eight studies into the single-center group (21, 22, 26, 27) and the multi-center group (14, 16, 25, 29). Compared with the pooled OR of all eigth studies (OR = 1.7, 95% CI: 1.5–1.9) and four multi-center studies (OR= 1.6, 95% CI: 1.4–1.8), it was worth noting that the pooled OR of single-center group seemed to be higher (OR = 2.4, 95% CI: 1.4–4.2) (**Table 2**) (**Supplementary Figure 4**).

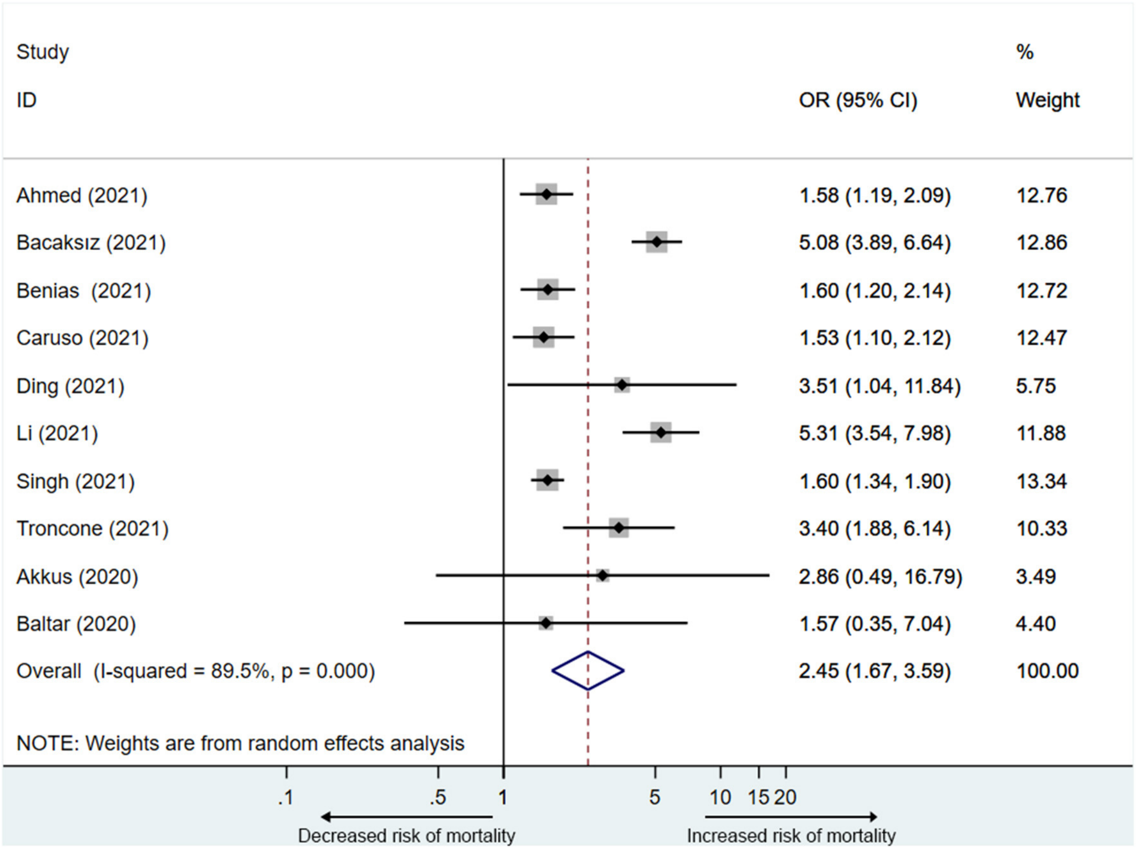

FIGURE 3 | Effect size analysis for mortality in COVID-19 patients with PE elevation.

Analysis of PE Elevation and Hospitalization

Six studies (14, 16, 21, 26–28) reported PE elevation was associated with ICU admission in COVID-19 patients. A total of 1,783 participants including 520 participants in the elevated PE group, of which 147 were admitted to the ICU, and 1,263 participants in the normal PE group, of which 138 were admitted to the ICU were included in the analysis. As is shown in **Figure 4**, PE elevation was significantly associated with ICU admission in COVID-19 patients (OR = 4.4, 95% CI: 2.8–6.8), with acceptable heterogeneity (I^2 = 36.8%).

Three studies reported that PE elevation was related to the length of stay (LOS). Ahmed et al. (14) reported that the median LOS for patients with elevated PE was 15 days (IQR: 8.3–30 days), and that for patients with normal PE was 11 days (IQR: 5.5–20.5 days). Akkus et al. (27) found that the median LOS for patients with elevated PE was 11.5 days (range: 3–41 days), and that for patients with normal PE was 8 days (range: 0–38 days). Benias et al. (29) reported that the LOS for patients with normal PE, 1–3 ULN PE, and >3× ULN PE was 11.19, 15.08, and 24.20 days respectively. Compared with normal PE, the median LOS for COVID-19 patients with elevated PE increased by about 40%.

In addition, Ahmed et al. (14) found that patients with elevated PE had longer ICU LOS. Compared with those without PE elevation (12days, IQR: 3.3–20 days), the median ICU LOS for patients with elevated PE (19 days, IQR: 7.5–33.5 days) increased by about 60%. Ding et al. (22) (20.7% vs. 47.8%) and Li et al. (23) (76.5% vs. 94.5%) found that patients with elevated PE had a lower discharge rate respectively. Singh et al. (25) reported that patients with or without PE elevation did not show significant difference in rehospitalization (42.0% vs. 42.8%).

Analysis of PE Elevation and Complications

Six studies (13, 22–26) reported complications in PE elevation patients. Among them, kidney injury (KI) was the most common complication. The meta-analysis suggested that elevated PE was significantly associated with the increased risk of KI (OR= 3.5, 95% CI: 1.6–7.4), with significant heterogeneity (I^2 = 95.0%) (**Supplementary Figure 5**). There were two studies each reporting respiratory failure (23, 25) and liver failure (24, 26). The pooled OR of respiratory failure in COVID-19 patients with elevated PE was 2.0 (95% CI: 0.5–8.7) (**Supplementary Figure 5**), and the pooled OR of liver failure was 2.3 (95% CI: 1.4–3.9) (**Supplementary Figure 5**). In addition, the reported complications included acute heart failure, cardiac injury, sepsis, and disseminated intravascular coagulation as well (23).

TABLE 2 | Subgroup analysis on the association between of pancreatic enzymes elevation and mortality in COVID-19 patients.

Subgroups	Number of studies	Sample size (n)	OR	95% CI	I^2 (%)	*P*-value
Definition of PE elevation						
1–3 ULN	6 (13, 14, 21, 23, 26, 29)	1330	2.3	1.5–3.5	87.5	< 0.001
>3 ULN	7 (13, 14, 21, 23, 25, 26, 29)	1754	4.4	2.1–9.4	92.9	< 0.001
Reference	10	3142	2.5	1.7–3.6	89.5	< 0.001
1–3 ULN*	4 (14, 21, 26, 29)	892	1.7	1.3–2.1	41.1	0.165
>3 ULN*	5 (14, 21, 25, 26, 29)	1680	1.9	1.3–2.6	61.1	0.036
Reference*	8	2630	1.7	1.5–1.9	13.3	0.326
Data source						
Single-center*	4 (21, 22, 26, 27)	470	2.4	1.4–4.2	54.4	0.087
Multi-center*	4 (14, 16, 25, 29)	3554	1.6	1.4–1.8	0.0	1.000
Reference*	8	2630	1.7	1.5–1.9	13.3	0.326

**After removing the two heterogeneous studies (13, 23).*
CI, confidence interval; OR, odds ratio; PE, pancreatic enzyme; ULN, upper normal limit.

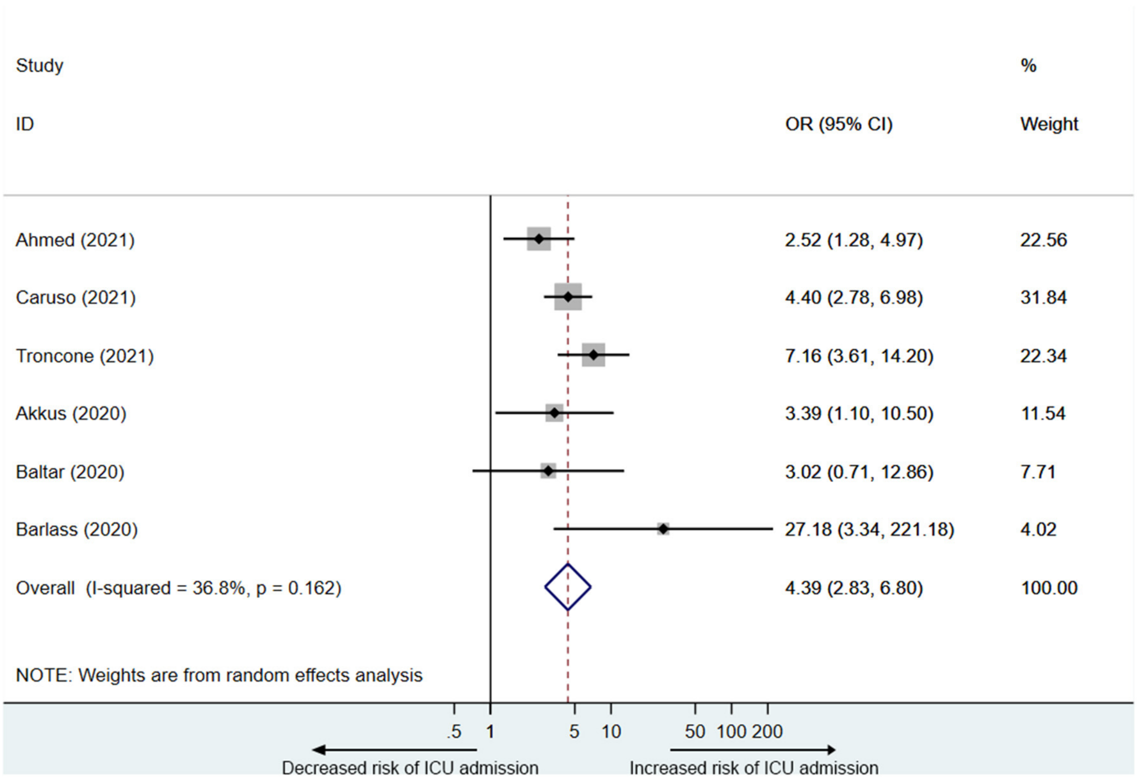

FIGURE 4 | Effect size analysis for ICU admission in COVID-19 patients with PE elevation.

Publication Bias

Egger's test revealed that, there was no significant publication bias for studies reporting mortality (P = 0.463), ICU admission (P = 0.647), and KI (P = 0.523) associated with PE elevation, except for PE prevalence (P = 0.006). **Supplementary Figure 6** for visual funnel plots.

DISCUSSION

To the best of our knowledge, this is the latest and most comprehensive systematic review and meta-analysis on the prevalence and clinical outcomes of PE elevation in COVID-19 patients. Our study demonstrated that, overall, PE elevation was common in COVID-19 patients. The pooled prevalence of

PE elevation was 24%, which was significantly higher than that of the previous mate-analysis by Goyal et al., and the risk of developing severe COVID-19 in patients with hyperlipasemia in their study was higher than that of adverse outcomes in our study (17). This is understandable because their meta-analysis included fewer and earlier studies. In addition, we also found that about 9% of patients with elevated PE > 3× ULN eventually developed AP, which was also higher than that of a previous meta-analysis on the prevalence and clinical outcomes of AP in COVID-19 patients reported by Yang et al. (31). In their study, the pooled prevalence of AP complicated by COVID-19 was about 3.1%, of which about 18.5% eventually died. COVID-19 patients with pancreatic injury often had poor clinical outcomes. According to the revised Atlanta classification of acute pancreatitis 2012, the diagnosis of AP included abdominal pain, the elevated PE > 3× ULN, and characteristic findings of AP on imaging. However, it cannot be denied that patients did not meet the diagnostic have no potential pancreatic injury and potential risk of poor prognosis. In this systematic review and meta-analysis, we extensively searched and included existing studies on PE elevation in patients with COVID-19 and included more participants to reveal the association between elevated PE and the clinical outcomes of COVID-19 patients.

At present, the cause of PE elevation was still unclear. In the autopsy of patients with severe acute respiratory syndrome, SARS-CoV was found to be present in pancreatic tissue (32). Due to the similarity of the two viruses and the ACE II receptors highly expressed in the pancreas, pancreatic injury caused by the direct invasion of SARS-CoV-2 was one of the potential causes of PE elevation. In the case report by Schepis et al., SARS-CoV-2 RNA was detected for the first time in a pancreatic pseudocyst fluid sample from a COVID-19 patient (33). In addition, a Chinese pathology study found that COVID-19 patients had a small amount of pancreatic islet cell degeneration (34). Although the above studies seemed to verify the possibility of direct damage by SARS-CoV-2, in critically ill patients, PE elevation often occurred. The most widely accepted explanation for PE elevation with non-viral causes was pancreatic ischemia (15, 35, 36). When the patient had severe infection, hypoperfusion and shock, the pancreas was insufficiently perfused, which will lead to pancreatic injury. In addition, non-pancreatic causes such as intestinal inflammation (37), diabetes (38), acidosis (39), and renal failure (38, 40, 41) can also lead to PE elevation. Although a variety of causes, including pancreatic injury, can lead to PE elevation, it was undeniable that when the above symptoms appeared in COVID-19 patients, it often indicated the occurrence of poor clinical outcomes.

Our meta-analysis and systematic review found that PE elevation in COVID-19 patients was significantly associated with the increase of mortality, ICU admission, LOS, and clinical complications as KI, respiratory failure and liver failure. In the analysis of mortality, the pooled OR without two heterogeneous studies (13, 23) was 1.7, which was significantly lower than the pooled OR of 2.5 for all studies. In these two studies, we found that 50.1% of the patients were diagnosed with severe COVID-19 and 43% with severe pneumonia, respectively. In a meta-analysis involving 30 studies, the proportion of severe COVID-19 was about 26% (42). In addition, studies have shown that severe COVID-19 and more comorbidities were the risk factors for higher clinical mortality (43, 44). Although the severity of COVID-19 was not clearly reported in other included studies, we believed that the heavier condition of patients contributed to the higher mortality, resulting in the overestimation of the risk of pooled mortality. Compared with the existing discovered risk factors for mortality of COVID-19 patients such as gender (45, 46), age (43, 45–47), diabetes (45, 48), history of COPD (45), and chronic cardiac disease (49), we found that PE elevation had a similar risk for mortality. Therefore, PE elevation may also serve as a risk indicator of mortality for patients with COVID-19.

In the subgroup analysis of mortality based on different definition of PE elevation, we found that patients with elevated PE of >3× ULN had a higher risk of death. In addition, it was also interesting that regardless of including or excluding the heterogeneous studies, the pooled OR of mortality in the 1–3 ULN group did not change a lot (2.3 vs. 2.5, 1.7 vs. 1.7), which indicated that a slight increase in PE, even if it did not satisfy the diagnostic criterion of AP, will have a hazardous effect on the clinical outcomes of COVID-19 patients. In other words, it is possible that PE is a sensitive marker for predicting the mortality in COVID-19 patients.

In the subgroup analysis on mortality based on different data sources, the pooled OR of mortality in single-center studies was higher than that of multi-center studies (2.4 vs. 1.6). Among the included multi-center studies, one was a database study (25), one study was based on two tertiary hospitals and four community hospitals (16), and two studies was based on several major tertiary medical systems (14, 29). Since the time of data recorded and the methods of measurement and testing in public databases were difficult to ensure consistency (50), and the conditions of patients in community hospitals were different from those in tertiary medical institutions, we believed that the existing multi-center studies may underestimate the real risk of mortality in COVID-19 patients with elevated PE. Therefore, we hoped that prospective studies based on several tertiary medical institutions can be carried out to explore the real risk of hospital mortality related to PE elevation in COVID-19 patients. And on this basis, further explore the specific sources and risk factors of PE elevation.

In addition, it is worth noting that Ahmed et al. (14) tried to explore the relationship between PE elevation, D-dimer and mortality, ICU admission. Existing studies have proved that laboratory factors including D-dimer levels, demographic factors, patient history factors, physical examination factors, and clinical scores were significantly related to the severity and poor prognosis of COVID-19 patients (51). Since the COVID-19 patients often underwent various examinations during hospitalization, which generated rich medical records, it will be a meaningful attempt to predict the clinical outcomes of COVID-19 patients through using these multi-dimensional data. At present, machine learning algorithm has been widely used in the prediction tasks of complications, mortality, etc. in COVID-19 (52–54). We hoped that future studies can develop similar predictive models based on multi-omics clinical data including PE elevation to predict the clinical outcome of COVID-19 patients.

This systematic review and meta-analysis also had certain limitations. First, we only searched articles in English, which may lead to potential bias of publication. Second, due to the limited number of articles included, the results showed significant heterogeneity. Although we attributed it to the differences in the severity of COVID-19, there may also be other potential factors that we overlooked. Third, although we tried to perform a subgroup analysis to explore the impact of PE elevation on specific clinical outcomes, due to the few studies reporting detailed complications, the result of our analysis was unstable and needed to be validated by including more studies in the future.

CONCLUSION

In conclusion, our research found that PE elevation was a risk factor for poor clinical outcomes in patients with COVID-19. Compared with patients with normal PE, patients with elevated PE had a higher risk of mortality, ICU admission, and complications. In addition, future studies are still needed for further analysis of more impacts of PE elevation 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.

AUTHOR CONTRIBUTIONS

All authors contributed to the development of the manuscript. YZ, Y-TG, L-HH, and G-TL designed the study. YZ and Y-TG conducted literature searching with the help of Y-BD and L-HH. X-XY and QC screened and reviewed the articles. YZ and QC assessed the quality of included studies. YZ and X-XY extracted the data from included studies. YZ and Y-TG drafted the manuscript. Y-BD, L-HH, and G-TL provided guidance and approved the final draft. All authors contributed to the article and approved the submitted version.

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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.2022.865855/full#supplementary-material

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Age, Sex, and Race/Ethnicity in Clinical Outcomes Among Patients Hospitalized With COVID-19, 2020

*Jusung Lee**

Department of Public Health, University of Texas at San Antonio, San Antonio, TX, United States

The COVID-19 pandemic revealed the disproportionate risk of poor clinical outcomes among population subgroups. The study investigates length of stay (LOS), intensive care unit (ICU) admission, and in-hospital death across age, sex, and race among patients hospitalized with COVID-19. A pooled cross-sectional study analyzed hospital discharge data of state-licensed hospitals in Texas from April to December 2020. Of 98,879 patients, males accounted for 52.3%. The age distribution was 31.9% for the 65–79 age group, 29.6% for those aged 50–64, and 16.3% for those older than 79. Whites constituted the largest proportion (42.6%), followed by Hispanics (36.2%) and Blacks (13.1%). Higher in-hospital death rates were found among patients aged 80 and over (Adjusted Risk Ratio (aRR) 1.12, 95%CI 1.11–1.13) and patients aged 65–79 (aRR 1.08, 95%CI 1.07–1.09) compared to patients aged 19 and below. Hispanics (aRR 1.03, 95%CI 1.02–1.03) and other minorities (aRR 1.02, 95%CI 1.02–1.03) exhibited higher in-hospital death rates than whites, and these patients also had longer LOS and higher ICU admission rates. Patients aged 65–79, 50–64, and 80 and over all had longer hospital stays and higher ICU admission rates. Males experienced poor health outcomes in all assessed outcomes. Findings showed that disparities in clinical outcomes among population subgroups existed and remained throughout 2020. While the nation has to continue practicing public health measures to minimize the harm caused by the novel virus, serious consideration must be given to improving the health of marginalized populations during and beyond the pandemic.

Keywords: COVID-19, clinical outcomes, age, race, sex

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Roger Nlandu Ngatu, Kagawa University, Japan

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Tian Gu, Harvard University, United States
Meng-Yun Lin, Wake Forest School of Medicine, United States

***Correspondence:**
Jusung Lee
Jusung.lee@utsa.edu

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INTRODUCTION

Ever since the first case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed in the United States, the COVID-19 pandemic has disrupted the lives of every American. One troubling feature of the public health crisis caused by the pandemic is the excess harm posed to marginalized and vulnerable populations, which has punctuated the national awareness of health disparities between population subgroups (1).

The unprecedented global pandemic has revealed the disproportionate risk of poor clinical outcomes among population subgroups. Age has been suggested as a strong predictor of mortality—that is, the risk of mortality from COVID-19 increases with age (2, 3). Older adults have been identified as the most vulnerable group to the effects of the pandemic.

Also, studies have reported that males are at a disproportionate risk of severe conditions and death caused by COVID-19 (4, 5). In the middle of the pandemic, the country was also exposed to racial/ethnic health disparities, which prompted a harsh national public health discourse. Studies, including Louisiana reports, have found significantly higher hospital admissions, intensive care unit (ICU) admission or severe illness, and in-hospital mortality among racial minorities compared to their white counterparts (6–9).

So far, studies on hospitalized patients often relied on data from a single or a few healthcare systems. Previous studies may exhibit a limitation in interpreting findings to a larger group of the patient population hospitalized with COVID-19. This study uses data on hospitalized patients with COVID-19 from all state-licensed hospitals in Texas except those that are statutorily exempt from reporting requirements. The inclusion of a large number of hospitals furthers representative evidence of hospitalized patient population and improves generalizability. Second, less is known about changing clinical outcomes across population subgroups. This study provides insight into the changes in clinical outcomes over the three quarters of 2020 across key demographic characteristics among patients with COVID-19. Also, Texas, one of the states hardest hit by COVID-19, has unique demographics, with a larger Hispanic or Latino population (39.7%) compared to the national average (18.5%). The study enhances the understanding of clinical outcomes in Texas, and how they vary from national trends.

The aim of the study is to investigate differences in length of stay (LOS), intensive care unit (ICU) admission, and in-hospital death across age, sex, and race/ethnicity and to examine how the variations change over time in 2020 using Texas inpatient discharge data.

METHODS

Study Design and Data

The pooled cross-sectional study used the de-identified public-use data of Texas hospital discharge for the last three quarters in 2020. The hospital discharge data from all state-licensed hospitals in Texas except those that are exempt from the reporting requirement contains patients' demographics and healthcare information related to hospitalization. The three quarterly inpatient discharge files were merged and then were linked with the 2013 Urban-Rural Classification Scheme from the National Center for Health Statistics using patients' residential county. The study patients were identified through confirmed COVID-19 (U07.1) using the International Classification of Disease, 10th revision, Clinical Modification (ICD 10-CM) diagnosis code, following the US Centers for Disease Control and Prevention's Official Coding and Reporting Guidelines (10). The analysis included 98,879 patients after excluding missing (2.8%) on any variables in the study.

Measurement

Outcomes

In-hospital death was a primary outcome of interest, capturing patients' expiration at the hospital. LOS and ICU admission were also outcomes of interest. In-hospital death and ICU admission were dichotomized, and LOS was treated as a count variable.

Independent Covariates

Age, sex, and race/ethnicity were key independent variables based on the literature review (7, 11). Age was categorized: below 20, 20–34, 35–44, 45–55, 55–64, 65–79, 80 and over. Sex was male and female. Patients' self-reported race/ethnicity was constructed using race and ethnicity variables: non-Hispanic whites, non-Hispanic blacks, Hispanics, and non-Hispanic other racial/ethnic minorities. Health insurance types of payment, type of admission, rural-urban classification, and comorbidity were included (7, 12, 13). The Elixhauser index was calculated for the comorbidity measure, using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10 CM) diagnosis code.

Statistical Analysis

In the descriptive analysis, the patients' characteristics and the bivariate relationship between the patients' clinical outcomes and key demographic covariates, such as age, sex, and race/ethnicity, were examined. Graphical descriptions of the quarterly trends in LOS, ICU admission, and in-hospital death by the key covariates were created. After an unadjusted Poisson regression model was fitted for key outcomes, multivariable models were run to estimate the adjusted risk ratios (aRR), accounting for secondary covariates, including the type of admission, health insurance type as a payment method, urban-rural classification, and provider and quarter fixed effect. Subsequent regression models further controlled for patients' comorbidity. Analysis was also conducted for the association between key outcomes and age, sex, and race/ethnicity, stratified by each quarter to examine the trend of their relationship over the study period. Additionally, as a sensitivity analysis, multivariable regression was performed for LOS and ICU admission after excluding patients who expired at the hospital. While Poisson regression is a suggested analytic approach for the risk of dichotomous outcomes, the errors of the estimation tend to be overestimated. The variance was rectified using robust standard errors so that adjusted test statistics can be used for the statistical significance of estimates (14, 15). This study used public-use hospital discharge data released from the Texas Department of State Health Services, and the information in the database could not be identified. Therefore, institutional review board approval was not required for the present study based on the US Title 45 Code of Federal Regulations, Part 46. All tests were two-tailed, and the statistical significance was set to $P < 0.05$. All analyses were performed using the R statistical software (version 4.1.2).

RESULTS

Patient Characteristics

Of a total 98,879 patients with COVID-19, males accounted for 52.3% as shown in **Table 1**. The age distribution was as follows: 31.9% for the 65–79 age group, 29.6% for those aged 50–64, 16.3% for those aged 80 or older, 16.0% for ages 35–49, 5.1% for ages 20–34, and 1.1% for those aged 19 and below. Whites

TABLE 1 | Characteristics of patients hospitalized with COVID-19.

Variable	*N*	% or mean (sd)
	98,879	100
Age		
≤19	1,114	1.1
20–34	5,031	5.1
35–49	15,821	16.0
50–64	29,273	29.6
65–79	31,507	31.9
≥80	16,133	16.3
Sex		
Male	47,127	52.3
Female	51,752	47.7
Race		
White	42,088	42.6
Black	12,960	13.1
Hispanic	35,751	36.2
Other	8,080	8.2
Insurance		
Private	50,628	51.2
Medicare	32,343	32.7
Medicaid	4,210	4.3
Other	11,698	11.8
Type of admission		
Emergency	79,537	80.4
Urgent	11,980	12.1
Elective	7,079	7.2
Other	283	0.3
Urban-Rural classification		
Large central metro	38,559	39.0
Large fringe metro	14,764	14.9
Medium metro	19,641	19.9
Small metro	8,681	8.8
Micropolitan	9,635	9.7
Non-core	7,599	7.7
Quarter		
2nd quarter	13,202	13.4
3rd quarter	37,492	37.9
4th quarter	48,185	48.7
Comorbidity	98,879	3.4 (2.0)

constituted the largest proportion (42.6%), followed by Hispanics (36.2%), Blacks (13.1%), and other minorities (8.2%). More than half of the patients were covered by private insurance (51.2%); and the rest were covered by Medicare (32.7%), Medicaid (4.3%), and other sources (11.8%). Most patients were admitted through emergency (80.4%) and were from various metro areas, such as large central (39.0%), large fringe (14.9%), and medium (19.9%).

Descriptive LOS, ICU Admission, and In-hospital Death

The bivariate analysis revealed that the patients' mean LOS was 7.4 days (sd 7.9), and the median LOS was 5 days

TABLE 2 | Summary of LOS, ICU admission, and in-hospital death by age, sex, and race/ethnicity among patients hospitalized with COVID-19.

	LOS (days) Mean (sd)/ Median	ICU admission %	In-hospital death %
Overall	7.4 (7.9) / 5	45.3	9.9
Age			
≤19	4.3 (6.0) / 3	38.5	0.4
20–34	5.4 (6.4) / 4	41.8	2.0
35–49	6.3 (7.3) / 4	43.1	3.6
50–64	7.7 (8.8) / 5	46.2	7.5
65–79	8.1 (8.2) / 5	47.2	13.0
≥80	7.2 (6.4) / 5	44.0	17.6
Sex			
Male	7.7 (8.2)/ 5	47.2	11.1
Female	7.1 (7.6)/ 5	43.4	8.6
Race			
White	7.2 (7.4)/ 5	43.6	10.3
Black	6.9 (7.5)/ 5	44.3	6.9
Hispanic	7.8 (8.5)/ 5	47.4	10.7
Other	7.5 (8.2)/ 5	47.5	9.7

(**Table 2**). About 45.3% of the patients were admitted to the ICU, and 9.9% expired at the hospital. Hispanics (10.7%), whites (10.3%), and other racial minorities (9.7%) had higher in-hospital death rates than blacks (6.9%). Older adults, particularly those aged 80 and over (17.6%) and those aged 65–79 (13.0%) had a significantly higher in-hospital death rate than patients below 20 years old (0.4%). LOS, ICU admission, and in-hospital death rates across demographic characteristics were largely consistent over the last three quarters of 2020 (**Figure 1**).

Differences in LOS From Multivariable Analysis

Compared to the youngest group (those aged 19 and below), patients, including those aged 65–79 (aRR 1.73, 95%CI 1.60–1.88; $p < 0.000$), 50–64 (aRR 1.70, 95%CI 1.57–1.84; $p < 0.000$), 80 and over (1.56, 95%CI 1.43–1.69; $p < 0.000$) all had longer LOS in **Table 4**. Males showed extended LOS relative to females (aRR 1.10, 95%CI 1.09–1.12; $p < 0.000$). Hispanics (aRR 1.14, 95%CI 1.12–1.16; $p < 0.000$) and other racial minorities (aRR 1.09, 95%CI 1.06–1.12; $p < 0.000$) had longer hospital stays, but blacks had shorter hospital stays (aRR 0.94, 95%CI 0.93–0.96; $p < 0.000$) than whites. From April through June, the LOS of Hispanics did not differ significantly from that of whites. However, in later months, Hispanics had a significantly longer LOS than whites, whereas blacks consistently showed a shorter LOS than whites (**Figure 2** and **Supplementary Table 1**). The variation in LOS between males and females slightly decreased in the fourth quarter, while the variations in age remained mostly the same.

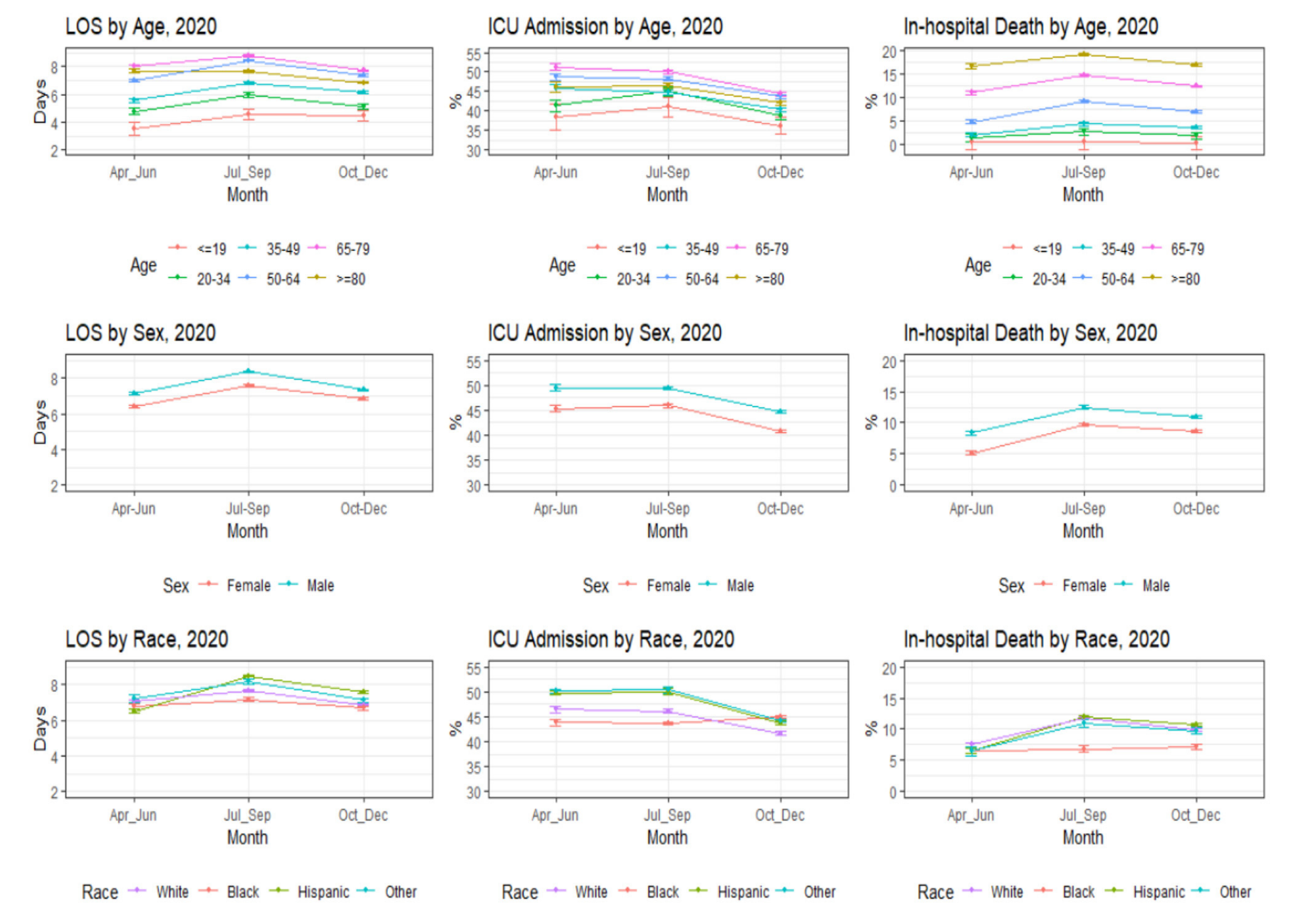

FIGURE 1 | Trends in LOS, ICU admission, and In-hospital death by age, sex, and race/ethnicity.

Differences in ICU Admission From Multivariable Analysis

The multivariable analysis showed that those aged 35–49 (aRR 1.04, 95%CI 1.01–1.07; $p \leq 0.012$), 50–64 (aRR 1.05, 95%CI, 1.02–1.08; $p = 0.001$), 65–79 (aRR 1.05, 95%CI 1.02–1.08; $p < 0.000$), and 80 and over (aRR 1.03, 95%CI 1.01–1.06; $p = 0.040$) had an increased risk of ICU admission compared to younger patients (**Table 4** and **Supplementary Table 2**). While other age groups compared to patients <19 years old did not show differences in the first two quarters, they had significantly higher ICU admission in the fourth quarter. Over the three quarters, Hispanics and other minorities had consistently higher ICU admission rates than their white counterparts (**Figure 2**). Males experienced more frequent ICU admissions than females (aRR 1.03, 95%CI 1.03–1.04; $p < 0.000$), and this pattern remained over time.

Differences in In-hospital Death From Multivariable Analysis

Consistent with the unadjusted model (**Table 3**), the adjusted analysis demonstrated that the oldest group (those aged 80 and over) had the highest risk of in-hospital death (aRR 1.13, 95%CI 1.11–1.14; $p < 0.000$). The 65–79 (aRR 1.08, 95%CI 1.07–1.09; $p < 0.000$) and 50–64 (aRR 1.04, 95%CI 1.03–1.05; $p < 0.000$) age groups also suffered higher mortality rates than those aged 19 and below (**Table 4** and **Supplementary Table 3**). These age differences in in-hospital deaths continued over time, with only slight changes (**Figure 2**). Males had a higher in-hospital death rate than females (aRR 1.03, 95%CI 1.02–1.03) although the difference slightly diminished over the three quarters. Hispanics (aRR 1.03, 95%CI 1.02–1.03; $p < 0.000$) and other minorities (aRR 1.02, 95%CI 1.01–1.03; $p < 0.000$) exhibited higher in-hospital death rates than whites, and the differences remained over quarters. In contrast, blacks had a lower in-hospital death rate than whites in later quarters. The results from sensitivity analysis with exclusion of patients who expired at the hospital were similar to the primary results (**Supplementary Table 4**).

DISCUSSION

This study examined age, sex, and racial/ethnic differences in LOS, ICU admission, and in-hospital death among patients

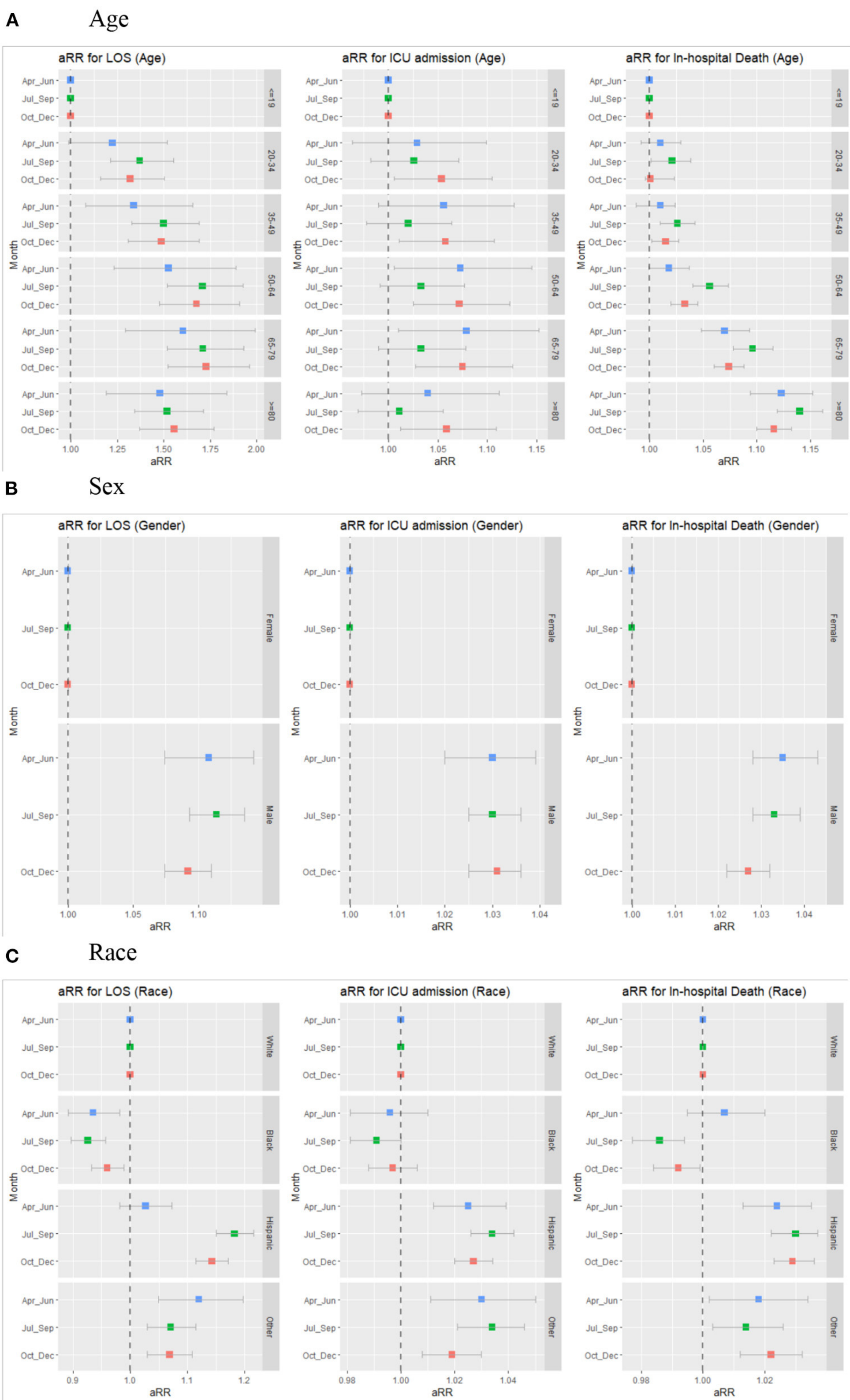

FIGURE 2 | Trends in adjusted risk ratios for LOS, ICU admission, and In-hospital death by age, sex, race/ethnicity over the last three quarters of 2020. **(A)** Age. **(B)** Sex. **(C)** Race. The estimates are from multivariable regression analysis stratified by each quarter, adjusting for covariates in Model 1 and comorbidity of patients.

TABLE 3 | Unadjusted association between key outcomes and age, sex, and race.

	Unadjusted					
	LOS		ICU admission		Death	
	RR (95%CI)	p	RR (95%CI)	p	RR (95%CI)	p
Age						
≤19	Ref.		Ref.		Ref.	
20–34	1.25 (1.14,1.36)	<0.000	1.02 (1.00,1.05)	0.044	1.02 (1.01,1.02)	<0.000
35–49	1.46 (1.34,1.58)	<0.000	1.03 (1.01,1.06)	0.003	1.03 (1.03,1.04)	<0.000
50–64	1.79 (1.65,1.94)	<0.000	1.06 (1.03,1.08)	<0.000	1.07 (1.07,1.08)	<0.000
65–79	1.88 (1.73,2.04)	<0.000	1.06 (1.04,1.09)	<0.000	1.13 (1.12,1.13)	<0.000
≥80	1.67 (1.53,1.81)	<0.000	1.04 (1.02,1.06)	<0.000	1.17 (1.16,1.18)	<0.000
Sex						
Female	Ref.		Ref.		Ref.	
Male	1.09 (1.07,1.10)		1.03 (1.02,1.03)	<0.000	1.02 (1.02,1.03)	<0.000
Race						
White	Ref.		Ref.		Ref.	
Black	0.96 (0.94,0.98)	0.001	1.00 (1.00,1.01)	0.162	0.97 (0.96,0.97)	<0.000
Hispanic	1.09 (1.08,1.11)	<0.000	1.03 (1.02,1.03)	<0.000	1.00 (1.00,1.01)	0.082
Other	1.06 (1.03,1.08)	<0.000	1.03 (1.02,1.04)	<0.000	0.99 (0.99,1.00)	0.124

TABLE 4 | Adjusted association between key outcomes and age, sex, and race.

	Model 1						Model 2 (Model 1 + comorbidity)					
	LOS		ICU admission		Death		LOS		ICU admission		Death	
	RR (95%CI)	p	RR (95%CI)	p	RR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	P
Age												
≤19	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
20–34	1.54 (1.40, 1.70)	<0.000	1.06 (1.03, 1.09)	<0.000	1.05 (1.04, 1.06)	<0.000	1.34 (1.24, 1.46)	<0.000	1.03 (1.00, 1.06)	0.033	1.01 (1.01, 1.02)	0.002
35–49	1.81 (1.65, 1.99)	<0.000	1.08 (1.05, 1.11)	<0.000	1.06 (1.05, 1.07)	<0.000	1.49 (1.38, 1.62)	<0.000	1.04 (1.01, 1.07)	0.012	1.02 (1.01, 1.03)	<0.000
50–64	2.23 (2.03, 2.44)	<0.000	1.11 (1.08, 1.15)	<0.000	1.10 (1.09, 1.11)	<0.000	1.70 (1.57, 1.84)	<0.000	1.05 (1.02, 1.08)	0.001	1.04 (1.03, 1.05)	<0.000
65–79	2.41 (2.19, 2.64)	<0.000	1.13 (1.10, 1.16)	<0.000	1.16 (1.15, 1.17)	<0.000	1.73 (1.60, 1.88)	<0.000	1.05 (1.02, 1.08)	<0.000	1.08 (1.07, 1.09)	<0.000
≥80	2.22 (2.02, 2.43)	<0.000	1.11 (1.08, 1.15)	<0.000	1.22 (1.21, 1.23)	<0.000	1.56 (1.43, 1.69)	<0.000	1.03 (1.01, 1.06)	0.040	1.13 (1.11, 1.14)	<0.000
Sex												
Female	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Male	1.08 (1.06, 1.09)	<0.000	1.02 (1.02, 1.03)	<0.000	1.03 (1.02, 1.03)	<0.000	1.10 (1.09, 1.12)	<0.000	1.03 (1.03, 1.04)	<0.000	1.03 (1.02, 1.03)	<0.000
Race												
White	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Black	0.99 (0.97, 1.02)	0.621	1.00 (1.00, 1.01)	0.621	1.00 (1.00, 1.01)	0.394	0.94 (0.93, 0.96)	<0.000	0.99 (0.99, 1.00)	0.051	0.99 (0.98, 1.00)	0.004
Hispanic	1.12 (1.10, 1.14)	<0.000	1.02 (1.02, 1.02)	<0.000	1.02 (1.02, 1.03)	<0.000	1.14 (1.12,1.16)	<0.000	1.03 (1.02, 1.03)	<0.000	1.03 (1.02, 1.03)	<0.000
Other	1.05 (1.03, 1.08)	<0.000	1.02 (1.01, 1.03)	<0.000	1.01 (1.00, 1.02)	0.002	1.09 (1.06,1.12)	<0.000	1.03 (1.02, 1.03)	<0.000	1.02 (1.01, 1.03)	<0.000

hospitalized with COVID-19. Overall, ICU admission decreased over time, consistent with previous reports (16). In contrast, rates of LOS and in-hospital mortality remained over the study period. The study findings showed that the assessed demographic characteristics were important predictors of LOS, ICU admission, and in-hospital death, and these associations were largely consistent throughout 2020.

Earlier investigations reported significant variations in health outcomes between age groups during the COVID-19 pandemic (2, 7). Consistent with previous findings, this study found that age was a strong predictor of higher mortality and ICU admission rates as well as longer hospital stays. While the overall ICU admission rate had decreased over time as revealed in the descriptive analysis, the adjusted analysis showed significant differences between age groups. Patients aged 80 and over and those aged 65–79 had the highest mortality rates; this pattern persisted from April to December 2020. The adjusted ICU admission rate was also significantly higher among the older age groups (ages 50–64, 65–79, and 80 and over), similar to the findings in previous studies, suggesting severe conditions disproportionally among older adults (3, 17).

The COVID-19 pandemic has shed light on racial health disparities. This study found that Hispanics and other racial minorities including Asian and Pacific Islanders had an increased risk of ICU admission and in-hospital mortality compared to whites, similar to earlier findings (8, 11, 18, 19). When stratified by quarters, the present study found continued racial variations in assessed health outcomes. These persistent disparities were also reported in multiple studies (8, 20); They suggested higher ICU admission and in-hospital mortality in Hispanics and Asian or Pacific Islanders over time. Although another study tended to show an increased risk in the assessed outcomes among racial minorities compared to whites over a period of time, the results were not statistically significant (16). While some variations across studies exist, the findings of the present study using a large database of the inpatient population strengthen the knowledge base and highlight significant health disparities among Hispanics and minorities (8, 11, 18). Moreover, there was also evidence of a significantly higher risk of prolonged hospital stays among Hispanic subgroups from the third quarter of 2020 in this study. The soaring risk of lengthy hospital stays in this group relative to the white group in later quarters may be driven by a lack of early testing and diagnosis of the coronavirus, leading to rapid deterioration of health conditions and so high mortality later (21). Markedly, Hispanic patients were the most vulnerable to in-hospital mortality and the intensified risk of death continued throughout the year. Although reasons for the poor clinical health outcomes are to be further explored in terms of both socio-economic or environmental and physiological factors, preexisting social and health inequities that a historically underserved minorities experience may have contributed to severe health conditions associated with COVID-19 (19, 22).

Conversely, blacks tended to show a lower likelihood of ICU admission and in-hospital mortality compared to their white counterparts. Overall, the findings of the present study are comparable with what has been reported from previous studies conducted in health care settings—blacks had either a lower or similar risk of ICU admission and hospital mortality compared to whites (7, 12, 16, 22). Although one study found higher ICU admission among blacks compared to whites, this pattern did not remain when the analysis was stratified by a certain time period (16). Notably, these findings contradict those from studies of the general population that showed more severe conditions in black persons (7, 8). The contrasting results between hospitalized patients and general populations may attribute to a number of factors. A lower or similar risk of severe conditions among black persons in the general population may be due to barriers to access to health care that blacks experience because of either a lack of insurance or underinsurance (23). Their poor access may cause exacerbated health conditions and increased deaths outside the hospital and, therefore, a higher overall mortality rate. On the other hand, undiagnosed cases due to asymptomatic infections and delayed diagnosis may lead to severe health conditions and later be recognized as deaths caused by COVID-19 (24). The findings of this study with those of previous studies suggest that, while the poor health outcomes are more marked among blacks outside of a hospital, once admitted, blacks may have an equal or lower likelihood of experiencing severe conditions compared to whites (12).

This study found that males had an increased risk of longer hospital stays, ICU admission, and in-hospital death compared to females. These results are consistent with prior reports on both hospitalized patients and the general population (7, 8, 25). Despite the slight decrease over time, these sex differences in the assessed clinical outcomes largely remained. While the drivers of these differences are still uncertain, the varying clinical outcomes might be driven by behavioral differences between males and females, such as the higher prevalence of smoking and drinking among males (5). Furthermore, biological pathways and immune responses have been suggested as likely explanations for the significant sex differences in clinical outcomes associated with COVID-19 (26, 27).

The study has several limitations. First, given the nature of the observational study, unmeasured patient information may remain. Also, as the database used for this study included mainly patients' data associated with hospitalization, unobserved information with respect to the cross-hospital variations may exist and confound the observed association between exposure and outcome. Although the multivariable analysis that adjusted for study covariates and a provider identifier as fixed effects would improve the unmeasured issues, the potential bias due to unmeasured confounding may still affect the estimation and undermine the study findings. Second, one of the strengths of the present study is the inclusion of all state-licensed hospitals in Texas with a few exceptions, which provides more robust and representative evidence of health outcomes among the inpatient population hospitalized with COVID-19. However, given the Texas context, a caution is still needed in interpreting the study findings in other contexts. Third, despite the adjusted regression models being performed to control for various patient characteristics, the analysis was not designed to assess causality given the nature of the observational study. Fourth, while analysis using months rather than quarters is more desirable, the study did not examine monthly analysis as only quarter indicators were available. Despite several limitations, this study documents important evidence of differential risks in clinical outcomes associated with COVID-19 across patient demographics.

CONCLUSIONS

The COVID-19 pandemic is one of the most disturbing public health challenges in the history of human disease. This study revealed the trend of clinical outcomes associated with COVID-19, showing population subgroups, such as older adults, males, and racial/ethnic minorities, disproportionately affected. The pandemic has raised our awareness not only of the danger of infectious disease but also of the amplified health disparities. While the nation has to continue practicing public health measures to minimize the harm caused by the novel virus and its variants, serious consideration must be given to improving the healthcare and health of the marginalized and vulnerable populations during and beyond the pandemic.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: The de-identified datasets for this study can be obtained from the Texas Health and Human Services https://www.dshs.texas.gov/thcic/hospitals/Inpatientpudf.shtm.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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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.2022.850536/full#supplementary-material

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The Commonwealth Caribbean COVID-19: Regions Resilient Pathway During Pandemic

Srikanth Umakanthan[1], Maryann M. Bukelo[2] and Somu Sekhar Gajula[3]*

[1] *Department of Para-Clinical Sciences, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad and Tobago,* [2] *Department of Anatomical Pathology, Eric Williams Medical Sciences Complex, North Central Regional Health Authority, Mount Hope, Trinidad and Tobago,* [3] *Forensic Science Centre, St. James, Trinidad and Tobago*

The coronavirus disease (COVID-19) has created severe humanitarian and socio-economic constrains in the world. The health crises caused by COVID-19 has focused on consistent co-operation and strong bonding between the developed, developing and the under-developed countries to overcome this challenging pandemic.

Keywords: COVID-19, caribbean, economic, regional healthcare, financial institutions

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****Correspondence:***
Srikanth Umakanthan
Srikanth.Umakanthan@sta.uwi.edu

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BACKGROUND

The Caribbean region has been exposed to numerous natural disasters and tropical diseases in the previous decade. The region formed several councils, agencies, and organizations to manage the evolving tropical infectious diseases and to maintain a stable economic platform. It was considered that the experiences gained from these calamities would motivate the Caribbean region to shield any future alarming health and financial debacles.

As COVID-19 hit the Caribbean region, the high-risk island nations had to compose adequate hospital infrastructure to tackle the roaring COVID-19 epidemic in the Caribbean. The smaller islands were prioritized to cater high standard COVID-19 care units to avoid the impetus of a devastating outcome. An increase in Intensive Care Units (ICUs) capacity would require increase in the number of fully trained hospital staff and hospital equipment's, including mechanical ventilators. Apart from health care sector, COVID-19 has hit the tourism, industry, education, and labor.

The Caribbean region has high prevalence of chronic diseases, and these diseases are the major causes of mortality and morbidity. The economically challenged population solely depend on the regional health facility for their health care and check-ups, resulting in a prolonged waiting period in the hospitals clinics. The significance of a robust health care strategy and healthcare programs should be pivotal in managing the regions epidemic.

In this commentary, we discuss the role of Commonwealth Caribbeans healthcare in combatting the ongoing COVID-19 crises, and how the region has been active in forming active healthcare and financial organizations between the regions island nations to fight the pandemic.

The COVID-19 pandemic was slow to affect the twin-Caribbean Island of Trinidad and Tobago (1). This Caribbean nation has a population of 1·395 million people and a Human Development Index (HDI) of 0.79, positioning it as the wealthiest Caribbean country. Trinidad and Tobago had reported around 130 cases of COVID-19 till July 16th, 2020. The situation was contrasting in Northern Caribbean Island, Haiti, where the COVID-19 cases surged from 85 cases in May 2020 to 8,161 cases in August 2020 (2). Haiti has an HDI of 0.51 and is positioned at 170 out of 189 countries in the World. The Haitian crisis is due to the ongoing tumultuous social and political breakdown causing a further humanitarian crisis. Other Caribbean islands (Jamaica, Aruba, Bahamas, Saint Vincent) experienced community transmission of COVID-19 during 2020 and were vigilantly monitored by the Caribbean Public Health Agency (CARPHA) by issuing frequent weekly situational reports. CARPHA was legally established in 2011 and is driven by its objective toward surveillance and management of disease by providing strategic directions to its member states (2).

Caribbean island reported its first COVID-19 case on March 10th, 2020, a lag period of almost 3 months since COVID-19 emerged in China. During this period, CARPHA, along with the Pan American Health Organization (PAHO) and the Caribbean Association of Medical Councils (CAMC), initiated swift regional epidemic control preparedness, activated incident management teams, issued updated situational reports, and statistical analysis, and developed rigid travel guidelines (2, 3). In April- May 2020, most of the Caribbean countries imposed strict border control measures and national lockdown. The control measures had a serious impact on the region's tourism sector, which forms the core of the country's economic resource in Aruba, Antigua, Bahamas, Barbados, and Dominica. COVID-19 wave caused a serious financial recession, with Aruba experiencing a GDP downfall of −13.7% in 2020. The household economic status also witnessed a serious drought as many people lost employment due to the closure of non-essential services within the Caribbean nations. Trinidad, Guyana, Suriname, and Cuba were financially surviving on their natural oil and mineral resources (4).

By June 2020, the regions health councils, in coordination with the various Caribbean national government has facilitated the individual island countries to transfer medical aids and to expand existing health care infrastructure by constructing new COVID-19 dedicated health care facility clinics, converting large public utility spaces into makeshift health care centers, increase in-hospital COVID-19 beds and ICU capacities, and medevac patients to tertiary care hospitals within the region. The CAMC, an independent non-profitable medical organization, conducted webinars to share clinical experiences within the region and receive updated COVID-19 treatment protocols from the USA and Europe, allowing access to high-standard of health care delivery within the region (5). The control measures undertaken by the Commonwealth Caribbean nations levied a heavy burden on the already stuttering region's economy. The World Bank stated that the region's economy is contracted by 7.2%, with a cumulative loss of 1.02 trillion dollars during the pandemic period of 2020–21. The region's economic crisis initiated the launch of the Caribbean Economic Recovery and Transformation plan. The economic relief provided by international financial councils (International Monetary Fund, G20's Debt Service suspension) and the perseverance of the "blue economy" has allowed the Caribbean region to sustain and safeguard its financial state during the COVID-19 pandemic era (4).

In 2021, the Caribbean nation's citizens experienced COVID-19 induced fatigue, which provoked the public to let their guard down, get involved in family gatherings, attend religious ceremonies, conduct election rallies, and travel around the island. The region also began to re-open its borders in a phased manner with strict regulations. The visitors were allowed into the island countries only after producing a negative RT-PCR result and a proper self-paid state quarantine to avoid further COVID-19 spikes. Jamaica created a resilient tourist corridor, providing a fort-like boundary between the locals and the tourists (6). The COVID-19 confirmed cases in the Caribbean region as of December 2021 is 2,193,737 with a case fatality rate (CFR) of 1·34%, seen in **Figures 1** and **2** (2). Antigua and Barbuda is a Caribbean nation in the Lesser Antilles island chain with the countries GDP maintained by tourism, investment banking and financial-services corporations. The Bahamas constitutes 97% of the Lucayan Archipelago's land area with strong bilateral relationships with the United Kingdom and the United States of America (4, 5). The Bahamas is one of the richest countries in the Americas with its financial resilience attained by tourism, banking, agriculture, and manufacturing industries. The economy of Barbados is mixed with moderately high standards of living. The economic status of the country has waxed and waned over the years, but due to its resilient financial plan and firm trading bonds with Canada, United states of America and United Kingdom, it has been able to reduce the unemployment rate. The literacy rate in Barbados is close to 100% and the health sector is strengthened by its numerous polyclinics (6).

The role of vaccination has been the foremost global defense strategy for the fight against COVID-19. The vaccine combat against COVID-19 across the Caribbean region is initiated by exceptional collaboration by the CARPHA- Caribbean Regulatory System with the WHO and PAHO. This uniform solidarity provided timely WHO-approved vaccine supplies to the Caribbean people (7). As of the COVID-19 vaccine updated supplement provided by CARPHA, eight WHO-approved vaccines are recommended to the member states, and 14 Caribbean countries have received vaccines through the COVAX facility. The Caribbean region's average percentage of the fully vaccinated population is 29·68% (ranging from 3·8% in Jamaica to 68% in the Cayman Islands) compared to the global average of 12·7% (8). The UK has provided many AstraZeneca vaccines to its overseas territories (Anguilla, the British Virgin Islands, the Cayman Islands, Montserrat, and the Turks and Caicos Islands). The Netherlands also provides the same vaccine facility to its Caribbean counterpart (Aruba, Curaçao, and Saint Martin) (9, 10). Other nations of the Caribbean region are dependent on either bilateral deal with the vaccine-producing countries or have joined the COVAX (COVID-19 Vaccines Global Access) joint initiative. The vaccine situation remained grim in Haiti until recently, as there was no available vaccine for their citizens until COVAX delivered 500,000 doses to the nation. This inequitable severe distribution of the vaccine in the Caribbean region has often been highlighted globally and by the WHO press conferences. The pathway for successful vaccination also

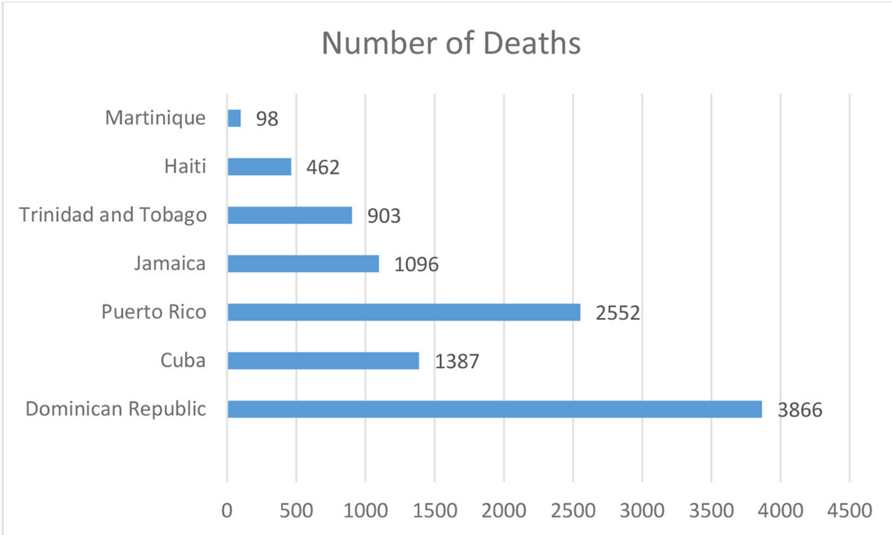

FIGURE 1 | The Caribbean region COVID-19 deaths as of December 2021.

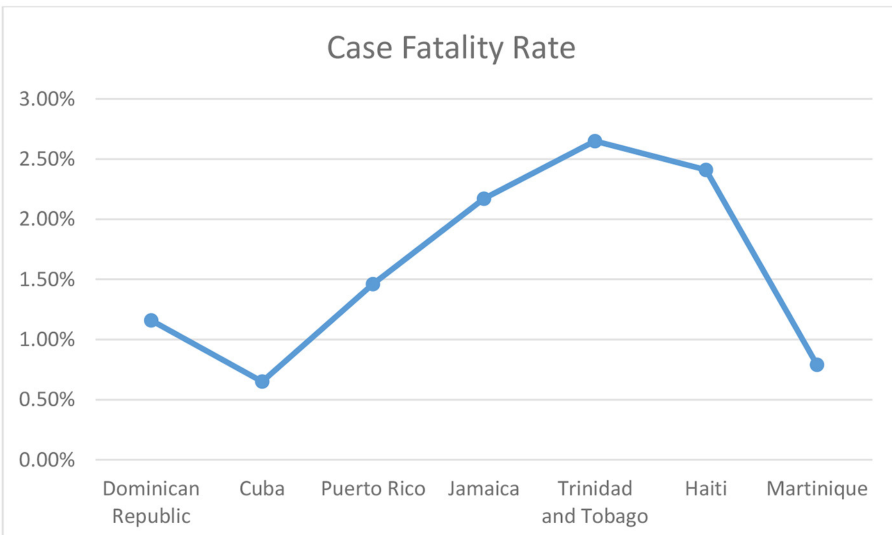

FIGURE 2 | The Caribbean regions case fatality rate as of December 2021.

depended on the pivotal role of information technology within the individual islands for conducting vaccination drives and awareness programs among the public to encourage vaccination (11, 12).

CONCLUSION

The Caribbean region's ability to identify community-specific requirements, recognizing self-reliance, coordinate political health care policies, and a sustainable, comprehensive health care approach has proved to be successful combat against the COVID-19 to date. Implementing rigid long-term health care and strategic financial plan using the region's COVID-19 experiences for future epidemic strikes seems to be the top priority in many Caribbean Island nations.

AUTHOR CONTRIBUTIONS

SU contributed in concept, design, writing the manuscript, and editing. MB and SG contributed in creating figures and data indexing. All authors contributed to the article and approved the final version.

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SYSTEMATIC REVIEW
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Real-Word Effectiveness of Global COVID-19 Vaccines Against SARS-CoV-2 Variants: A Systematic Review and Meta-Analysis

Kai Wang[1], Lin Wang[1], Mingzhe Li[2], Bing Xie[3], Lu He[4], Meiyu Wang[5], Rumin Zhang[1], Nianzong Hou[3], Yi Zhang[3]* and Fusen Jia[3]**

[1] Department of Critical Care Medicine, Zibo Central Hospital, Shandong First Medical University and Shandong Academy of Medical Sciences, Zibo, China, [2] Independent Researcher, Leeds, United Kingdom, [3] Department of Hand and Foot Surgery, Zibo Central Hospital, Shandong First Medical University and Shandong Academy of Medical Sciences, Zibo, China, [4] Hubei University of Medicine, Shiyan, China, [5] Department of Cardiology, The People's Hospital of Zhangdian District, Zibo, China

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Claudio Fenizia, University of Milan, Italy

Reviewed by:
Alberto Antonelli, University of Florence, Italy
Andrew Jeremijenko, Hamad Medical Corporation, Qatar

***Correspondence:**
Nianzong Hou
hounianzong@163.com
Yi Zhang
Zhangyi830219@163.com
Fusen Jia
ajia33@sina.com

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Background: Currently, promoted vaccinations against SARS-CoV-2 are being given out globally. However, the occurrence of numerous COVID-19 variants has hindered the goal of rapid mitigation of the COVID-19 pandemic by effective mass vaccinations. The real-word effectiveness of the current vaccines against COVID-19 variants has not been assessed by published reviews. Therefore, our study evaluated the overall effectiveness of current vaccines and the differences between the various vaccines and variants.

Methods: PubMed, Embase, Cochrane Library, medRxiv, bioRxiv, and arXiv were searched to screen the eligible studies. The Newcastle–Ottawa scale and the Egger test were applied to estimate the quality of the literature and any publication bias, respectively. The pooled incident rates of different variants after vaccination were estimated by single-arm analysis. Meanwhile, the pooled efficacies of various vaccines against variants were evaluated by two-arm analysis using odds ratios (ORs) and vaccine effectiveness (VE).

Results: A total of 6,118 studies were identified initially and 44 articles were included. We found that the overall incidence of variants post first/second vaccine were 0.07 and 0.03, respectively. The VE of the incidence of variants post first vaccine between the vaccine and the placebo or unvaccinated population was 40% and post second vaccine was 96%, respectively. The sub-single-arm analysis showed a low prevalence rate of COVID-19 variants after specific vaccination with the pooled incidence below 0.10 in most subgroups. Meanwhile, the sub-two-arm analysis indicated that most current vaccines had a good or moderate preventive effect on certain variants considering that the VE in these subgroups was between 66 and 95%, which was broadly in line with the results of the sub-single-arm analysis.

Conclusion: Our meta-analysis shows that the current vaccines that are used globally could prevent COVID-19 infection and restrict the spread of variants to a great extent. We would also support maximizing vaccine uptake with two doses, as the effectiveness of which was more marked compared with one dose. Although the mRNA vaccine was the most effective against variants according to our study, specific vaccines should be taken into account based on the local dominant prevalence of variants.

Keywords: COVID-19, SARS-CoV-2, variant, vaccine, effectiveness, meta-analysis

HIGHLIGHTS

What We Already Know About This Topic

COVID-19 has not been fully controlled yet, which has placed a substantial burden on health-care systems and imposed profound negative effects on the economy and society.

A universal SARS-CoV-2 vaccination campaign plays the most critical role in controlling the highly transmissible and pathogenic SARS-CoV-2 infection.

The hope for a rapid mitigation of the COVID-19 pandemic through effective mass vaccination has been dampened by the emergence of numerous SARS-CoV-2 variants worldwide.

The real-word effectiveness of the current COVID-19 vaccines against SARS-CoV-2 variants has not been assessed by a published systematic review and meta-analysis.

What This Article Tells Us That Is New

Reassuringly, we confirmed the efficacy of vaccines against COVID-19 variants and proved the importance of the booster inoculation after the prime inoculation for the variants, because maximizing vaccine uptake with two doses showed more marked effectiveness than with one dose.

Despite the fact that we found a downward tendency among the effectiveness of vaccines against the newly emerging evolution of SARS-CoV-2 variants in our study, the current vaccines that are used globally could prevent the infection and restrict the transmission of SARS-CoV-2 variants to a great extent.

A two-dose regimen of the mRNA vaccine was the most effective against COVID-19 variants compared to the traditional viral vector vaccine and inactivated vaccine against the placebo group or unvaccinated populations.

The mRNA vaccine was found to be the most effective against variants in our study, however, specific vaccines should be taken into account based on the local dominant prevalence of variants.

INTRODUCTION

In the past 2 years since December 2019, COVID-19, caused by the etiological agent of SARS-CoV-2, has evolved into a global pandemic and a public crisis event, which caused the world to experience a life-changing transition (1, 2). Up to 5:08 pm on 10 March 2022, Central European Time, there were 450,229,635 confirmed cases of COVID-19 and 6,019,085 deaths, according to WHO (3). The considerable morbidity and mortality have brought a heavy economic burden on health-care systems of most countries worldwide and the SARS-CoV-2 virus continues to impose profound negative effects on the economy and society due to measures implemented to control the pandemic. COVID-19 has not been fully controlled yet. Therefore, mask wearing, cleaning our hands, quarantining, ensuring good ventilation indoors, social distancing, avoiding crowds, and therapeutic interventions for treatment are still imperious measures to prevent COVID-19 infection for the foreseeable future. However, an extensive vaccination program for SARS-CoV-2 that shows safety, effectiveness, and cost-efficiency, which is generally thought to be the most promising intervention to eventually end the COVID-19 pandemic by establishing herd immunity among populations, plays the most critical role in controlling the highly transmissible and pathogenic SARS-CoV-2 infection (4, 5).

As a game-changing tool, clinically available COVID-19 vaccines are undergoing unprecedented development by private and public institutions. As of 8 March 2022, 147 vaccine products were in clinical development and another 195 were in the pre-clinical stage (6). Based on traditional and novel technology platforms, these COVID-19 vaccines in clinical development can be divided into at least 10 categories, among which the top five were protein subunit vaccines (48.33%), RNA vaccines (25.17%), viral vector vaccines (non-replicating and replicating, 25, 17%), inactivated vaccines (21.14%), and DNA vaccines (16, 11%) according to the quantity and percentage (7). As of 3 June 2021, WHO proclaimed that some COVID-19 vaccines manufactured by AstraZeneca/Oxford, Pfizer/BioNTech, Moderna, Johnson and Johnson, Sinopharm/Sinovac etc. had reached the required standards of safety and efficacy (8). According to the data of WHO up to now, at least 10 kinds of COVID-19 vaccines, represented by Ad26.COV2.S, BNT162b2, ChAdOx1, mRNA-1273 etc., have been granted WHO Emergency Use Listing (EUL) and prequalification (PQ) (9). A few vaccines in the COVID-19 pandemic have been approved for Emergency Use Authorization (EUA) and/or conditional marketing in several countries, such as Sputnik V, a viral vector vaccine in Russia which was approved on 11 August 2020; BNT162b2, an mRNA vaccine approved in the USA, UK, Canada, and the European Union; an inactivated vaccine produced by Sinopharm in China that was approved on 30 December 2020; and the mRNA-1273 vaccine manufactured by Moderna in the United States (10–12). It is not vaccines that will stop the pandemic, it is vaccination. With the further promotion in the research, development, and application of COVID-19 vaccines by WHO and the regulatory authorities mentioned above, mass SARS-CoV-2 vaccination programs are

Abbreviations: OR, Odds ratio; VE, Vaccine effectiveness; CI, Confidence intervals; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; RNA, Ribonucleic acid; WHO, World Health Organization; EUL, Emergency use listing; PQ, Prequalification; VOIs, Variants of interest; VOCs, Variants of concern; CDC, The Centers for Disease Control and Prevention; PRISMA, The Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE, Meta-analyses of Observational Studies in Epidemiology; PICOS, Population, intervention/exposure, comparator, outcome, and study; C.Ts, Comparative trials; C.Ss, Cohort studies; O.Ss, Observational studies; SD, Standard deviation; RBD, Receptor-binding domain; mAbs, Monoclonal antibodies.

being widely implemented all over the world. As a result, the global rollout of vaccines offers a glimmer of hope toward terminating COVID-19.

Because SARS-CoV-2 is a class of ribonucleic acid (RNA) coronavirus, its genome changes over time (13). Although most of these changes have little or no influence on the properties of SARS-CoV-2, some may affect the virus' transmission, severity, or how COVID-19 is diagnosed and treated. Since the end of 2020, the occurrence of numerous variants of SARS-CoV-2 has brought a growing threat to global public health. WHO have defined the concepts of variants of interest (VOIs) and variants of concern (VOCs), which could prompt monitoring and research into the variants of global concern (14). Currently, the Centers for Disease Control and Prevention (CDC) are monitoring the four most significant variants (P.1, B.1.1.7, B.1.351B.1.617.2, and B.1.1.529), which may lead to more cases, more hospitalizations, and potentially more deaths than other variants (15). New outbreaks, even in some regions where the virus was initially controlled, and variant strains discovered in multiple countries, either community transmitted or imported, reduced the chance of a rapid termination of the pandemic.

The incidence of variants after vaccination and the effectiveness of vaccines against specific variants of SARS-CoV-2 have always been of interest to WHO, experts, national authorities, institutions, researchers, professionals, common people, and medical workers, however, the conclusions are controversial due to insufficient data. To date, no published systematic reviews or meta-analyses have so far been proved relevant conclusively, therefore, we searched for relevant studies and conducted the present meta-analysis to obtain more precise conclusions on the pooled incidence of variants after vaccination and the vaccine effectiveness (VE) of vaccines against variants compared with placebo. Our systematic review and meta-analysis will offer a few critical guidelines for vaccine selection and promotion, and assist in the current clinical work for preventing and treating COVID-19 variants.

MATERIALS AND METHODS

Search Strategy and Articles Selection

The protocol of our article was according to the PRISMA and MOOSE reporting guidelines (16, 17). We searched PubMed, Cochrane Library, and Embase from 30 December 2019 to 8 March 2022. We also queried medRxiv, bioRxiv, and arXiv for preprints about SARS-CoV-2 variant prevalence after vaccination and the effectiveness of various vaccines against variants. The search terms included ("SARS-CoV-2" OR "COVID-19" OR "2019-nCoV") AND "vaccin*" AND ("varian*" OR "mutat*"). Key words, subject words, or free words were adjusted according to different requirements of these databases. The references of previously published reviews and articles included in our study were also browsed to acquire more relevant clinical publications.

The records were browsed and all irrelevant papers were removed according to the titles and abstracts by two independent authors from a team of ten. Then, another two authors reviewed the remaining papers to screen potentially eligible ones. Finally, disputes in the process were resolved by discussion of the research group until an agreement was reached for each article.

Inclusion/Exclusion Criteria

We took into account articles which assessed the prevalence of any type of COVID-19 variant or the efficacy of any type of vaccine against the variants. We evaluated the eligibility criteria of studies using the PICOS (population, intervention/exposure, comparator, outcome, and study) principle (18), which could offer structured approaches to identify relevant data from each paper included. The PICOS principle is as follows: Population—people participating in research associated with vaccines against variants of SARS-CoV-2; intervention/exposure—COVID-19 vaccination; comparator(s)—placebo or unvaccinated population or not applicable due to the single-arm analysis in this study; outcomes—prevalence of SARS-CoV-2 variants after vaccination and/or vaccine effectiveness for prevention or treatment of SARS-CoV-2 variants were evaluated; and study designs—randomized controlled trials, non-randomized studies, comparative trials (C.Ts), cohort studies (C.Ss), observational studies (O.Ss), commentaries, and also letters to the editor were eligible for evaluation, however, editorials, personal opinions, reviews, meta-analyses, conference abstracts, and animal studies were dismissed. We also tried to contact the relevant authors to gain the unpublished data which were required in our study.

The following inclusion criteria were also used to screen all appropriate articles: (1) Articles in English, (2) at least one of the observation indicators was the effectiveness of vaccines against a SARS-CoV-2 variant, (3) studies consisting of at least five patients, and (4) studies with extractable data. The exclusion criteria were as follows: (1) Duplicate studies or study population completely overlapped by other studies, (2) non-accessible full texts, (3) a sample size less than five, (4) studies about pregnant women or neonates, and (5) corresponding outcome parameters that could not be acquired or separated even by contacting the corresponding author.

Data Extraction

Two relevant authors fetched data from the included articles. The following items were extracted from each article: The first author, publish date, study design, sample size, involved countries or regions, mean or median ages, sex ratio, vaccine name, dose, vaccine type, vaccine developer, comparator, characteristics of vaccine recipients, number of scheduled doses (time of inoculations), study duration, and types of variants. The third author reviewed extracted data at random and disagreements were determined by discussion in the group until a consensus was established.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was applied to estimate the quality of the included literature from three points: Patient selection, comparability between groups, and objectivity of results (19). Each aspect received up to 4, 2, and 3 points, respectively and the possible maximum score was 9 points. If the scores were above 4 points, the articles included were considered to have a low or moderate risk of bias. However, studies with points of 4 or fewer were considered to have a high risk of bias and subsequently excluded from our meta-analysis. Two authors independently used NOS to evaluate the quality of the included articles. If they differed in any respect in the quality assessment, other authors offered their opinions to resolve the inconsistencies.

Statistical Analysis

We used the I^2 (inconsistency indexes) statistical parameter to estimate the heterogeneity between studies included. The value of I^2 assesses the proportion of heterogeneity of all the observed variations and an $I^2 > 50\%$ is the level of heterogeneity that is attributed to between-study variance. We conducted a fixed-effect model when $I^2 < 50\%$, but a random-effect model when $I^2 \geq 50\%$ in the testing of heterogeneity. We performed the Egger test to objectively assess the publication bias of the included studies which were considered to not have publication bias if $p > 0.05$.

The pooled prevalence rate outcomes were evaluated by the incidence rate of a COVID-19 variant after vaccination in single-arm analysis. Meanwhile, the pooled efficacy of vaccines against a SARS-CoV-2 variant was assessed by an odds ratio (OR) and vaccine effectiveness (VE) through comparing the differences of variant cases of SARS-CoV-2 between the vaccination group and placebo or unvaccinated population in two-arm analysis. We calculated the pooled vaccine effectiveness as (1-odds ratio)$\times$100%, where the odds ratio was equal to the odds of the vaccination population divided by the odds of unvaccinated group.

We also conducted subgroup analyses with delimited and sufficient data based on various vaccines/variants and different doses. If the data of the single-arm analysis were consistent with those of the two-arm analysis in one group, only the two-arm meta-analysis was conducted. All statistical analysis were carried out by R software (version 3.6.1). 95% confidence intervals (CIs) were applied to present the outcomes and a two-tailed $p<0.05$ indicated statistical significance.

RESULTS

Literature Selection and Characteristics of Studies Included

In our preliminary retrieval, we obtained 6,118 studies from PubMed (687), Embase (873), the Cochrane Library (103), medRxiv (2,287), bioRxiv (2072), and arXiv (20). According to the eligible criteria above, 2,639 studies remained after duplicates were initially excluded. Then, 2,411 studies were excluded by title and abstract for the following reasons: Irrelevant articles ($n = 1,783$), post-hoc analysis ($n = 72$), pre-clinical studies ($n = 85$), animal studies ($n = 34$), and reviews/ personal opinions/ meta-analysis/ conference abstracts/ editorials ($n = 437$). After a full-text review, 184 studies without relevant or clear data were further excluded; Consequently, 44 studies (21–64) were finally brought into this systematic review and meta-analysis. The flow diagram summarizing the literature selection process is presented in **Figure 1**.

Of these studies, 42 were officially published (21–33, 36–64), and two were published on the preprint platform which had not yet been certified by peer review (34, 35). A total of four were blinded, randomized, placebo-controlled trials (21, 22, 42, 55); one was a multicenter, single-blind, randomized phase II/III trial (30); two were multicenter, randomized, placebo-controlled trials (36, 48); 14 were test-negative and case-control trials (23–25, 38, 44, 45, 47, 51, 53, 54, 56, 59, 61, 62); three were matched multicenter or case-control trials (46, 57, 60); two were cross-sectional trials (26, 28); one was a prospective cohort trial (27); three were case-control trials (32, 33, 37); and 14 were observational cohort trials (29, 31, 34, 35, 39–41, 43, 49, 50, 52, 58, 63, 64). These included studies contained eight kinds of COVID-19 vaccines: ChAdOx1 (21, 25, 30, 36, 37, 40, 46, 47, 54, 63), ChAdOx1-S (49), NVX-CoV2373 (22, 42, 55), CoronaVac (23, 35, 45, 56), BBV152 (51), BNT162b2 (24–29, 31–34, 37–41, 43, 44, 48, 50, 52, 57–64), mRNA-1273 (38, 40, 48, 52, 53, 57), and JNJ-78436735 (52). All of which could be classified into viral vector vaccines, subunit vaccines, inactivated vaccines, and mRNA vaccines, respectively, on the basis of different technology platforms. The variants involved in the studies included B.1.1.7 (Alpha), B.1.351 (Beta), P.1/P.1.1/P.1.2/B.1.1.28 (Gamma), B.1.617.2 (Delta), B.1.427/B.1.429 (Epsilon), P.2 (Zeta), B.1.525 (Eta), B.1.526/B.1.526.1/B.1.526.2 (Iota), B.1.617.1 (Kappa), B.1.621/B.1.621.1 (Mu), B.1.1.529/BA (Omicron), R.1, B.1, and B.1.1.33. Among them, four studies were conducted in South Africa (21, 22, 36, 62), seven in the USA (28, 32, 34, 48, 52, 57, 61), seven in the UK (27, 30, 40, 42, 49, 53, 63), five in Brazil (23, 35, 46, 54, 56), four in Israel (29, 33, 60, 64), four in Qatar (24, 38, 44, 59), three in India (25, 47, 51), three in Italy (26, 39, 41), three in France (31, 37, 50), 1 in China (45), 1 in Korea (43), 1 in the USA and Mexico (55), and 1 in French Guiana (58). The baseline characteristics of the literature are presented in **Supplementary Table 1**.

Quality Assessment and Publication Bias

All the 44 studies were quality-assessed based on NOS. Among them, 18 studies had nine points (21, 22, 30, 37, 38, 40, 42, 44, 47, 48, 51–56, 60, 61), five had 8 points (31, 33, 36, 46, 59), seven had 7 points (24, 25, 32, 39, 45, 57, 62), 10 had 6 points (23, 26, 28, 34, 41, 43, 50, 58, 63, 64), and four had 5 points (27, 29, 35, 49). There were relatively high risks of bias in the literature of Hall et al. (27), Haas et al. (29), de Faria et al. (35), and Williams et al. (49) in which "selection of the non-exposed patients" and "comparability between groups" were the two most important deduction items. The summary and figures of risk bias in the eligible studies are shown in **Table 1**.

The p values derived from Egger's test indicated the inexistence of publication bias in most meta-analyses. High probabilities of publication bias existed in the following subgroup meta-analyses: Incidence of variants post second vaccine, incidence of the B.1.1.7 (Alpha) variant post first vaccine, incidence of the B.1.1.7 (Alpha) variant post second vaccine, incidence of the B.1.1.7 (Alpha) variant post first mRNA vaccine,

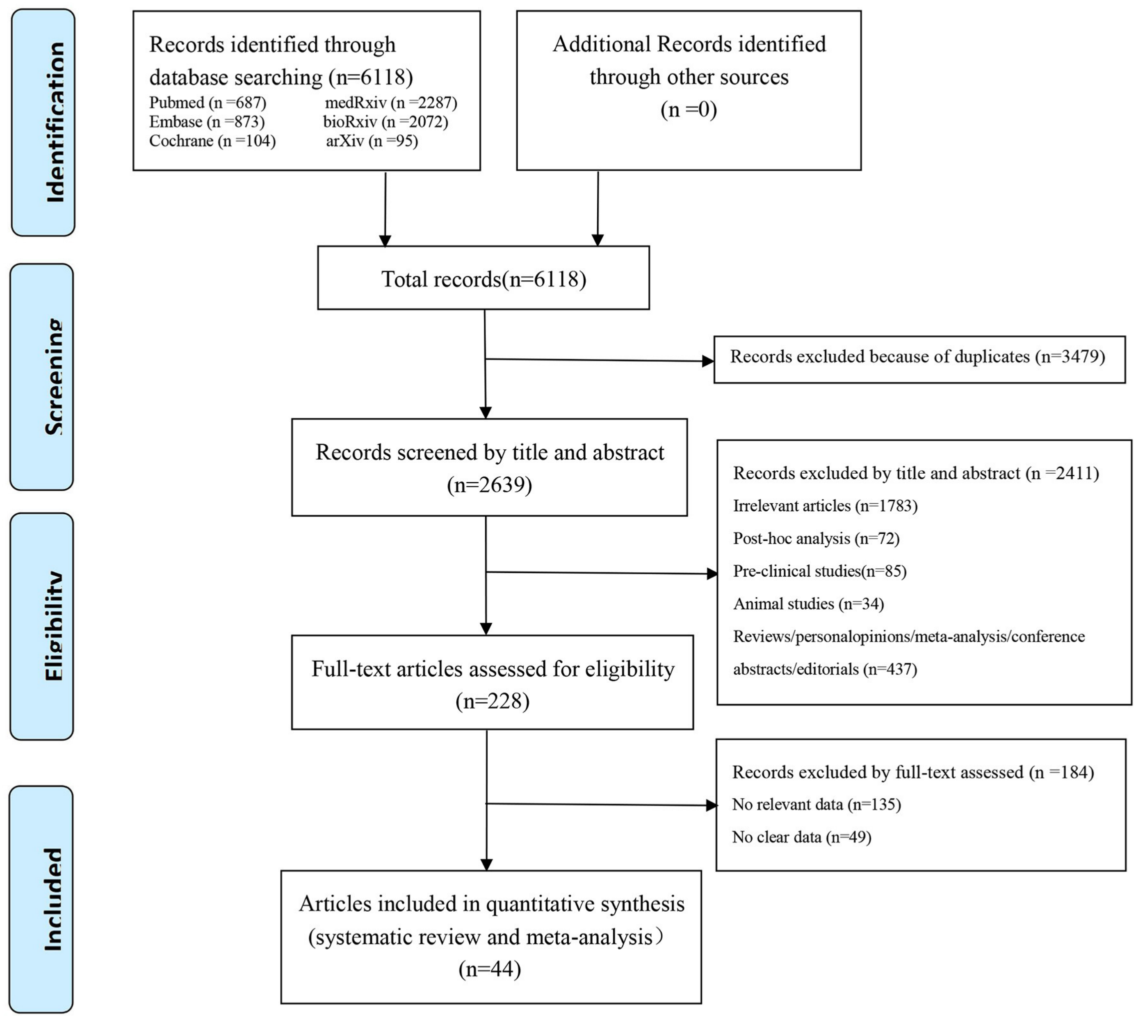

FIGURE 1 | PRISMA flow diagram of the study selection process.

incidence of the B.1.351 (Beta) variant post second vaccine, incidence of the B.1.351 (Beta) variant post second mRNA vaccine, incidence of the B.1.617.2 (Delta) variant post first vaccine, incidence of the B.1.617.2 (Delta) variant post first viral vector vaccine, efficacy of vaccines against variants post second dose, efficacy of vaccines against the B.1.1.7 (Alpha) variant post second dose, and efficacy of an mRNA vaccine against the B.1.1.7 (Alpha) variant post second dose. The publication bias of these sub-analyses (incidence of variants post second protein subunit vaccine, incidence of variants post second inactivated vaccine, incidence of the B.1.1.7 (Alpha) variant post second protein subunit vaccine, incidence of the B.1.351 (Beta) variant post second viral vector vaccine, incidence of the B.1.351 (Beta) variant post second protein subunit vaccine, incidence of the P.1 (Gamma) variant post second viral vector vaccine, incidence of the B.1.427 (Epsilon) variant post second mRNA vaccine, incidence of the P.2 (Zeta) variant post second vaccine, incidence of the B.1.526 (Iota) variant post second vaccine, incidence of the B.1.526 (Iota) variant post second mRNA vaccine, efficacy of a subunit vaccine against the B.1.1.7 (Alpha) variant post second dose, efficacy of a viral vector vaccine against the P.1 (Gamma) variant post second dose, efficacy of vaccines against the B.1.427 (Epsilon) variant post first dose, efficacy of an mRNA vaccine against the B.1.427 (Epsilon) variant post first dose, efficacy of an mRNA vaccine against the B.1.427 (Epsilon) variant post second dose, efficacy of vaccines against the P.2 (Zeta) variant post second dose, and efficacy of mRNA vaccines against the B.1.526 (Iota) variant post second dose) could not be evaluated for fewer studies were included in each subgroup. The results of the Egger's test are summarized in **Supplementary Table 2**.

Meta-Analyses Results

There was substantial heterogeneity ($I^2 \geq 50\%$, $p \leq 0.05$) in most of the groups, hence, the random effects model was conducted in most of these meta-analyses. However, the fixed effects models were used in these analyses as follows: Incidence of the B.1.351

TABLE 1 | Quality evaluation of eligible studies based on the Newcastle-Ottawa Scale.

References	Selection				Comparability	Outcomes			Total scores
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Madhi et al. (21)	1	1	1	1	2	1	1	1	9
Shinde et al. (22)	1	1	1	1	2	1	1	1	9
Hitchings et al. (23)	1	Nil	1	Nil	1	1	1	1	6
Abu-Raddad et al. (24)	1	1	1	Nil	1	1	1	1	7
Lopez Bernal et al. (25)	1	1	1	Nil	1	1	1	1	7
Sansone et al. (26)	1	Nil	1	Nil	1	1	1	1	6
Hall et al., (27)	1	Nil	1	Nil	Nil	1	1	1	5
Jacobson et al., (28)	1	Nil	1	1	Nil	1	1	1	6
Haas et al. (29)	1	Nil	Nil	1	Nil	1	1	1	5
Emary et al. (30)	1	1	1	1	2	1	1	1	9
Bailly et al. (31)	1	1	1	1	1	1	1	1	8
Cavanaugh et al. (32)	1	1	1	1	1	1	Nil	1	7
Kustin et al. (33)	1	1	Nil	1	2	1	1	1	8
Magalis et al. (34)	1	Nil	1	1	Nil	1	1	1	6
de Faria et al. (35)	1	Nil	Nil	1	Nil	1	1	1	5
Irfan et al. (36)	1	1	1	1	2	1	Nil	1	8
Grant et al. (37)	1	1	1	1	2	1	1	1	9
Tang et al. (38)	1	1	1	1	2	1	1	1	9
Rovida et al. (39)	1	1	Nil	1	1	1	1	1	7
Pouwels et al. (40)	1	1	1	1	2	1	1	1	9
Trunfio et al. (41)	1	1	Nil	1	1	1	1	1	6
Heath et al. (42)	1	1	1	1	2	1	1	1	9
Yi et al. (43)	1	Nil	1	1	Nil	1	1	1	6
Chemaitelly et al. (44)	1	1	1	1	2	1	1	1	9
Li et al. (45)	1	1	1	1	1	1	Nil	1	7
Clemens et al. (46)	1	1	1	1	1	1	1	1	8
Thiruvengadam et al. (47)	1	1	1	1	2	1	1	1	9
Tenforde et al. (48)	1	1	1	1	2	1	1	1	9
Williams et al. (49)	1	Nil	Nil	1	Nil	1	1	1	5
Lefèvre et al. (50)	1	Nil	1	1	Nil	1	1	1	6

(Continued)

TABLE 1 | Continued

References	Selection				Comparability	Outcomes			Total scores
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Desai et al. (51)	1	1	1	1	2	1	1	1	9
Duerr et al. (52)	1	1	1	1	2	1	1	1	9
Bruxvoort et al. (53)	1	1	1	1	2	1	1	1	9
Hitchings et al. (54)	1	1	1	1	2	1	1	1	9
Dunkle et al. (55)	1	1	1	1	2	1	1	1	9
Ranzani et al. (56)	1	1	1	1	2	1	1	1	9
Dickerman et al. (57)	1	1	1	1	Nil	1	1	1	7
Vignier et al. (58)	1	Nil	1	1	Nil	1	1	1	6
Abu-Raddad et al. (59)	1	1	1	1	1	1	1	1	8
Reis et al. (60)	1	1	1	1	2	1	1	1	9
Olson et al. (61)	1	1	1	1	2	1	1	1	9
Collie et al. (62)	1	1	1	1	1	1	Nil	1	7
Eyre et al. (63)	1	Nil	1	1	1	1	Nil	1	6
Mor et al. (64)	1	Nil	1	1	1	1	Nil	1	6

(Beta) variant post second viral vector vaccine, incidence of the B.1.427 (Epsilon) variant post second mRNA vaccine, incidence of the P.2 (Zeta) variant post second vaccine, efficacy of a subunit vaccine against the B.1.1.7 (Alpha) variant post second dose, efficacy of vaccines against the B.1.351 (Beta) variant post first dose, efficacy of an mRNA vaccine against the B.1.351 (Beta) variant post first dose, efficacy of an mRNA vaccine against the P.1 (Gamma) variant post first dose, efficacy of vaccines against the B.1.427 (Epsilon) variant post first dose, efficacy of vaccines against the B.1.427 (Epsilon) variant post second dose, efficacy of an mRNA vaccine against the B.1.427 (Epsilon) variant post first dose, efficacy of an mRNA vaccine against the B.1.427 (Epsilon) variant post second dose, and efficacy of vaccines against the P.2 (Zeta) variant post second dose. The I^2 and p values of which were all <50% and >0.05, respectively. The results of the heterogeneity test are shown in **Supplementary Table 2**.

The Pooled Incident Rates of COVID-19 Variants After Vaccination

In the meta-analysis, we found that the overall incidence of variants post first vaccine was 0.07 [95%CI: 0.01, 0.15] and post second vaccine was 0.03 [95%CI: 0.02, 0.04]. According to the types of vaccines/variants and the first/second dose, the subgroup meta-analyses were divided into 37 categories. The results of subgroup analyses (incidence of variants post first vaccine, incidence of variants post second vaccine, incidence of variants post first mRNA vaccine, incidence of variants post second mRNA vaccine, incidence of variants post second viral vector vaccine, etc.) revealed a significant protective effect of the vaccines against COVID-19 variants with the fact that the pooled incident rates were below 0.10 (pooled incidence=0.07, 95%CI: 0.01, 0.15; 0.02, 95%CI: 0.00, 0.13; 0.07, 95%CI: 0.00, 0.21; 0.06, 95%CI: 0.04, 0.09; 0.02, 95%CI: 0.01, 0.02, etc., respectively). However, the results of the remaining seven subgroup analyses (incidence of variants post second inactivated vaccine, incidence of the B.1.1.7 (Alpha) variant post first mRNA vaccine, incidence of the B.1.351 (Beta) variant post first vaccine, incidence of the B.1.351 (Beta) variant post first mRNA vaccine, incidence of the P.1 (Gamma) variant post first vaccine, incidence of the B.1.617.2 (Delta) variant post first vaccine, and incidence of the B.1.526 (Iota) variant post second mRNA vaccine) presented a moderate protective effect of the vaccines against COVID-19 variants considering that the pooled incident rates were over 0.10 (pooled incidence= 0.37, 95%CI:0.19, 0.57; 0.16, 95%CI: 0.15,0.16; 0.35, 95%CI: 0.04, 0.66; 0.30, 95%CI: 0.14, 0.50; 0.36, 95%CI: 0.26, 0.46; 0.14, 95%CI: 0.11, 0.18; 0.12, 95%CI: 0.01, 0.59, respectively). The details of the meta-analysis results are shown in **Table 2**, **Figure 2**, **Supplementary Table 2**, and **Supplementary Figure 1**.

The Pooled Efficacy of Vaccines Against SARS-CoV-2 Variants

Generally, we observed that the vaccine effectiveness (VE) of incidence of variants post first vaccine between the vaccine and the placebo or unvaccinated population was 0.40 [95%CI: 0.38, 0.42] and post second vaccine was 0.96 [95%CI: 0.93, 0.98] in the meta-analysis. We also conducted 30 subgroup meta-analyses according to the classifications mentioned above. The results of 20 subgroup (efficacy of an mRNA vaccine against variants post second dose, efficacy of vaccines against the B.1.1.7 (Alpha) variant post second dose, efficacy of an mRNA vaccine against the B.1.1.7 (Alpha) variant post second dose, efficacy of a subunit vaccine against the B.1.1.7 (Alpha) variant post second dose, efficacy of a viral vector vaccine against the B.1.1.7 (Alpha) variant post second dose, etc.) analyses implied that some vaccines had a better preventive and therapeutic effect on certain variants among those cases following the vaccination, placebo, or unvaccinated populations, considering that the VE in these subgroups was between 60% and 95% (VE= 0.85, 95%CI: 0.28, 0.97; 0.90, 95%CI: 0.79, 0.95; 0.89, 95%CI: 0.74, 0.95; 0.89, 95%CI: 0.80, 0.94; 0.94, 95%CI: 0.30, 1.00, etc., respectively). Besides, the remaining results of another 10 subgroup analyses (efficacy of vaccines against the B.1.351 (Beta) variant post first dose, efficacy of vaccines against the P.1 (Gamma) variant post first dose, efficacy of an mRNA vaccine against variants post first dose, efficacy of vaccines against the B.1.351 (Beta) variant post second dose, efficacy of a viral vector vaccine against the P.1 (Gamma) variant post second dose, efficacy of a viral vector vaccine against the P.1 (Gamma) variant post second dose, etc.) showed a passable protective effect of some vaccines against certain COVID-19 variants in view that the VE in these subgroups was between 16% and 57% (VE=0.16, 95%CI: 0.11, 0.20; 0.35, 95%CI: 0.05, 0.56; 0.35, 95%CI: 0.13, 0.51; 0.42, 95%CI: 0.00, 0.70; 0.57, 95%CI: 0.25, 0.75, etc., respectively). All details of the meta-analysis results are shown in **Table 2**, **Figure 3**, **Supplementary Figure 2**, and **Supplementary Table 2**.

DISCUSSION

The emergence of COVID-19 variants and their mutations, especially those identified in the UK (B1.1.7, Alpha), South Africa (B1.351, Beta; B.1.1.529, Omicron), Brazil (P.1, Gamma; P.2, Zeta), India (B.1.617.2, Delta; B.1.617.1, Kappa), the USA (B.1.427/B.1.429, Epsilon; B.1.525, Eta; B.1.526, Iota), the Philippines and Japan (P.3, Theta), the South American region (C.37, Lambda), and Columbia (B.1.621, Mu), highlight the conspicuous abilities of SARS-CoV-2 to rapidly generate new gene variants, which have raised concerns about the possibility that these mutants may evade vaccines (65, 66). At present, the lack of understanding of pathogenic and immunologic mechanisms and duration of immunity of vaccines are still the main challenges against combatting the variants of SARS-CoV-2 (67). Although these variants have been demonstrated to dramatically reduce the neutralization by specific antibodies or sera elicited by vaccination against SARS-CoV-2 in several studies recently (68–71), multiple works have verified that vaccine-induced human antibodies could protect against emerging SARS-CoV-2 variants and mitigate the vaccine resistance caused by the current VOCs (72–74). Indeed, the process of neutralizing vaccine-induced antibodies *in vivo* could not mirror the complicated interaction and cross-talk between SARS-CoV-2 and humans *in vivo*. Furthermore, the results of real-world clinical trials were controversial in terms of the conclusions about the effectiveness of vaccines against variants

TABLE 2 | Results of the meta-analysis.

Variants vaccines	**Overall Variants**	**B.1.1.7 (Alpha) variant**	**B.1.351 (Beta) variant**	**P.1 (Gamma) variant**	**B.1.617.2 (Delta) variant**	**B.1.427 (Epsilon) variant**	**P.2 (Zeta) variant**	**B.1.526 (Iota) variant**
Overall vaccines	0.07 [0.01; 0.15]*	0.07 [0.05; 0.10]*	0.35 [0.04; 0.66]*	0.14 [0.02; 0.34]*	0.14 [0.11; 0.18]*	0.00 [0.00; 0.04]*	NA	NA
	0.03 [0.02; 0.04]†	0.04 [0.03; 0.05]†	0.09 [0.03; 0.19]†	0.09 [0.06; 0.16]†	0.08 [0.05; 0.11]†	0.00 [0.00; 0.01]†	0.00 [0.00; 0.22]†	0.01 [0.00; 0.80]†
	0.40 [0.38, 0.42]§	0.66 [0.36; 0.82]§	0.16 [0.11; 0.20]§	0.35 [0.05; 0.56]§	0.38 [0.15; 0.55]§	0.78 [0.54; 0.90]§	NA	NA
	0.96 [0.93; 0.98]¶	0.90 [0.79; 0.95]¶	0.42 [0.00; 0.70]¶	0.61 [0.50; 0.70]¶	0.68 [0.57; 0.76]¶	0.95 [0.87; 0.98]¶	0.69 [0.55; 0.78]¶	0.71 [0.00; 0.96]¶
mRNA vaccine (BNT162b2/mRNA-1273/JNJ-78436735)	0.07 [0.00; 0.21]*	0.16 [0.15; 0.16]*	0.30 [0.14; 0.50]*	0.09 [0.00; 0.26]*	0.09 [0.03; 0.18]*	0.00 [0.00; 0.04]*	NA	NA
	0.06 [0.04; 0.09]†	0.09 [0.06; 0.14]†	0.10 [0.03; 0.22]†	0.06 [0.01; 0.16]†	0.09 [0.05; 0.14]†	0.00 [0.00; 0.04]†	NA	0.12 [0.01; 0.59]†
	0.35 [0.13; 0.51]§	0.64 [0.00; 0.87]§	0.16 [0.11; 0.20]§	0.57 [0.05; 0.81]§	NA	0.78 [0.54; 0.90]§	NA	NA
	0.85 [0.28; 0.97]¶	0.89 [0.74; 0.95]¶	0.40 [0.00; 0.72]¶	0.68 [0.00; 0.95]¶	0.74 [0.62; 0.82]¶	0.95 [0.86; 0.98]¶	NA	0.62 [0.00; 0.98]¶
Viral vector vaccine (ChAdOx1/ChAdOx1-S)	NA	0.10 [0.07; 0.14]*	NA	NA	0.06 [0.02; 0.14]*	NA	NA	NA
	0.02 [0.01; 0.02]†	0.00 [0.00; 0.01]†	0.02 [0.02; 0.03]†	0.05 [0.00; 0.67]†	0.03 [0.00; 0.09]†	NA	NA	NA
	NA	NA	NA	NA	0.50 [0.35; 0.61]§	NA	NA	NA
	0.66 [0.51; 0.77]¶	0.94 [0.30; 1.00]¶	NA	0.57 [0.25; 0.75]¶	0.62 [0.31; 0.79]¶	NA	NA	NA
Protein subunit vaccine (NVX-CoV2373)	NA	NA	NA	NA	NA	NA	NA	NA
	0.03 [0.00; 0.03]†	0.00 [0.00; 0.00]†	0.00 [0.00; 0.02]†	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	NA
	NA	0.89 [0.80; 0.94]¶	NA	NA	NA	NA	NA	NA
Inactivated vaccine (CoronaVac/BBV152)	NA	NA	NA	NA	NA	NA	NA	NA
	0.37 [0.19; 0.57]†	NA	NA	0.36 [0.26; 0.46]†	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	NA

* *Incidence of variants post first vaccine (95% CI).*
† *Incidence of variants post second vaccine (95% CI).*
§ Vaccine effectiveness post first vaccine (95% CI).
¶ Vaccine effectiveness post second vaccine (95% CI).
NA, not applicable; CI, confidence interval.

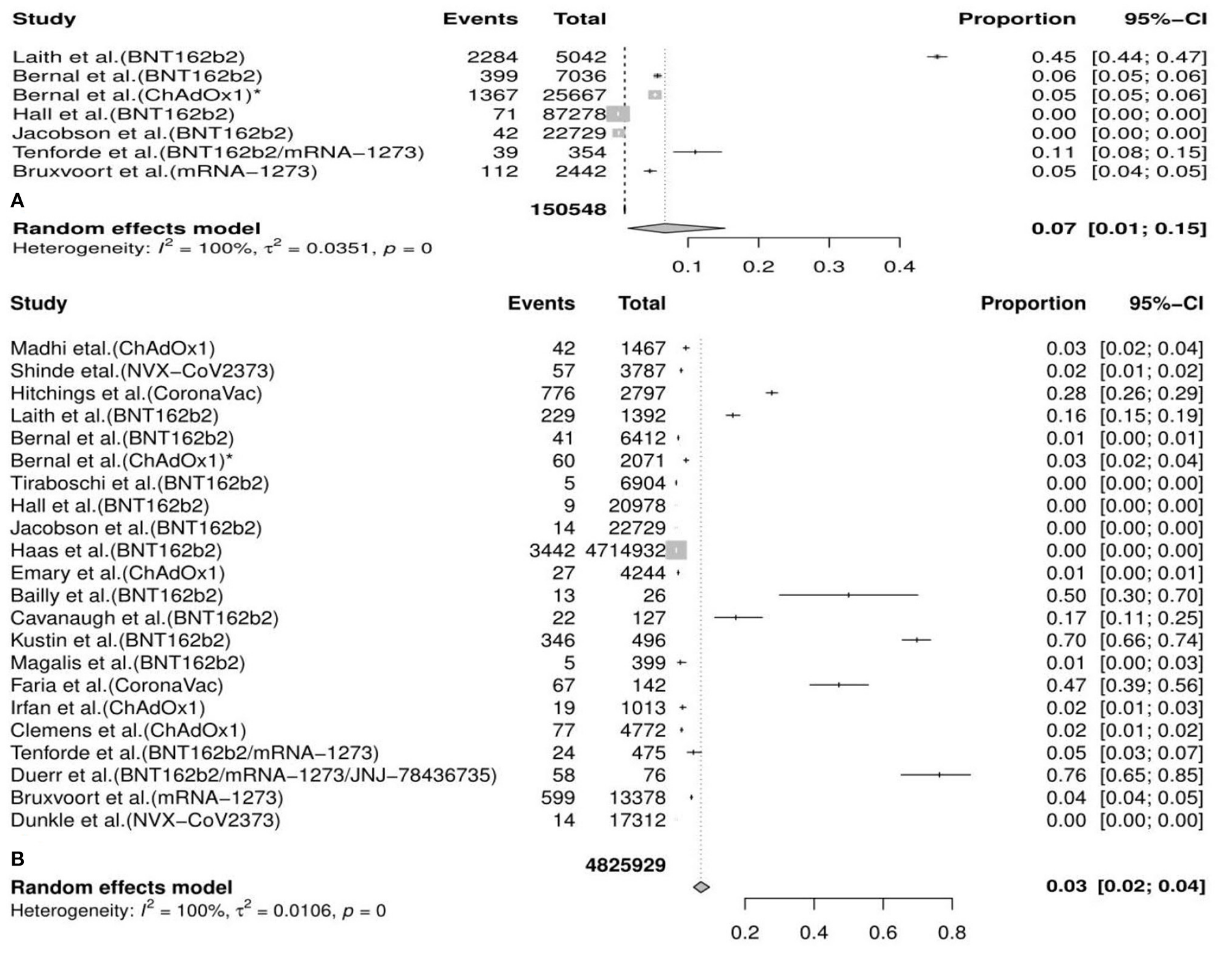

FIGURE 2 | Meta-analysis for the overall incidence of various COVID-19 variants post first vaccine **(A)** and post second vaccine **(B)**.* indicates the second arm in the study of Bernal et al. CI, confidence interval.

(21–23, 30, 31, 34, 36). On account of the fact that the current vaccines' efficacy has not yet been comprehensively discussed, many unsubstantiated claims have been made by popular media and politicians, which often negatively affect real-world mass vaccination campaigns. Therefore, we mainly focused on existing and available studies and strived to provide a systematic and comprehensive review regarding the incidence of variants after vaccination and the efficacy of vaccines against variants if possible in the meta-analysis.

Based on the consequences of the meta-analysis, we found that the overall incidence of variants post first vaccine was 0.07 [95%CI: 0.01, 0.15] and post second vaccine was 0.03 (95%CI: 0.02, 0.04). The definition of "incidence" in our study indicated the number of cases with any specific variants but other variants detected in the same patients were not repeatedly included. Although SARS-CoV-2 mutates all the time, the newly emerging variants could be predicted and probably be identified by all sequenced genomes. In a neutralizing trial about human monoclonal antibodies induced by vaccines against variants of SARS-CoV-2, Schmitz et al. reported that the escaped variants accounted for <0.008% of sequenced clinically isolated viruses through all publicly available SARS-CoV-2 genome sequences (72). Currently, breakthrough infections in partial or full vaccination populations have been reported but the initial findings indicated that these cases (PVSCs) were uncommon (75, 76). In a cross-sectional study conducted in northern California, Jacobson et al. reported that the incidence of COVID-19 after vaccination was about 0.83% (189/22,729) and the incidence of VOCs (B.1.427 and B.1.429) was only about 0.19% (43/22,729) (28). Our results basically aligned with the conclusions in real-word clinical trials (22, 25, 27, 29, 30). Hence, the estimation in the meta-analysis for the incidence of variants post vaccination was reliable and the relatively low overall incidence confirmed the efficacy of vaccines against COVID-19 variants. Based on the two-arm meta-analysis, the overall vaccine effectiveness (VE) against variants post first vaccine was 0.40 [95%CI: 0.38, 0.42]

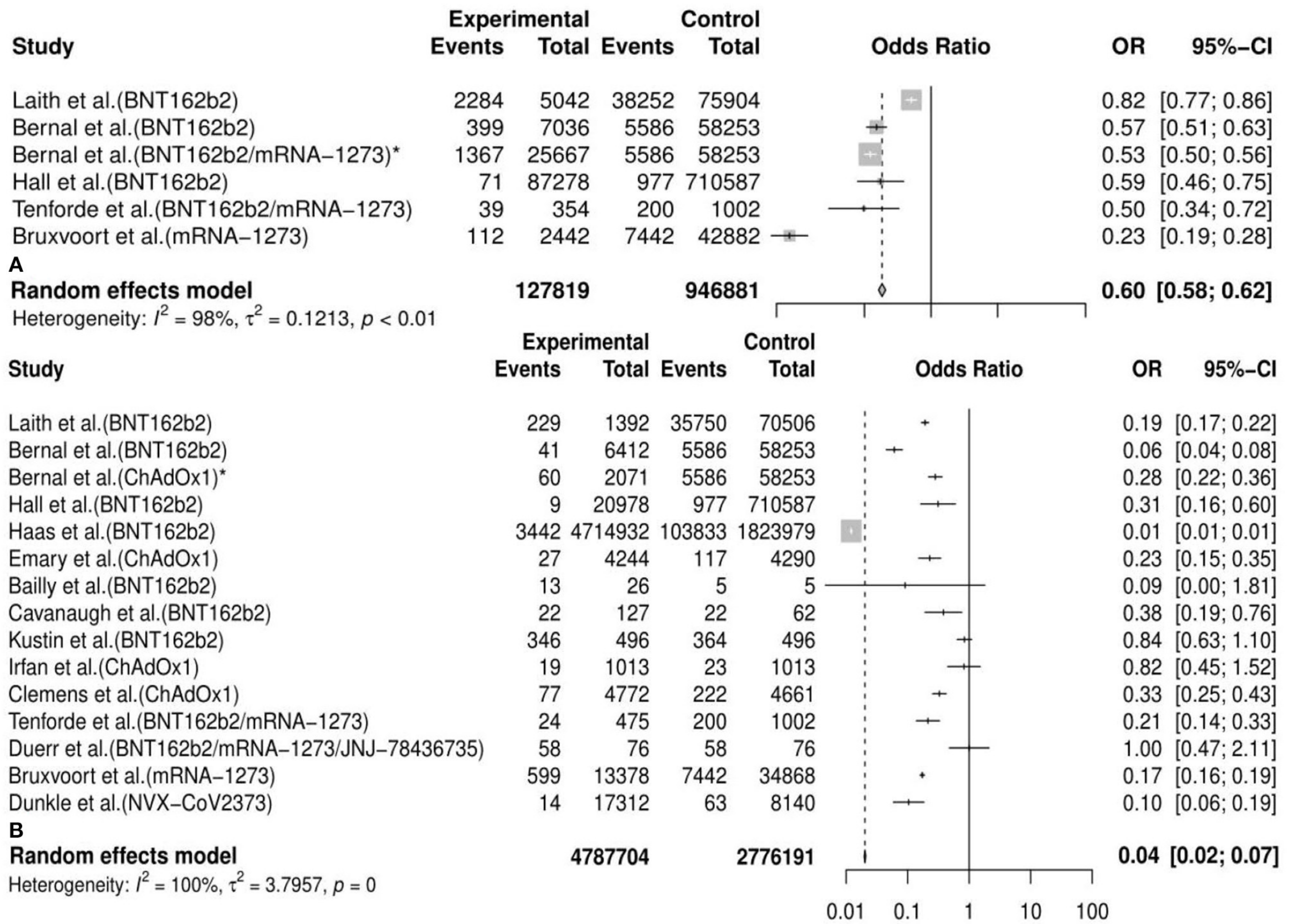

FIGURE 3 | Meta-analysis for the overall efficacy of vaccines against COVID-19 variants post first vaccine **(A)** and post second vaccine **(B)**. * indicates the second arm in the study of Bernal et al. CI. confidence interval; OR, odds ratio.

and post second vaccine was 0.96 [95%CI: 0.93, 0.98]. Regarding the effectiveness of current vaccines against COVID-19, several reviews and meta-analyses have been published, which did not make a distinction between wild-type SARS-CoV-2 and variants (77–79). In a meta-analysis about vaccines of COVID-19 in phase III trials, Cheng et al. concluded that overall vaccines currently had a good protective effect against COVID-19 among patients after vaccination with an efficiency of 83% (95%CI: 0.68–0.91) (77). In another meta-analysis of randomized clinical trials, Pormohammad et al. found that the pooled efficiency of vaccines based on different technical platforms was from 80.2 to 94.6% (79). Therefore, we have reason to think that there are not many differences in vaccines' ability to elicit immune responses when they confront COVID-19 and its variants.

Most vaccines currently in use require two doses and this two-step vaccination process is called "prime-boost". Generally, individuals were deemed to be fully vaccinated 14 days or longer after acquiring their second dose in a two-vaccination procedure with a mean interval time over 2 weeks (75, 76, 80). Whereas, single-dose vaccination is more feasible and contributes to a higher acceptance of vaccination for the mass population in the real world (80, 81). Both the pressure from the vaccine supply chain and the vaccine hesitation in the public caused by the concern over safety inevitably impede full vaccination (82, 83). Most studies showed that two-dose vaccination had better immunogenicity and efficacy compared with a single-dose regimen for most vaccines. Kow et al. found that the pooled protective rate of the BNT162b2 mRNA vaccine after the first dose was 82%, which was lower than the efficacy of 95% after the second dose (78). Pormohammad et al. concluded that there were no differences among the effectiveness of some COVID-19 vaccines after the first and second dose, such as adenovirus-vectored vaccines (97.6 vs. 99.9%), inactivated vaccines (91.3 vs. 94%), and pro-subunit vaccines (87.3 vs. 95.6%) (79). Nevertheless, they also admitted that this efficacy was estimated according to the amount of neutralizing antibodies but not the incidence rate, which could not substitute the protection rate in the real world. However, the author emphasized that the introduction of the second dose of vaccine could produce more reliable results, because the variation in the efficacy after the second dose was more notable (79). Saad-Roy et al. built a model of immuno-epidemiology and explored whether a one-dose vaccine policy generally protected individuals against COVID-19 in the short run but that partial vaccination inevitably promoted antigenic evolution (84). Our results showed that the vaccines reduced the incidence rate of variants by 71.4% and increased the efficacy against the variants of concern by 140% after the second dose relative to after the first dose, which again proved the importance of the booster inoculation after the prime inoculation, especially for the COVID-19 variants. The theory we suspected may be that if the vaccines train the immune system to recognize a virus repeatedly, then, the immune response might become more durable and broader which could help to screen for SARS-COV-2 with slightly less virulent variants. Moreover, Jacobson et al. reported that the majority of breakthrough cases occurred <2 weeks after the first/second dose of vaccine and emphasized that excellent vaccine effectiveness usually appeared > 2 weeks after the second vaccine (28). Therefore, we suggest that the public should be vaccinated as soon as possible with two doses to build up full immunity against variants of SARS-CoV-2 and highlight the necessity to build strict preventive measures until herd immunity is established after 14 days post the second dose.

When the breakthrough patients began to increase in the early summer of 2021, the necessity of a third dose of COVID-19 vaccine was being comprehensively discussed and analyzed, which still warrants intensive scientific interest and practical importance. In view that our study suggested a second dose of vaccine is more effective in protecting individuals against COVID-19 variants compared with receiving only one dose, it is reasonable to presume that a higher level of protection could be observed in those who completed the three-dose vaccine regime. Admittedly, it is indeed a valid point that a third booster could relieve potential waning vaccine-induced humoral and cellular immunity, possibly increasing immune escape and reducing the effectiveness of vaccines against SARS-CoV-2 variants over time. The findings of Barda et al. demonstrated that a third dose of the BNT162b2 vaccine could address severe COVID-19-related outcomes compared with the standard two-dose strategy (85). In a study of heterologous vaccination, health-care workers in Thailand who received a third dose of ChAdOx1 after completing a two-dose CoronaVac vaccine regime elicited higher neutralizing activity against all variants of concern (86). Thompson et al. emphasized that all unvaccinated adults should get vaccinated with a third dose of an mRNA vaccine as soon as possible when considering that the mRNA vaccine effectiveness was 90 and 82% ≥14 days after dose 3 during the Delta and Omicron predominant periods, respectively (87). Moreover, a booster third dose is necessary for cancer patients, organ transplant recipients, people aged >60 years, etc., whose immune responses are inadequate (88–90). Nevertheless, a third vaccine dose may seem like a luxury and nothing could be more urgent than the elimination of vaccine discrimination and vaccine inequity. Firstly, worldwide vaccine campaigns remain extremely unfair. Numerous industrialized countries such as the UK and the USA have managed to fully vaccinate >60% or covered 50% of their populations, whereas some countries in African have shockingly low vaccination coverage in their population. The administration of a third booster dose is expected to further damage the disequilibrium and it has become an ethical issue (91). Secondly, it remains unclear whether there is an upper limit of mutation, beyond which SARS-COV-2 would not evolve in respect to transmission, virulence, or immune evasion (92). When the ceiling is overcome, for example, a hyperexponential increase in the transmissibility, the need of a third dose and the implementation of Draconian measures are much more valuable (93). Last but not least, vaccine discrimination and vaccine inequity will encourage viral epidemic relapses, even in developed countries with broad vaccination coverage. People should be aware that in an infected individual without vaccination the virus is more prone to mutations than in a vaccinated person (94), and the viral mutation potential is higher in countries that have lower vaccination coverage (95). Thus, we think that the two-dose vaccine schedule could achieve the initial target to prevent COVID-19 variant infection, but in the meantime, a third booster dose is necessary for patients with inadequate immune responses or people who need to safeguard against Omicron immune escape.

For the subgroup-analyses according to different types of vaccines, we found that the incidence of overall variants and the efficacy of a specific vaccine post first mRNA vaccine (BNT162b2/mRNA-1273/JNJ-78436735) were 0.07 and 35%, and post second dose were 0.06 and 85%, respectively; the incidence of overall variants and the efficacy of a specific vaccine post second viral vector vaccine (ChAdOx1/ChAdOx1-S) were 0.02 and 66%, respectively; the efficacy of a specific vaccine post first inactivated vaccine (CoronaVac) was 37%. As the results showed, a two-dose regimen of an mRNA vaccine was more effective against COVID-19 variants than a traditional viral vector vaccine and inactivated vaccine compared with the placebo group or unvaccinated populations. As a gene-based vaccine, BNT162b2 became an mRNA vaccine candidate and went from concept to clinical development in <3months, a rate unprecedented in the history of vaccine development (20). Phase III clinical trials and real-world data showed that a two-dose procedure of BNT162b2 could effectively prevent individuals across all age groups from infections with or without COVID-19 symptoms, and in the meantime significantly reduce the incidence of hospitalizations and decrease the rate of severe disease and death caused by COVID-19 infections (24, 25, 28, 29, 96). mRNA vaccines could elicit broad immune responses against a wide range of SARS-CoV-2 variants, including neutralizing antibodies combined with $CD4^+$ and $CD8^+$ T cells, which may be responsible for the significant efficacy of BNT162b2/mRNA-1273/JNJ-78436735 (38, 40, 48, 52, 53, 57, 97). Viral vector vaccines and inactivated vaccines are both based on traditional platforms. ChAdOx1 contains the replicated defective adenovirus gene encoding the spike protein of SARS-CoV-2. Although several studies confirmed that ChAdOx1 could elicit specific neutralizing antibodies and an immune response mediated by T cells against SARS-CoV-2, the pooled efficacy of ChAdOx1 was lower than mRNA vaccines (80.2 vs. 94.6%) (30, 98, 99). CoronaVac/BBV152, as a vaccine containing inactivated SARS-CoV-2 that could be suitable for mass production and stably express antibodies with good immunologic tolerant, had fine effectiveness against COVID-19 confirmed by PCR (23, 51, 100).

However, it is worth noting that some studies demonstrated that the efficacy of CoronaVac was only 50.39% and it could not induce immune memory (35, 101). Unfortunately, data for the Pro-Subunit and other types of vaccines were not available, hence, the analysis of these vaccines was not included in our study. Just from the respect of efficacy, we recommend mRNA vaccines as the "first-order" promising candidate against COVID-19 variants.

B.1.1.7, containing D614G and eight other spike mutations, was first detected in the UK on 14 December 2020 (66). This variant could enhance transmissibility up to 71% and caused mortality to increase substantially compared with previous mutations (66, 102). We found that the incidence of B.1.1.7 and the effectiveness of vaccines against B.1.1.7 post a second vaccine were 0.04 and 90%, respectively. This moderate effectiveness may be the proof that B.1.1.7 did not demonstrate enhanced immune escape capability. In addition, the efficacy of an mRNA vaccine and vector vaccine against B.1.1.7 post second dose were 89 and 94%, respectively. The difference in the efficacy against B.1.1.7 between BNT162b2 and ChAdOx1 is well grounded in neutralization tests and clinical trials. Muik et al. found the immune sera induced by BNT162b2 generally retained immunocompetence against B.1.1.7 even though there was a slight reduction (73), but Gavin et al. reported that the sera-neutralizing titers induced by ChAdOx1 showed a 2.1–2.5-fold reduction against B.1.1.7 (103). In the real-world setting, the studies of Hall et al. (27), Abu-Raddad et al. (24), and Munitz et al. (74) concluded that the mRNA vaccine of BNT162b2 could prevent the infection of SARS-COV-2 when B1.1.7 was the dominant variant, whereas, Emary et al. (30) found that the efficacy of ChAdOx1 against symptomatic B.1.1.7 patients was 70.4%, which was obviously lower than for non-B.1.1.7 infections (81.5%). B.1.351, containing D614G and nine other spike mutations, was first identified on 18 December 2020 in South Africa (66). This variant caused much greater concern because the diminished protective effectiveness of the current vaccines meant that the South African vaccination strategy completely shifted (104). Our results showed that the incidence of B.1.351 and the effectiveness of vaccines against B.1.351 post second vaccine were 0.09 and 42%, respectively, which indicated that the vaccines provided a less effective protection against B.1.351 than against B.1.1.7. Moreover, the incidence of the B.1.351 variant post second BNT162b2 dose and the effectiveness of the mRNA vaccine against B.1.351 were 0.10 and 40%, respectively, which also demonstrated that the prevention ability of BNT162b2 against B.1.351 decreased significantly when compared with B.1.1.7. The downward tendency among the neutralizing abilities of vaccines against B.1.351 and B.1.1.7 was consistent with our findings. The study by Gavin et al. showed that the decline in the neutralizing abilities against B.1.351 was 7.6-fold but against B.1.1.7 was only 3.3-fold (105). Furthermore, results from Wang et al. revealed that the average loss in neutralization titers against B.1.1.7/B.1.351 was 2/6.5-fold, respectively (68). Liu and Xie et al. (106, 107) believe the drop in neutralization titers against B.1.351 in sera induced by the vaccine could be mainly due to E484K mutation, which is located at the region of the receptor-binding domain (RBD). Our results could also be confirmed by the real-world condition reported by Abu-Raddad et al. (24) who performed a cohort study in Qatar and found that the effectiveness of BNT162b2 was estimated to be 87.0% against B.1.1.7 and 72.1% against the B.1.351. P.1 (Gamma) variant. This variant, which harbors 17 nonsynonymous mutations, was detected in Brazil, and first reported in the USA, showed a 2.6 times more transmissible capacity and significantly increased the risk of hospitalization and ICU admission (66). Similar to the results of B.1.351, the efficacy of vaccines against P.1, including mRNA and viral vector vaccines, were abolished in our study and fall in line with the results of a nationwide study by Wibmer et al. in France which showed that the effectiveness of the mRNA vaccine was estimated at 77% [95% CI:0.63, 0.86] (108). Although the neutralization of convalescent plasma and vaccine sera was reduced by 3.8–4.8-fold during the P.1 epidemic (109), we perceived that the threat posed by P.1 could not be as severe as previous variants in view that the diminution of vaccine protection against P.1 was not as great as B.1.351 and others. The B.1.617.2 (Delta) variant with 10 mutations in the spike protein was initially considered a VOI (variant of interest), but was rapidly classified as a VOC by WHO in view of its sharp rise in infections and mortality. It appears that the ongoing vaccines still offer substantial protection against the B.1.617.2 (Delta) variant, at slightly higher levels compared with P.1 on the basis of the findings in our study. Our results could also be further reproduced in several meta-analyses and neutralization tests, which reported that the B.1.617.2 variant could be neutralized by post-vaccination sera and convalesced successfully with only a mild decrease in its neutralization sensitivity and confirmed that current vaccines could offer higher protection against B.1.617.2 in real-world settings (110, 111). B.1.427 (Epsilon), first identified in California, increased transmissibility by approximately 20% and exhibited moderate resistance to neutralization when using convalescent and post-vaccination sera. However, the efficacy of pooled vaccines against B.1.427 was 95% and, thus we considered the completion of a two-dose vaccine schedule to have a favorable protective effect which helped explain why B.1.427 was classified as a VOC only in the USA but a VOI in other countries (15). Due to the lack of sufficient data about other types of vaccines such as Pro-Subunit and inactivated vaccines and other types of variants such as P.2 and B.1.526, it is regrettable that only a few incidences of some specific vaccines post one or two specific doses could be pooled, which were hard to explain and verify by neutralization tests and clinical trials in a real-world setting.

Yet, there are, at the moment, limited data to systematically evaluate the effectiveness of the existing vaccines against B.1.1.529 (Omicron), which is the fifth VOC categorized by WHO and has become the most widely distributed variant since December 2021. It is suggested that the viral infectivity of Omicron increases 2.8-fold compared to B.1.617.2 which could contribute to the explosive rise in cases (112). Mutations in Omicron, which are responsible for more vaccine breakthroughs and have an overwhelmingly disruptive effect, could substantially reduce or impair the neutralization by monoclonal antibodies (mAbs), convalescent plasma, and vaccine sera compared to mutations in predecessor variants (113–115). Importantly, SARS-CoV-2 may not have reached the top of its evolution and

Omicron is perceived to have opened up the broadly untapped potential for future mutations, which may possess more virulent strains and severely affect the global population (116). In this present scenario, it is unlikely that the ongoing vaccines will completely fail against Omicron, considering the findings in our study that the previous VOCs (Alpha, Beta, Gamma, and Delta) have been curbed by COVID-19 vaccines. Dejnirattisai et al. reported that the sterilizing immunity against Omicron induced by vaccines may be diminished, however, cell-mediated immunity might be less affected and ensure that vaccines are still useful in terms of containing infection progression, etc. (113). Most neutralization assays about Omicron were performed *in vivo* which did not fully quantify the immune response *in vivo*. The booster third dose of vaccines, including mRNA, viral vector, and inactivated vaccines, could significantly enhance the neutralizing activity against Omicron both *in vivo* and *in vivo* (85–90, 117, 118). Hence, we perceived that the impact of Omicron has not yet threatened global conformational alterations, and vaccines may still protect people from COVID-19 variants until further information is available.

The strength of this meta-analysis lies in its rapid analysis of the incidence of variants in the COVID-19 pandemic and the efficacy of current vaccines against these variants, which could provide useful insight for the implementation of COVID-19 vaccination in the setting of numerous variants. In the meantime, we must acknowledge that the results of our study should be interpreted with a very cautious approach because it was subject to certain limitations that warrant mention. Firstly, most of the included articles were cohort studies or observational studies, which could not provide the sufficient statistical power of randomized controlled trials (RCTs). Besides, high statistical heterogeneity existed for some subgroup analyses and must be considered when interpreting the outcomes. Secondly, some studies included insufficient or inexact numbers of participants or variants, which suggested there was a contingent risk of misestimation of the incidence of variants or the efficacy of the vaccines. Thirdly, up to now, most of the included vaccines and variants were mRNA vaccines or vector vaccines and B.1.1.7, B.1.351, etc., respectively. Some current vaccines and variants were not brought into the present study because of the incomplete data. Thus, the summaries of the clinical trials may not coincide with the real world reality, and the generalizability of our findings is unknown. Last but not least, the safety or the adverse events of COVID-19 vaccines and the ability to spread or virulence of the variants were not evaluated in our study, which might lead to one-sidedness in a comprehensive understanding of COVID-19 vaccines against variants.

In this study, we first presented the preliminary conclusions about the results of the current vaccines against the emerging variants. According to the situation, scientists around the world are focusing on learning more about whether the current authorized vaccines will protect people from infection caused by SARS-CoV-2 variants in the real world. The next generation of vaccines, such as a bivalent vaccine by Johnson & Johnson, a booster vaccine by Moderna, mRNA multivalent vaccines by GlaxoSmithKline and CVNV, etc., might play a pivotal role in preventing and controlling the variants of SARS-CoV-2 worldwide.

CONCLUSION

Our meta-analysis shows that the current vaccines that are used globally could restrict the spread and prevent infection of SARS-CoV-2 variants to a great extent. We would also support maximizing vaccine uptake with two doses as the most effective compared to only one dose. Although the mRNA vaccine was found to be the most effective against variants in our study, specific vaccines should be taken into account based on the local dominant prevalence of variants. Furthermore, the conclusions should be used cautiously in consideration of the limited data. In the future, we emphasize the importance of continued testing and case management which will be further elucidate whether vaccines play a protective role against the ongoing evolution of SARS-CoV-2 variants.

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

NH, KW, YZ, and FJ designed the work. NH, KW, BX, LW, LH, YZ, and MW performed the literature review and data abstraction. NH, KW, ML, RZ, and FJ were involved in the statistical analysis. All authors read and approved the final manuscript.

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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.2022.820544/full#supplementary-material

Supplementary Figure 1 | Subgroup analysis for the pooled incidence of variants post first mRNA vaccine **(A)**, variants post second mRNA vaccine **(B)**, variants post second viral vector vaccine **(C)**, variants post second protein subunit vaccine **(D)**, variants post second inactivated vaccine **(E)**, B.1.1.7 (Alpha) variant post first vaccine **(F)**, B.1.1.7 (Alpha) variant post second vaccine **(G)**, B.1.1.7 (Alpha) variant post first mRNA vaccine **(H)**, B.1.1.7 (Alpha) variant post second mRNA vaccine **(I)**, B.1.1.7 (Alpha) variant post first viral vector vaccine **(J)**, B.1.1.7 (Alpha) variant post second viral vector vaccine **(K)**, B.1.1.7 (Alpha) variant post second protein subunit vaccine **(L)**, B.1.351 (Beta) variant post first vaccine **(M)**, B.1.351 (Beta) variant post second vaccine **(N)**, B.1.351 (Beta) variant post first mRNA vaccine **(O)**, B.1.351 (Beta) variant post second mRNA vaccine **(P)**, B.1.351 (Beta) variant post second viral vector vaccine **(Q)**, B.1.351 (Beta) variant post second protein subunit vaccine **(R)**, P.1 (Gamma) variant post first vaccine **(S)**, P.1 (Gamma) variant post second vaccine **(T)**, P.1 (Gamma) variant post first mRNA vaccine **(U)**, P.1 (Gamma) variant post second mRNA vaccine **(V)**, P.1 (Gamma) variant post second inactivated vaccine **(W)**, P.1 (Gamma) variant post second viral vector vaccine **(X)**, B.1.617.2 (Delta) variant post first vaccine **(Y)**, B.1.617.2 (Delta) variant post second vaccine Zz), B.1.617.2 (Delta) variant post first mRNA vaccine **(AA)**, B.1.617.2 (Delta) variant post second mRNA vaccine **(BB)**, B.1.617.2 (Delta) variant post first viral vector vaccine **(CC)**, B.1.617.2 (Delta) variant post second viral vector vaccine **(DD)**, B.1.427 (Epsilon) variant post first vaccine **(EE)**, B.1.427 (Epsilon) variant post second vaccine **(FF)**, B.1.427 (Epsilon) variant post first mRNA vaccine **(GG)**, B.1.427 (Epsilon) variant post second mRNA vaccine **(HH)**, P.2 (Zeta) variant post second vaccine **(II)**, B.1.526 (Iota) variant post second vaccine **(JJ)**, and B.1.526 (Iota) variant post second mRNA vaccine **(KK)**. * and ** indicate the second and third arm in the corresponding studies, respectively. CI, confidence interval; OR, odds ratio.

Supplementary Figure 2 | Subgroup analysis for the pooled efficacy of mRNA vaccine against variants post first dose **(A)**, mRNA vaccine against variants post second dose **(B)**, viral vector vaccine against variants post second dose **(C)**, vaccines against the B.1.1.7 (Alpha) variant post first dose **(D)**,vaccines against the B.1.1.7 (Alpha) variant post second dose **(E)**, mRNA vaccine against the B.1.1.7 (Alpha) variant post first dose **(F)**, mRNA vaccine against the B.1.1.7 (Alpha) variant post second dose **(G)**, subunit vaccine against the B.1.1.7 (Alpha) variant post second dose **(H)**, viral vector vaccine against the B.1.1.7 (Alpha) variant post second dose **(I)**, vaccines against the B.1.351 (Beta) variant post first dose **(J)**, vaccines against the B.1.351 (Beta) variant post second dose **(K)**, mRNA vaccine against the B.1.351 (Beta) variant post first dose **(L)**, mRNA vaccine against the B.1.351 (Beta) variant post second dose **(M)**, vaccines against the P.1 (Gamma) variant post first dose **(N)**, vaccines against the P.1 (Gamma) variant post second dose **(O)**, mRNA vaccine against the P.1 (Gamma) variant post first dose **(P)**, mRNA vaccine against the P.1 (Gamma) variant post second dose **(Q)**, viral vector vaccine against the P.1 (Gamma) variant post second dose **(R)**, vaccines against the B.1.617.2 (Delta) variant post first dose **(S)**, vaccines against the B.1.617.2 (Delta) variant post second dose **(T)**, mRNA vaccine against the B.1.617.2 (Delta) variant post second dose **(U)**, viral vector vaccine against the B.1.617.2 (Delta) variant post first dose **(V)**, viral vector vaccine against the B.1.617.2 (Delta) variant post second dose **(W)**, vaccines against the B.1.427 (Epsilon) variant post first dose **(X)**, vaccines against the B.1.427 (Epsilon) variant post second dose **(Y)**, mRNA vaccine against the B.1.427 (Epsilon) variant post first dose **(Z)**, mRNA vaccine against the B.1.427 (Epsilon) variant post second dose **(AA)**, vaccines against the P.2 (Zeta) variant post second dose **(BB)**, vaccines against the B.1.526 (Iota) variant post second dose **(CC)**, and mRNA vaccines against the B.1.526 (Iota) variant post second dose **(DD)**. * and ** indicate the second and third arm in the corresponding studies, respectively. CI, confidence interval; OR, odds ratio.

Supplementary Table 1 | Characteristics of the studies included.

Supplementary Table 2 | Results of the Egger test, the heterogeneity test, and the meta-analysis.

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Knowledge, Attitude and Practice Toward COVID-19: A Cross-Sectional Study of Staff in China-Guinea Friendship Hospital, Guinea

*Wenyan Ji[1], M'Bemba Abdoulaye Camara[2], Jinggang Xia[3], Xiaobo Ma[4], Xintong Chen[5] and Ying Liu[6]**

[1] Beijing Center for Disease Prevention and Control, Beijing Research Center for Preventive Medicine, Institute for Immunization and Prevention, Beijing, China, [2] Department of Emergency, China-Guinea Friendship Hospital, Conakry, Guinea, [3] Department of Cardiology, Xuanwu Hospital, Capital Medical University, Beijing, China, [4] Department of Finance, Xuanwu Hospital, Capital Medical University, Beijing, China, [5] Department of Pharmacy, Xuanwu Hospital, Capital Medical University, Beijing, China, [6] Office of Medical Affairs, Beijing Municipal Heath Commission, Beijing, China

Background: The purpose of this study was to assess the level of knowledge, attitude and practice of COVID-19 among staff in China-Guinea Friendship Hospital, and to confirm the effect of nosocomial infection management.

Methods: This cross-sectional study was conducted in December 2021. Information on socio demographic data, knowledge, attitude and practices related to COVID-19 was collected through a self-administered questionnaire.

Results: A total of 143 employees participated in the survey, with a response rate of 99.31% and a vaccination rate of 95.10%. The average knowledge score of COVID-19 was 8.39 ± 1.3 points (10 points in total), without significant differences between subgroups with different demographic variables ($P > 0.05$); more than 80% of the participants had a positive attitude, and 72.03–93.01% of the participants could take appropriate preventive practices in different environments such as hospital, outdoor or home.

Conclusion: The staff of the China-Guinea Friendship Hospital has good knowledge of COVID-19, a positive attitude and appropriate preventive practices. It can be concluded that the current nosocomial infection management is active and effective. Therefore, this study suggests that comprehensive activities such as training, promotion and supervision of COVID-19-related knowledge and countermeasures should be widely and continuously implemented in healthcare facilities, which will continuously improve the overall KAP level of hospital staff and play an important role in curbing the COVID-19 pandemic.

Keywords: COVID-19, hospital staff, knowledge, attitude, practice, Guinea (Conakry)

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****Correspondence:***
Ying Liu
13901124008@139.com

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel highly contagious respiratory disease caused by a novel coronavirus. It was first detected in Wuhan, China in December 2019. World Health Organization (WHO) declared COVID-19 was a global pandemic disease on March 11th, 2020 (1). As of February 25th, 2022, over 432 million confirmed cases and about 6 million deaths have been reported globally. According to the Guinean Ministry of Health and Security, the first case was confirmed on March 14th, 2020. Guinea reported 36,393 confirmed cases and 440 deaths on March 25th, 2022 (2).

People's knowledge, attitude and practice (KAP) toward COVID-19 are fairly crucial and critical to ensuring successful disease control (3, 4). In the KAP assessment of COVID-19, knowledge usually refers to the level of mastery of biomedical concepts (5). Typical questions for knowledge assessment include causes and symptoms of COVID-19. Attitude is expressed in people's beliefs, emotions and tendencies. Practice refers to the lifestyle related to preventing COVID-19.KAP studies provide baseline information for identifying interventions (6), and can be used to assess the appropriateness of existing interventions (7). Hospital staff, who are on the front lines of the COVID-19 pandemic, are more vulnerable to infection. If they have insufficient knowledge about COVID-19 and/or inappropriate preventive behavior, treatment will be delayed and COVID-19 will spread rapidly (8, 9). Therefore, hospital staff have been an important population for assessing the KAP of COVID-19. In addition to relying on information and resources from WHO and governments, appropriate nosocomial infection management also plays an important role in improving KAP levels in healthcare workers (10).

The China-Guinea Friendship Hospital is located in Conakry, the capital of Guinea, and is one of the many hospitals jointly built by China and African countries. In March 2021, the 28th Chinese Medical Aid Team to Guinea and the hospital jointly established the Nosocomial Infection Management Committee, and subsequently carried out a series of nosocomial infection prevention and control work. To assess the effects of these interventions and provide a basis for adjusting interventions, a KAP questionnaire survey toward COVID-19 among hospital staff was conducted in December 2021.

MATERIALS AND METHODS

Study Design and Subjects

This cross-sectional study was conducted among all staff at the China-Guinea Friendship Hospital in Conakry, Guinea, during December 2021. A self-administered questionnaire was used to assess subjects' KAP levels related to COVID-19. Participants gave informed consent to be included in the study, and the study protocol was approved by the ethics committee of China-Guinea Friendship Hospital.

Those employees who were working at the hospital at that time and had a direct employment relationship with the hospital were included in the study, with no exceptions.

Questionnaire

The questionnaire consisted of four parts. The first part included questions about the demographic characteristics of the participants (age, gender, the specific department, working years, specific job categories and whether vaccinations were administered, etc.). The other three parts in the questionnaire were COVID-19-related KAP questions. There were 10 questions in each part (For the knowledge part, each question was assigned 1 point, a total of 10 points). The questions of knowledge included the etiology, epidemiology, pathogenesis of COVID-19. The information collected by the attitude questions included: the degree of concern and worry about the epidemic, the degree of concern for one's own health, the confidence in curbing its spread, the satisfaction with the cleaning, disinfection and material supply of the hospital, as well as the satisfaction of training and information exchange of the hospital, etc. The questions of practice included the participants' self-protection in different scenarios, such as outdoors, workplace and home.

For the convenience of participants, the questionnaire was in French.

Statistical Analysis

Descriptive statistics were used to present demographic data, participants' knowledge scores, and the frequency of COVID-19 knowledge, attitude and preventive practice. The 95% confidence intervals (95% CI) were compared with or without crossover to determine the differences in values between subgroups with different characteristics. For continuous variable (such as age, working years), if it is a normal distribution, it is divided into two groups by the mean; if it is a skewed distribution, it is divided into two groups by the median; the specific departments were grouped into three big sectors: medical sector, medical technology sector, administrative and logistic sector; in addition, the specific positions were divided into medical-related positions and non-medical-related positions. Data were coded and analyzed by SAS software (version 19.0; SAS Institute Inc., Cary, NC).

RESULTS

Participants' General Characteristics

A total of 143 participants completed the questionnaire with a response rate of 99.31% (143/144), except for one logistics staff member, who was unable to participate due to intellectual problems. Of all respondents, 58.74% (84/143) were males, 75.52% (108/143) were in medical-related positions, with a mean age of 42.86 $\pm$ 11.60 years, ranging from 22 to 65 years. Regarding the sector of work, 65.03% (93/143) were in the medical sector, 17.48% (25/143) in the medical technology sector, and 17.48% (25/143) in the administrative and logistic sector. The range of participants' working years was 1–39 years, with a Quartile (P25, P75) of 9 (4, 16) years. And the vaccination rate of participants was 95.10% (136/143).

Participants' Knowledge Toward COVID-19

The overall accuracy rate was 83.92% for the knowledge. More than 90% knew the main sources of COVID-19 transmission, the main symptoms, the incubation period of the disease, the effectiveness of the vaccine, and the role of chlorine-containing disinfectants. The proportion of people who correctly understood the knowledge of the transmission route, infectivity, susceptible population, and the presence of seasonal patterns of the virus varied between 54.55 and 79.72% (**Table 1**).

The COVID-19 knowledge scores in this study were normally distributed, with an average of 8.39 $\pm$ 1.3 points. At the level of $\alpha = 0.05$, there were no significant differences in which between

TABLE 1 | Participants' correct responses to questions bordering on knowledge of COVID-19 ($n = 143$).

Knowledge items	*N*	Proportion (%)
1. Infected persons (patients and asymptomatic infected persons) are the main source of infection	135	94.41
2. Droplet transmission is its main mode of transmission	114	79.72
3. The virus is not transmitted by aerosols or dirt	109	76.22
4. At the end of the incubation period is infectious, and the infection is relatively strong in the first 2 days of the disease.	109	76.22
5. The elderly and children are not susceptible to COVID-19	114	79.72
6. Some patients have fever, dry cough and weakness as the main symptoms, some patients have loss of smell and taste as the first symptoms, a few patients have nasal congestion, runny nose, sore throat, conjunctivitis, myalgia and diarrhea, etc.	138	96.50
7. The incubation period of COVID-19 virus infection is usually 1-14 days, mostly 3-7 days.	132	92.31
8. COVID-19 epidemic has a significant seasonality.	78	54.55
9. Vaccination can reduce morbidity.	138	96.50
10. The virus is sensitive to chlorine-containing disinfectants.	133	93.01
Mean	**120**	**83.92**

subgroups with different characteristics (including department, gender, age, years of work, and whether the position was related to medicine).

Participants' Attitude Toward COVID-19

Participants' attitude toward COVID-19 is shown in **Table 2**. Of all the respondents, 99.30% expressed "concern" and "worry" about the pandemic; 100% were "concerned" about their own health during the pandemic; 65.03% expressed "confidence" that the pandemic would be overcome in the end; 92.31% and 86.71% were "particularly satisfied" with the current environmental cleanliness and disinfection of the hospital, respectively; 89.51% thought that the current quantity and quality of the hospital's supply and stock of epidemic prevention materials could "meet the needs"; 74.83% were "particularly satisfied" with the hospital's training in knowledge and techniques of COVID-19; and 84.62% were "particularly satisfied" with the hospital's current communication and delivery of information.

In addition, 35.97% expressed "not easy to say" or "no confidence" or "Doesn't matter" in overcoming the epidemic, and they were widely distributed across departments, with the top three departments being neurosurgery, abdominal surgery and emergency department.

Participants' Practice Toward COVID-19

The results of participant's practices toward COVID-19 are shown in **Table 3**. The proportion of wearing masks in public places was 93.01%; 73.43% intentionally reduced unnecessary outings (such as parties, meals, etc.); 72.03% of people were careful to maintain a social distance of at least one meter; 96.5% washed their hands ≥3 times a day; 46.15% opened windows ≥2 times a day; 79.72% disinfected the environment and objects; 43.36% strengthened physical exercise; 82.52% carried out garbage sorting; and 89.51% of staff wore disposable medical masks at work. When there were symptoms of suspected infection such as fever, fatigue, and dry cough, 97.90% of them chose to seek medical treatment.

DISCUSSION

Today, every country in the world is facing the COVID-19 pandemic. At present, taking preventive measures is the only effective way to copy with this infectious disease for which there is no effective treatment. The preventive effect is largely dependent on the KAP level of susceptible populations, and particularly, the KAP level of hospital staff is more important in controlling the spread of COVID-19 (10). Since the establishment of the nosocomial Infection Management Committee of the China-Guinea Friendship Hospital in March 2021, a series of COVID-19 prevention and control measures have been carried out in the hospital, including training in the knowledge and techniques of COVID-19, developing a prevention and control system, strengthening supervision and inspection, and replenishing epidemic prevention materials through multiple channels. The results of this study showed that most staff had good knowledge, positive attitude and appropriate preventive practices in the prevention and control of COVID-19, which identify that nosocomial infection management measures are active and effective.

The results of this study showed that the staff of the China-Guinea Friendship Hospital had a good knowledge of COVID-19, with an overall correct rate of 83.92%. This result is higher than that of surveys in the general population (11, 12) and some hospital workers (10, 13), whose overall correct knowledge estimates ranged from 48.97 to 77.00%. There are also some studies conducted among hospital staff (whose overall correct rate of knowledge was estimated to be 80–90%) consistent with our results (14–17). Of course, there are also some studies of hospital workers that had higher results than ours, up to 90% or more (18–21). It is worth noting that in addition to the different survey populations, the results of each study may also vary due to other factors, such as knowledge definition standards, question design, survey methods, and the development stage of the epidemic at the time of the survey.

In this study, although hospital staff had a level of knowledge above 90% on the source of virus transmission, main clinical symptoms, incubation period, vaccines and the effects of chlorinated disinfectants, the level of knowledge on other issues remained low, such as virus transmission route, virus infectivity, susceptible population and whether there is seasonality, etc., their correct rate of was 53.96–79.86%. Because more scientific knowledge is gradually enriched and proposed with the progress of the epidemic, we need to continuously enrich and update

TABLE 2 | Responses of the participants to the attitude items on the questionnaire ($n = 143$).

Attitude items	Categories	*N*	Proportion (%)
1. Degree of concern in information toward the COVID-19:	Particularly concern	129	90.21
	Concern	13	9.09
	No concern	1	0.70
2. Degree of worry in information toward the COVID-19:	Particularly worry	118	82.52
	Worry	24	16.78
	No worry	1	0.70
3. Degree of concern your own health during the pandemic:	Particularly concern	126	88.11
	concern	17	11.89
	No concern	0	0.00
4. Confidence in the ability to overcome the COVID-19:	Have confidence	93	65.03
	Not easy to say	47	32.87
	No confidence	2	1.40
	Doesn't matter	1	0.70
5. Degree of satisfaction with the current environmental cleanliness in the hospital:	Particularly satisfy	132	92.31
	Not sure	1	0.70
	No satisfy	9	6.29
	Doesn't matter	1	0.70
6. Degree of satisfaction with the current environmental disinfection in the hospital	Particularly satisfy	124	86.71
	Not sure	10	6.99
	No satisfy	8	5.59
	Doesn't matter	1	0.70
7. In terms of the number, the extent to which the current supply and stockpile of epidemic prevention materials in the hospital meet the needs of the post:	Particularly sufficient	49	34.27
	Tightly meet the needs only	79	55.24
	Can't meet the needs	9	6.29
	Not sure	6	4.20
8. In terms of the type, the extent to which the current supply and stockpile of epidemic prevention materials in the hospital meet the needs of the post:	Particularly sufficient	50	34.97
	Tightly meet the needs only	78	54.55
	Can't meet the needs	8	5.59
	Not sure	7	4.90
9. Degree of satisfaction with relevant knowledge and technical training within the hospital:	Particularly satisfy	107	74.83
	Not sure	10	6.99
	No satisfy	15	10.49
	Doesn't matter	11	7.69
10. Degree of satisfaction with the communication and delivery of information related to the epidemic in the hospital:	Particularly satisfy	121	84.62
	Not sure	8	5.59
	No satisfy	6	4.20
	Doesn't matter	8	5.59

the relevant training for hospital staff and strengthen weak knowledge points.

In terms of attitude, more than 80% of the staff of China-Guinea Friendship Hospital had a positive attitude. This result is higher than those of previous studies among medical staff (those participants had a moderate or positive attitude rate of 50.5–72.2%) (10, 22–24), and the reason may be related to the higher rate of knowledge correctness (17, 23, 25). Almost 65.03% of hospital staff believed that COVID-19 would eventually be overcome in our study, which is similar to the results of some previous studies (10). The staff of low-confidence in this study were mainly concentrated in the emergency, neurosurgery and abdominal surgery. There are two possible reasons: on the one hand, there are a large number of staff in these departments; on the other hand, as the front line of the hospital's prevention and control, these staff are under great mental pressure. Therefore, it is necessary to strengthen training, especially encourage and support these important departments, so as to enhance their confidence in overcoming the epidemic.

In the term of practice, ~72.03–93.01% of staff had appropriate protective practices at different places, such as workplace, outside or at home. The results are better than the results of a systematic review and meta-analysis, which

TABLE 3 | Responses of the participants to the practice items on the questionnaire (n = 143).

Attitude items	Categories	N	Proportion (%)
1. Do you wear a mask when you are in public places during an epidemic?	Always	133	93.01
	Occasionally	1	0.70
	Never	0	0.00
2. Do you intentionally reduce on unnecessary outings (e.g., fewer parties, meals, etc.) during the epidemic?	Always	105	73.43
	Occasionally	35	24.48
	Never	3	2.10
3. Are you careful to maintain a social distance of at least one meter during the epidemic?	Always	103	72.03
	Occasionally	37	25.87
	Never	3	2.10
4. During the epidemic, how many times a day do you wash your hands?	<3 times/day	5	3.50
	≥. times/day	13	9.09
	≥7 times/day	33	23.08
	≥10 times/day	92	64.34
5. During the epidemic, how many times do you open the windows in your room (office or home) to ventilate?	0 time/day	38	26.57
	1 time/day	39	27.27
	2 times/day	22	15.38
	≥3 times/day	44	30.77
6. During the epidemic, do you pay attention to the disinfection of the environment and goods?	Always	114	79.72
	Occasionally	27	18.88
	Never	2	1.40
7. During the epidemic, do you intend to be more physically active?	Always	62	43.36
	Occasionally	67	46.85
	Never	14	9.79
8. Do you sort your garbage?	Always	118	82.52
	Occasionally	25	17.48
	Never	0	0.00
9. What do you do when you feel fever, malaise, dry cough and other suspected symptoms of infection during an outbreak? (Multiple choice possible)	Seeking Medical Attention	140	97.90
	Home isolation	29	20.28
	Go to work normally	2	1.40
	Concealment of illness and refusal to seek medical attention	1	0.70
10. During the epidemic, what is your mode of protection during work? (Multiple choice possible)	Wearing disposable caps	107	74.83
	Wearing disposable medical masks	128	89.51
	Wearing disposable non-medical masks	24	16.78
	Wearing disposable gloves	113	79.02
	Wear goggles and face screen	85	59.44
	Wear a disposable barrier suit	91	63.64
	Wear disposable protective clothing	63	44.06
	No protective measures	2	1.40
	Other	0	0.00

researched on globally practice studies of COVID-19 by 70% [95% CI (66, 74%)], with Africa practice score lower than 60% (11). Effective preventive measures, such as swearing masks, hand hygiene, vaccinations, and maintaining safe social distancing, can reduce the transmission of COVID-19, which is always recommended by World Health Organization. And people's adherence to preventive measures is affected by their COVID-19 knowledge and attitude (25–27).

Based on the survey results, it is recommended to continue to strengthen and enrich knowledge training associated with COVID-19 in healthcare facilities, strengthen inspection, supervision, encouragement and support focusing on front-line departments to protect the health of hospital staff and patients, which will play an important role in curbing the COVID-19 pandemic.

LIMITATIONS

The major limitation of this study is the lack of the control, resulting in a weak persuasive power. One more methodological limitation is that the questionnaire was self-administered by the respondents and was not based on objective observations, which resulted in a certain degree of information bias.

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 human participants were reviewed and approved by the Ethics Committee of China-Guinea. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Determinants of COVID-19 Vaccine Engagement in Algeria: A Population-Based Study With Systematic Review of Studies From Arab Countries of the MENA Region

Salah Eddine Oussama Kacimi[1†], Selma Nihel Klouche-Djedid[1†], Omar Riffi[1], Hadj Ahmed Belaouni[2], Farah Yasmin[3], Mohammad Yasir Essar[4], Fatma Asma Taouza[5], Yasmine Belakhdar[6], Saliha Chiboub Fellah[1], Amira Yasmine Benmelouka[7], Shoaib Ahmed[8], Mohammad Aloulou[9], Abdellah Bendelhoum[1], Hafida Merzouk[10], Sherief Ghozy[11,12], Jaffer Shah[13] and Mohamed Amine Haireche[14]*

[1] Department of Medicine, Faculty of Medicine, University of Tlemcen, Tlemcen, Algeria, [2] Laboratoire de Biologie des Systèmes Microbiens (LBSM), Ecole Normale Supérieure de Kouba, Algiers, Algeria, [3] Dow University of Health Sciences, Karachi, Pakistan, [4] Kabul University of Medical Sciences, Kabul, Afghanistan, [5] Faculty of Medicine, University of Oran, Oran, Algeria, [6] Faculty of Medicine, University of Annaba, Annaba, Algeria, [7] Faculty of Medicine, University of Algiers, Algiers, Algeria, [8] Punjab Medical College, Faisalabad, Pakistan, [9] Faculty of Medicine, University of Aleppo, Aleppo, Syria, [10] Laboratory of Physiology, Physiopathology and Biochemistry of Nutrition, Department of Biology, Faculty of Natural and Life Sciences, Earth and Universe, University of Tlemcen, Tlemcen, Algeria, [11] Neurovascular Research Lab, Radiology Department, Mayo Clinic, Rochester, MN, United States, [12] Nuffield Department of Primary Care Health Science, Medical Science Division, Oxford University, Oxford, United Kingdom, [13] Medical Research Center, Kateb University, Kabul, Afghanistan, [14] Research Department, Scientia Vallis, Paris, France

Edited by:
Chiara de Waure, University of Perugia, Italy

Reviewed by:
Dilaram Acharya, Université de Montréal, Canada
Malik Sallam, The University of Jordan, Jordan

***Correspondence:**
Mohammad Yasir Essar
yasir.essar@gmail.com

† These authors have contributed equally to this work

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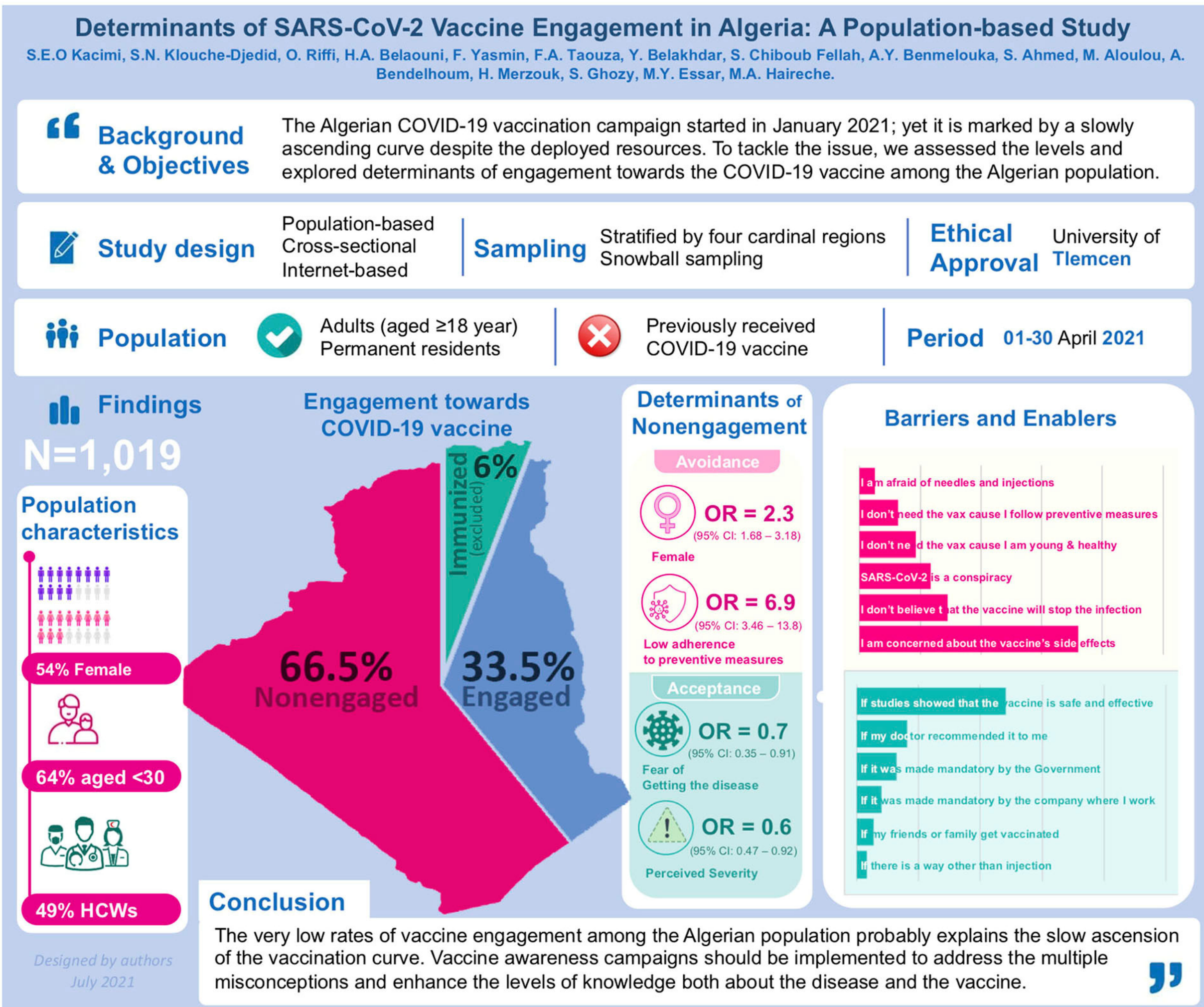
Background: The Algerian COVID-19 vaccination campaign, which started at the end of January 2021, is marked by a slowly ascending curve despite the deployed resources. To tackle the issue, we assessed the levels and explored determinants of engagement toward the COVID-19 vaccine among the Algerian population.

Methods: A nationwide, online-based cross-sectional study was conducted between March 27 and April 30, 2021. A two-stage stratified snowball sampling method was used to include an equivalent number of participants from the four cardinal regions of the country. A vaccine engagement scale was developed, defining vaccine engagement as a multidimensional parameter (5 items) that combined self-stated acceptance and willingness with perceived safety and efficacy of the vaccine. An Engagement score was calculated and the median was used to define engagement vs. non-engagement. Sociodemographic and clinical data, perceptions about COVID-19, and levels of adherence to preventive measures were analyzed as predictors for non-engagement.

Results: We included 1,019 participants, 54% were female and 64% were aged 18–29 years. Overall, there were low rates of self-declared acceptance (26%) and willingness (21%) to take the vaccine, as well as low levels of agreement regarding vaccine safety (21%) and efficacy (30%). Thus, the vaccine engagement rate was estimated at 33.5%, and ranged between 29.6-38.5% depending on the region ($p > 0.05$). Non-engagement was independently associated with female gender (OR = 2.31, $p < 0.001$), low adherence level to preventive measures (OR = 6.93, $p < 0.001$), private-sector jobs (OR = 0.53, $p = 0.038$), perceived COVID-19 severity (OR = 0.66, $p = 0.014$), and fear from contracting the disease (OR = 0.56, $p = 0.018$). Concern about vaccine side effects (72.0%) and exigence for more efficacy and safety studies (48.3%) were the most commonly reported barrier and enabler for vaccine acceptance respectively; whereas beliefs in the conspiracy theory were reported by 23.4%.

Conclusions: The very low rates of vaccine engagement among the Algerian population probably explain the slow ascension of the vaccination curve in the country. Vaccine awareness campaigns should be implemented to address the multiple misconceptions and enhance the levels of knowledge and perception both about the disease and the vaccine, by prioritizing target populations and engaging both healthcare workers and the general population.

Keywords: COVID-19, vaccine, Algeria, acceptance, hesitancy, Middle-East and North African (MENA), SARS-CoV-2, immunization



GRAPHICAL ABSTRACT | Visual summary of the structure and main findings of the study.

BACKGROUND

Amid the ongoing COVID-19 pandemic and the lack of effective curative treatments, mass vaccination is perceived as the only effective strategy to control the pandemic and reduce its global impact on individuals and societies. Different types of COVID-19 vaccines have been developed so far, using different techniques including mRNA, adenovirus vector, adjuvanted protein, or live-attenuated or inactivated virus vaccines. The current evidence supports the efficacy of the majority of the commercialized and recommended vaccines in eliciting robust production of neutralizing antibodies in the short- and median-term, correlating with a significant reduction in the incidence of COVID-19 infection both in the clinical trial and real life (1–4).

As of February 2022, the number of vaccine doses that have been administered globally was estimated at more than 10 billion, with nearly 60% of the world's population being fully vaccinated (5). However, there is a great discrepancy in vaccination rates between the industrialized countries such as Canada (212.6 doses per 100 population), the United Kingdom (205 doses per 100 population), and the European countries, and developing and low-income countries such as Algeria (31.1 doses per 100 population), Egypt (69.7 doses per 100 population), and Sudan (13.0 doses per 100 population) (5, 6). The COVID-19 Vaccines Global Access (COVAX) initiative's campaign efforts to finance and distribute the vaccine in poor countries are limited by multiple factors including the difficulty of providing all the needs of these countries and the limited funding sources (7). On the other hand, the recent emergence and spread of novel viral variants, notably the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617 (Delta), B.1.617.2 (Delta-plus), B.1.525 (Eta), B.1.429 (Epsilon), and B.1.1.529 (Omicron) variants compromised the forecasted transition, in the short run, to the pre-pandemic normal life (8–12). As a consequence, the resolution of the issue depends on a three-fold concern, including the success of the global mass immunization, the long-term efficacy of the vaccines, and the dreaded scenario of resistance of the emerging variants to the vaccine-induced immunity (13–15).

In addressing the determinants of success for this global strategy, people's engagement to local vaccination campaigns constitutes a major determinant, besides the adherence to prevention policies and recommendations. Although the modern experience with mass vaccination proved to be effective in controlling and eradicating outbreaks such as Polio, Smallpox, and other diseases (16), vaccine hesitancy has long been identified as one of the major threats facing global health (17–19). Due to several factors, the COVID-19 vaccine is subject to recurrent popular misconceptions and uncertainties, which constitutes further barriers to public adherence to the vaccination strategy (20). Such misconceptions are reported to be particularly prevalent in developing countries and conservative societies, associated with high rates of vaccine hesitancy (21). Consequently, substantial discrepancies have been observed in vaccine acceptance rates across the different regions and cultures (22), with remarkably higher vaccine hesitancy in Eastern Europe, North Africa, the Middle-East, and Central Asia (23).

In Algeria, the largest African country and the 9th country in Africa in terms of population size, the fight against the virus has gone through successive phases since the first confirmed case was declared on February 25, 2020. Since the early phase of the pandemic, the Algerian government opted for broad travel cancellations combined with the intermittent implementation of restrictive and semi-restrictive measures locally, in addition to the deployment of tremendous healthcare resources to treat the infected population (24–26). As of 21 May 2021, date of start of the current study, the country has recorded 126,434 confirmed cases and 3,405 deaths (27). In March 2022, date of last revision of the paper, these figures have doubled with 265,346 confirmed cases and 6,860 deaths (28). The national vaccination campaign started by the end of January 2021 and the current local policy targets all vulnerable groups. However, the vaccination rate remains remarkably low, reaching only 2.5 million doses by 14 July 2021, which represented a coverage rate estimated at 5.8% of the population (6, 29). To date, i.e., 10 March 2022, the coverage rate remains low with only 15% of the population being fully vaccinated (28). This represents a concern, contrasting with the country's efforts to promote the vaccination.

In an attempt to explain this low vaccination rate, the present study was designed to evaluate the levels of engagement among Algerians toward the COVID-19 vaccine and to analyze the associated sociodemographic factors. Additionally, it explored the associated misconceptions and eventual barriers and enablers of vaccine acceptance. Such data would assist the decision-makers in implementing strategic amendments on the vaccination policy and the related communication approaches. We further conducted a systematic review on vaccine acceptance in the Arab countries of the Middle-East and North African (MENA) region.

METHODS

Cross-Sectional Study

Design & Population

A nationwide online-based cross-sectional study was conducted among the general population of Algeria, between March 27 and April 30, 2021. It involved adult (aged 18 years and older) males and females of all regions, who were permanently residing inside the country during the study period. Since the study aimed to understand the contribution of non-engagement to vaccine in explaining the low vaccination rates, individuals who had previously received the COVID-19 vaccine were excluded. The study was approved by the institutional review board of the University of Tlemcen [14/2021 EDCTU]. All participants provided informed consent prior to their participation.

Algeria is a North African republic, on the Mediterranean Sea, whose capital is Algiers. It has a population estimated at 45.2 million, 73% of them living in urban areas, mainly in the north of the country. Algerian population is considered young with a

Abbreviations: AD, Algerian Dinars; KSA, Kingdom of Saudi Arabia; MENA, Middle-East and North African; OR, Odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; UAE, United Arab Emirates.

median age of 28.5 years and a total fertility rate is estimated at 3.1 live births per women (30).

Sample Size and Sampling Technique

The sample size ($N = 385$) was calculated using the single proportion sample size calculation formula, to detect an unknown vaccine acceptance rate ($P = 50\%$) with 95% confidence interval (95%CI), 80% statistical power, and 5% margin error, among the total Algerian population. According to the WorldOMeter estimates, based on the United Nations data, the Algerian population was 44,594,368 as of May 30, 2021 (31).

A two-stage stratified, non-probability snowball sampling method was used in this study. In Stage 1, Algeria was divided into four cardinal regions (strata) including North/Center, East, West, and South. In stage 2, participants who were directly reached by the investigator were solicited to disseminate the questionnaire among their acquaintances until reaching a comparable number (∼N/4) of participants in each region (stratum).

Instrument Development and Validation

The questionnaire used in the present study was designed based on previously published papers related to vaccine acceptance (32–36). It was developed in English and translated into the Arabic language by a native speaker, considering the vocabulary specificities of the Algerian population (**Supplementary Material**). The final questionnaire was administered in Arabic and comprised the following 5 mandatory sections:

1) Sociodemographic data: including participant's age, gender, marital status, residency region, monthly income in Algerian Dinars (AD), educational level, occupation, living mode (alone or with family), children (yes or no), and living area (rural or urban); and whether the participant has a chronic disease or lives with someone with a chronic disease.
2) Health perception: including perceived health status (1 item) and perception about COVID-19 as an illness (3 items) including the perceived probability of contracting COVID-19 infection, level of fear of being infected, and perceived severity of COVID-19.
3) Levels of adherence to government recommendations and preventive measures against COVID-19: including 7 items, such as social distancing, hand cleaning, care-seeking behavior in case of suggestive symptoms, etc. Each of the 7 items was formulated as a Likert-type agreement scale with 5 levels, including "Strongly Disagree (score = 1)," "Disagree (2)," "Neutral (3)," "Agree (4)," and "Strongly agree (5)".
4) Attitudes and beliefs toward COVID-19 vaccination: including the 5 following items: "I think that COVID-19 vaccination is effective"; "In principle, I accept to get the COVID-19 vaccination"; I will receive the COVID-19 vaccination as soon as possible whenever it is available"; "I think that the best way to avoid the complications of COVID-19 is by being vaccinated"; "I think that COVID-19 vaccination is safe". A 5-score Likert-type agreement scale was used to encode the answers from "Strongly disagree (score = 1)" to "Strongly agree (score = 5)."
5) Barriers and enablers of COVID-19 vaccine acceptance: including a predefined list of potential factors that may negatively (barriers) or positively (enablers) impact the participant's decision to receiving the COVID-19 vaccine. The list comprised 6 barriers such as concerns regarding vaccine's side effects, conspiracy theory beliefs, etc., and 6 enablers such as vaccination enforcement policy, recommendation by a physician, etc.

The questionnaire sections and items underwent face and content validity by the research team members, with the help of two public health and epidemiology experts. Further, the questionnaire was administered in a pilot sample ($n = 31$) to assess the clarity and full understanding of questions and items. Data collected from the pilot sample was not used in the final analysis. A copy of the Arabic or English questionnaire is available upon request from the first or corresponding author.

Data Collection Procedure

The final, validated version of the questionnaire was edited as an online survey in Google Forms, where all items were set to "mandatory" mode. An introduction was embedded in the first page of the survey consisting of the study description, an informed consent agreement, and one question related to previous COVID-19 vaccination history (eligibility criterion). The online survey link was disseminated through social media platforms including Facebook, WhatsApp, and Messenger. Additionally, we distributed the survey link through specific Facebook groups targeting healthcare workers and medical students, both regarding their enrollment and to enhance the snowball sampling. No incentive was offered for participation or data collection. Data collection was anonymous and identity collecting options of Google Forms were deactivated. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting this study (37).

Statistical Methods

Score Calculation and Outcome Definition

Engagement score, the primary outcome, was calculated by summing the scores of the 5 items (**Supplementary Table 1**) from efficacy, prevention of complications, safety, acceptance, and willingness subscales; high scores indicated higher levels of engagement to the vaccination. The use of an engagement score was based on the assumption that actual engagement to the vaccine is a multidimensional concept depending on the participant's perceptions and attitudes toward the vaccine safety, efficacy, prevention from complications (items 1, 4, and 5), and declared acceptance and willingness to receive it (items 2 and 3).

Adherence score (range 7−35) was calculated by summing the scores of the 7 items (**Supplementary Table 2**) from the Adherence Level subscale; higher scores indicated higher adherence levels to recommendations and preventive measures. The variable related to adherence level was categorized into

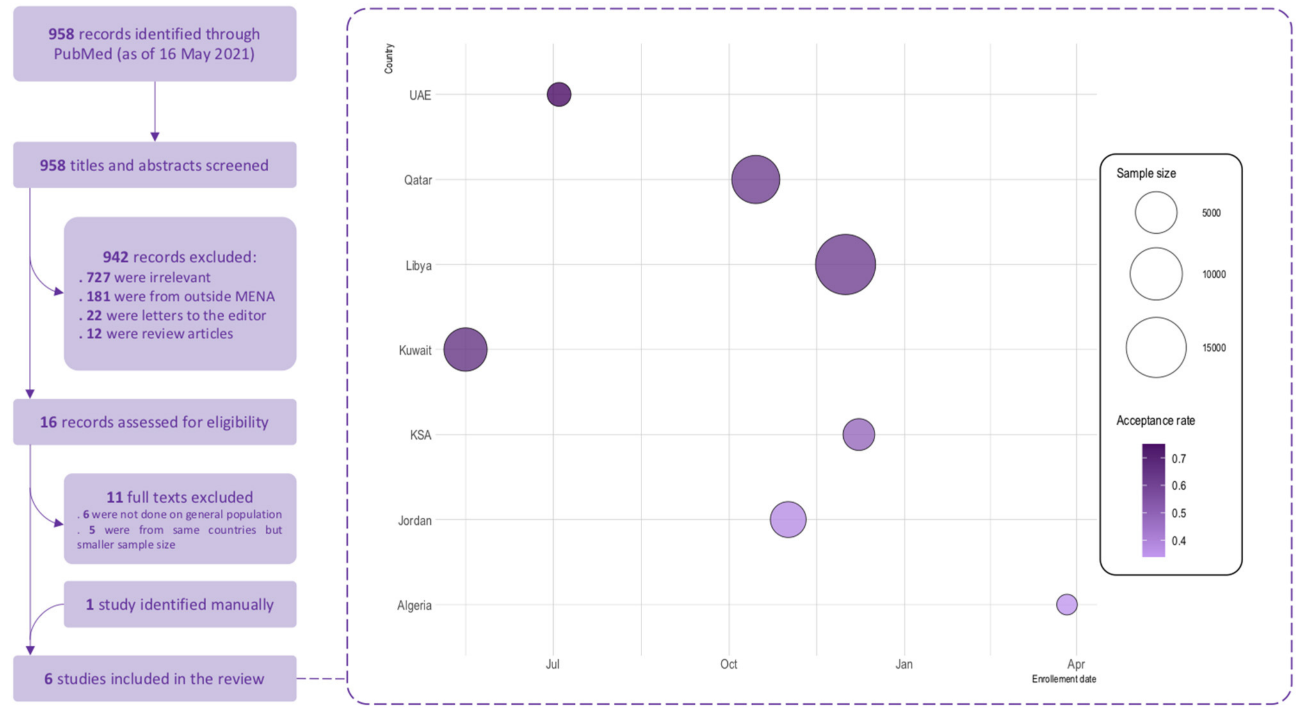


FIGURE 1 | COVID-19 vaccine acceptance in the Arab countries from the MENA region–Systematic review flowchart and findings. Size of the bubbles represents the sample size used and the color gradient represents the acceptance rate of vaccination reported in each study; light colors represents lower acceptance rates and dark colors represents higher acceptance rates. Enrollement date is the starting date of data collection.

three subcategories (Low level, medium level, and high adherence level).

Statistical Analysis

Categorical variables were presented as frequency and percentage, while continuous variables were presented as mean and standard deviation (SD) in the descriptive statistical analyses. The Chi-square test was used to analyze the association between categorical variables. Bivariate correlations between numerical variables were tested using Pearson's correlation. Moreover, a multivariate logistic regression was used to analyze the determinants of COVID-19 vaccine's engagement. A $p < 0.05$ was indicative of statistical significance. Statistical analysis was performed by means of IBM's SPSS for Windows, Version 25.0 (SPSS Inc., Chicago, IL, USA).

Systematic Review

Database Search and Eligibility Criteria

We conducted a systematic review in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (38). Medline was searched through the PubMed database using the following search strategy: (COVID-19 OR SARS-CoV-2) AND (vaccine OR vaccination) AND (hesitancy OR acceptance) to retrieve related studies published from the database inception to May 16th, 2021. Only studies targeting the general population and reporting COVID-19 vaccination acceptance rate and studies conducted in Arab countries of the MENA region were included. Review articles, editorials, case reports, and case series were excluded. Additionally, the reference list of included articles was scrutinized to identify extra articles (**Figure 1**).

Study Selection

Two authors independently screened titles and abstracts of retrieved articles against the inclusion/exclusion criteria. Full-texts of potentially eligible articles were further assessed by two authors for final decision. Discrepancies were resolved via discussion. In the case of multiple reports from the same country, the one containing the greatest amount of information (for example, largest sample size) was included in the review.

Data Extraction

Three investigators extracted data from relevant articles using a data extraction form. The collected data included the author's name, study country, study period, sampling method, sample size, percentages of males and older age, acceptance rate, the predictors for COVID-19 vaccine acceptance and avoidance. A fourth experienced investigator double-checked all collected evidence for accuracy.

Quality Assessment

The quality assessment of the included studies was performed using to the National Institute of Health study quality assessment tool (35).

RESULTS

Sociodemographic Characteristics

A total of 1,019 respondents were included, with equal distribution across the four cardinal regions in Algeria. Of these, 545 (54%) were female, 650 (64%) were aged 18–29 years, and 500 (49%) were in the healthcare sector including medical students (36%) or healthcare professionals (13%). The majority were single (70%) and had a high educational level (84%). Regarding comorbidities, 136 (13.3%) had a chronic disease and 531 (52.1%) were living with at least one family member having a chronic disease. Otherwise, 87.0% of the participants rated their health status to be good or excellent (**Table 1**).

History of and Perceptions Toward COVID-19 Infection

The majority of participants (70.0%) declared fearing to contract COVID-19, and 16.0% reported a positive history of COVID-19 infection. On the other hand, only 263 (26.0%) perceived the infection to be severe, while 43.0% believed the disease had no severity. Regarding preventive measures, almost half the participants (48.0%) had a moderate level of adherence, while 43.0% had a high level (**Table 1**).

Engagement Toward COVID-19 Vaccine

Overall, we observed low agreement levels regarding vaccine safety (21%), effectiveness (30%), and efficiency to avoid complications (32%). Likewise, a minority declared accepting the COVID-19 vaccine (26%) or willing to take it (21%). Paradoxically, there were lower levels of agreement regarding vaccine safety (14% vs. 25% and 26%), as well as declared acceptance (21% vs 28% and 31%) and willingness (15% vs. 24% and 25%), among healthcare professionals compared with the general population and medical students respectively ($p < 0.001$). Using the engagement score 15 (median) as cutoff, two-thirds of the participants had a low likelihood of engagement (engagement score $\leq$ 15, 66%) (**Table 2**).

Barriers and Enablers of COVID-19 Vaccine Acceptance

The barriers and enablers of COVID-19 vaccine acceptance are depicted in **Figure 2**. Concern about vaccine side effects was the most commonly reported barrier to COVID-19 vaccine acceptance (72.0%), followed by skepticism regarding vaccine efficacy in preventing the infection (29.0%) and beliefs in the conspiracy theory (23.4%). Regarding enablers, exigence for more efficacy and safety studies was the most commonly reported (48.3%), followed by a condition that the vaccine is recommended by the physician (16.3%) or become mandatory (12.9%).

Factors Associated With COVID-19 Vaccine Non-engagement

In unadjusted models, younger age, female gender, unmarried status, higher income, and higher perceived healthiness; were associated with a higher likelihood for non-engagement to the vaccine, by reference to their respective counterparts. On the other hand, having children, being afflicted with a chronic disease, highly perceived severity of COVID-19, and fear of being infected were associated with a lower likelihood for non-engagement to the vaccine, by reference to their respective counterparts. Further, the level of adherence to preventive measures was inversely associated with non-engagement to the vaccine (**Table 3**).

The Adjusted model showed that the likelihood for non-engagement was independently associated with female gender (OR = 2.31; 95%CI: 1.68–3.18, $p < 0.001$), medium (OR = 2.07, 95%CI: 1.54–2.78, $p < 0.001$) and low adherence level to preventive measures (OR = 6.93; 95%CI: 3.46–13.87, $p < 0.001$), work in private sector (OR = 0.53; 95%CI: 0.29–0.97, $p = 0.038$), high perceived COVID-19 severity (OR = 0.66; 95%CI: 0.47–0.92, $p = 0.014$), and fear from contracting the disease (OR = 0.56; 95%CI: 0.35–0.91, $p = 0.018$) (**Table 3**, **Figure 3**).

COVID-19 Acceptance in Arab Countries From MENA Region—Results of the Systematic Review

A total of six studies were included in this systematic review, with sample sizes ranging from 1,019 to15,087 participants. Eleven studies were excluded, out of which six were not conducted among the general population, and five studies from the same countries comprised a smaller sample size as shown in **Figure 1**. The included studies were conducted in the United Arab Emirates (UAE), Kuwait, Qatar, Libya, Kingdom of Saudi Arabia (KSA), and Jordan (**Table 4**). All studies were internet-based, nationwide surveys; three studies (32–34) were conducted only amongst the general population, while the remaining comprised the general population and healthcare workers (31, 32, 36). The quality ranking of the included cross-sectional studies across different criteria is reported in the (**Supplementary Table 3**) a green color for "yes," red for "no," grey for not applicable and yellow for "cannot determine" respectively. The overall quality was considered as fair for all the studies. The highest COVID-19 vaccine acceptance rate (75%) was reported in UAE (32), followed by Kuwait (65%) (33), Qatar (61%) (35), and Libya (61%) (36). Predictors of vaccine acceptance varied between the studies, and included adherence to government recommendations, married status, positive COVID-19 status, having friends died or infected with COVID-19, high income, fear of contracting COVID-19, perception of high severity, and private-sector workers. History of flu vaccination was a positive predictor of COVID-19 vaccination in three studies by Alabdulla et al. (35), Alfageeh et al. (34), and El-Elimat et al. (39). Female gender was a significant predictor for vaccine avoidance in the study by Alfageeh et al. (34). Other vaccine avoidance predictors that were reported comprised younger age, self-employment, safety concerns, conspiracy theory, and low and medium adherence to COVID-19 preventive measures.

DISCUSSION

This is the first nationwide study addressing the Algerian population's attitude toward the COVID-19 vaccine. Using

TABLE 1 | Sociodemographic characteristics and answering patterns to different questionnaire scales in total population and by comparison between healthcare workers vs. medical students vs. the general population.

Characteristics	Total, *n* (%)	General population, *n* (%)	Healthcare workers, *n* (%)	Medical students, *n* (%)	P-value
Total	1019	519	136	364	
Age					<0.001
More than 60	54 (05%)	52 (10%)	2 (01%)	0 (0%)	
40–59	107 (11%)	99 (19%)	7 (05%)	1 (0.2%)	
30–39	208 (20%)	174 (34%)	32 (24%)	2 (1%)	
18–29	650 (64%)	194 (37%)	95 (70%)	361 99%)	
Gender					<0.001
Males	474 (47%)	306 (59%)	42 (31%)	126 (35%)	
Female	545 (54%)	213 (41%)	94 (69%)	238 (65%)	
Region					<0.001
Center	250 (25%)	146 (28%)	28 (21%)	76 (21%)	
East	257 (25%)	107 (21%)	32 (24%)	118 (32%)	
West	252 (25%)	112 (22%)	42 (31%)	98 (27%)	
South	260 (26%)	154 (30%)	34 (25%)	72 (20%)	
Area					0.651
Urban	825 (81%)	417 (80%)	114 (84%)	294 (81%)	
Rural	194 (19%)	102 (20%)	22 (16%)	70 (19%)	
Marital status					<0.001
Ever married	307 (30%)	262 (50%)	38 (28%)	7 (02%)	
Never married	712 (70%)	257 (50%)	98 (72%)	357 (98%)	
House setting					0.001
With family	962 (94%)	477 (92%)	129 (95%)	356 (98%)	
Alone	57 (6%)	42 (8%)	7 (5%)	8 (2%)	
Income					<0.001
>100K AD	199 (20%)	95 (18%)	33 (24%)	71 (20%)	
50K−100K AD	347 (34%)	157 (30%)	62 (46%)	128 (35%)	
<50K AD	473 (46%)	267 (51%)	41 (30%)	165 (45%)	
Children					<0.001
No	763 (75%)	296 (57%)	106 (78%)	361 99%)	
Yes	256 (25%)	223 (43%)	30 (22%)	3 (1%)	
Having chronic disease					<0.001
No	883 (87%)	427 (82%)	120 (88%)	336 (92%)	
Yes	136 (13%)	92 (18%)	16 (12%)	28 (08%)	
Living with someone who has a chronic disease					0.863
No	488 (48%)	246 (47%)	68 (50%)	174 (48%)	
Yes	531 (52%)	273 (53%)	68 (50%)	190 (52%)	
Perceived health status					0.023
Below average	131 (13%)	439 (85%)	126 (93%)	323 (98%)	
Good or excellent	888 (87%)	80 (15%)	10 (7%)	41 (11%)	
Fear of getting the disease					0.011
No	144 (14%)	79 (15%)	9 (07%)	56 (15%)	
Got the disease	164 (16%)	80 (15%)	33 (24%)	51 (14%)	
Yes	711 (70%)	360 (69%)	94 (69%)	257 (71%)	
Perception of COVID-19 severity					0.013
Low	439 (43%)	244 (47%)	50 (37%)	145 (40%)	
Moderate	317 (31%)	161 (31%)	50 (37%)	106 (29%)	
High	263 (26%)	114 (22%)	36 (36%)	113 (31%)	
Level of Adherence to preventive measures					0.024
Low	93 (9%)	50 (10%)	7 (05%)	36 (10%)	
Moderate	491 (48%)	245 (47%)	56 (41%)	190 (52%)	
High	435 (43%)	224 (43%)	73 (54%)	138 (38%)	

AD, Algerian Dinar (1 AD = 0.0070 US$).

TABLE 2 | Engagement toward COVID-19 vaccine in total population and by comparison between healthcare workers vs. medical students vs. the general population.

Item/agreement level	Total, *n* (%)	General population, *n* (%)	Healthcare workers, *n* (%)	Medical students, *n* (%)	P-value
I think that SARS-CoV-2 vaccination, whenever available, would be safe					<0.001
Strongly disagree	193 (19%)	113 (22%)	14 (10%)	66 (18%)	
Disagree	136 (13%)	73 (14%)	11 (08%)	52 (14%)	
Neutral	473 (46%)	203 (39%)	75 (55%)	195 (54%)	
Agree	184 (18%)	108 (21%)	29 (21%)	47 (13%)	
Strongly agree	33 (3%)	22 (04%)	7 (05%)	4 (01%)	
I think that SARS-CoV-2 vaccination is effective to prevent infection					0.008
Strongly disagree	150 (15%)	89 (17%)	14 (10%)	47 (13%)	
Disagree	167 (16%)	95 (18%)	19 (14%)	53 (15%)	
Neutral	399 (39%)	179 (34%)	56 (41%)	164 (45%)	
Agree	266 (26%)	131 (25%)	41 (30%)	94 (26%)	
Strongly agree	37 (4%)	25 (5%)	6 (4%)	6 (2%)	
I think that the best way to avoid the complications of COVID-19 is by getting vaccinated					0.005
Strongly disagree	172 (17%)	101 (19%)	12 (09%)	59 (16%)	
Disagree	196 (19%)	103 (20%)	29 (21%)	64 (18%)	
Neutral	319 (31%)	156 (30%)	44 (32%)	119 (33%)	
Agree	268 (26%)	118 (23%)	40 (29%)	110 (30%)	
Strongly agree	64 (6%)	41 (8%)	11 (8%)	12 (3%)	
In principle, I accept to get the SARS-CoV-2 vaccination					<0.001
Strongly disagree	285 (28%)	170 (33%)	21 (15%)	94 (26%)	
Disagree	190 (19%)	78 (15%)	32 (24%)	80 (22%)	
Neutral	279 (27%)	123 (24%)	41 (30%)	115 (32%)	
Agree	201 (20%)	104 (20%)	33 (24%)	64 (18%)	
Strongly agree	64 (6%)	44 (8%)	9 (7%)	11 (3%)	
I will receive the SARS-CoV-2 vaccination as soon as possible whenever it is available					<0.001
Strongly disagree	326 (32%)	181 (35%)	25 (18%)	120 (33%)	
Disagree	195 (19%)	79 (15%)	33 (24%)	83 (23%)	
Neutral	280 (27%)	132 (25%)	43 (32%)	105 (29%)	
Agree	157 (15%)	84 (16%)	29 (21%)	44 (12%)	
Strongly agree	61 (6%)	43 (8%)	6 (4%)	12 (3%)	
Likelihood of engagement					0.145
High (engaged)	342 (34%)	181 (35%)	52 (38%)	109 (30%)	
Low (non-engaged)	677 (66%)	338 (65%)	84 (62%)	255 (70%)	

a multidimensional model to measure the likelihood of engagement to vaccination, our study revealed that only 34% of the participants would be engaged to receive the COVID-19 vaccines. The Adjusted regression analysis demonstrated multiple predictors for non-engagement, including female gender, and low/intermediate levels of adherence to preventive measures, whereas a high perception of the disease severity and fear of being infected predicted vaccine acceptance. Additionally, the systematic review findings suggested that Algeria had the lowest vaccine acceptance rate in comparison with other MENA countries, where acceptance rates ranged from 37.4% in Jordan (39) and 75% in the UAE (32). More recent data showed greater disparity in vaccine acceptance rates in the MENA region (23). In comparison with Europe, the lowest acceptance rate of 53.7%, reported in Italy (40), was relatively higher than the acceptance rate observed in our study.

The high perceived severity of COVID-19 was among the independent risk factors for engagement; however, only 25.8% of participants perceived the disease to be severe. Regardless of the acceptability of the vaccine, the severity of the disease will affect the vaccination intention. Perception about the disease severity may be assimilated to a personal opinion or belief regarding the level of hazard or exposure to the crisis and the extent of its adverse impact on the individual (41). In the case of COVID-19, but not specifically, the risk perception may change over time and is further determined by the individual's awareness about and interpretation of the relationship between the virus/pandemic and the observed undesirable effects—and such interpretation may be biased or distorted by other opinions, (mis)beliefs and (mis)conceptions. A theoretical approach by Cori et al. (42), suggested that both risk perception and fear of COVID-19 are determined by cognitive factors, and the

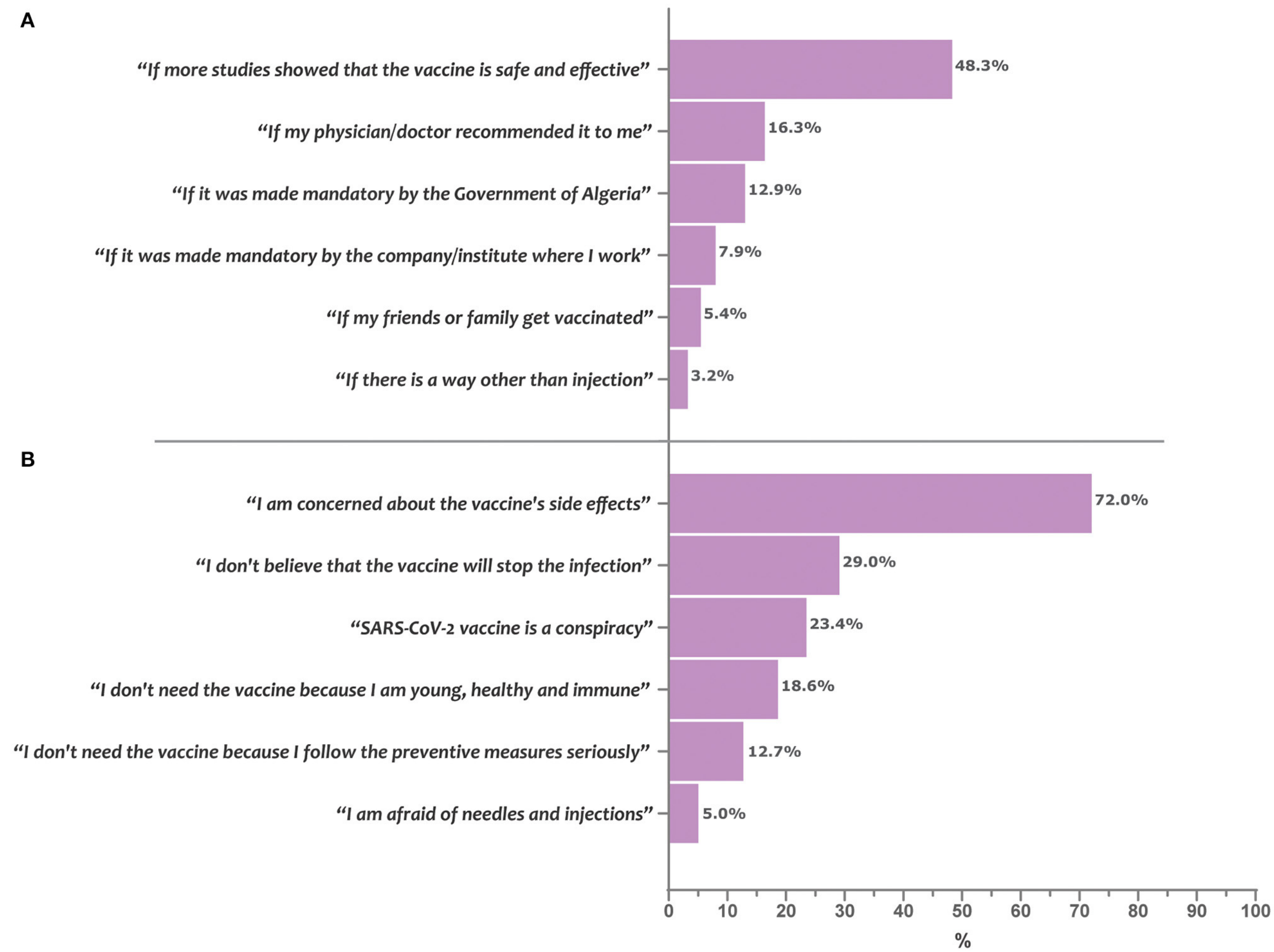


FIGURE 2 | Enablers and barriers of COVID-19 vaccine acceptance in Algeria. Bars represent the percentage of participants who reported the given item as being a determining enabler **(A)** or barrier **(B)** for acceptance of the COVID-19 vaccine uptake.

author mentioned four key factors including knowledge about the disease/virus, visibility of the risk, trust in the authorities, and healthcare institutions, and voluntary exposure to the virus/infection. The aforementioned factors may be modified by means of awareness-raising campaigns and authoritarian corrective or restrictive measures, aiming at enhancing the risk perception and ultimately increasing the vaccination rates. Evidence from previous data suggests that risk perception about COVID-19 increased in the lockdown phase and decreased in the re-opening phases (43), which was positively associated with the change in vaccine acceptance rate. At the time when the present study was conducted, the country was in a post-re-opening phase, which may explain the low engagement rates observed. Another longitudinal study from the US assessed the trend of people's attitude toward the vaccine, between March and August 2020, and showed heterogeneous results with perceived severity of the disease being one of the determinants of the vaccine acceptance. Furthermore, the authors demonstrated that the trends in both risk perception and vaccine acceptance were likely to be determined by the individual's specific political positions and exposure to media (44). Such observation supports the importance of correcting the cognitive and behavioral factors at the population's level to enhance vaccine uptake.

Similar to other reports from the MENA region, including Kuwait (33), Qatar (35), KSA (34), and Jordan (39), men were more likely to accept the Covid-19 vaccine in Algeria. This can be explained by the increased severity of the disease among men and the higher mortality reported in the majority of countries (45, 46). This statement was extensively mediatized and may have played a role in men's motive to vaccination, developing a relatively more positive attitude toward the vaccine. While such an explanation requires further evidence, notably the associated levels of awareness about the specific health risks on males, other factors may explain the less negative attitude among males that was found in the present study. Among these factors, the impact of the pandemic and restrictive measures on incomes and businesses, which may be more perceived by males in some societies. This explanation may be in line with the significant

TABLE 3 | Factors associated with vaccine engagement levels.

Parameter/category	Total (n = 1019)	Engagement score	Non-engagement (Engagement score≤15)				
	N (%)	Mean ± SD	Rate, *N* (%)	Unadjusted OR (95%CI)	P-value	Adjusted OR (95%CI)*	P-value
Age							
More than 60 y	54 (5.3%)	15.91 ± 6.77	23 (42.6%)	Ref		Ref	
40–59 y	107 (10.5%)	13.41 ± 5.96	66 (61.7%)	**2.17 (1.12–4.22)**	**0.023**	1.77 (0.82–3.83)	0.145
30–39 y	208 (20.4%)	13.13 ± 6.08	134 (64.4%)	**2.44 (1.33–4.49)**	**0.004**	1.46 (0.68–3.13)	0.329
18–29 y	650 (63.8%)	13.41 ± 4.57	454 (69.8%)	**3.12 (1.78–5.49)**	**<0.001**	1.39 (0.61–3.17)	0.432
Gender							
Males	474 (46.5%)	13.90 ± 5.74	284 (59.9%)	Ref		Ref	
Female	545 (53.5%)	13.13 ± 4.70	393 (72.1%)	**1.73 (1.33–2.25)**	**<0.001**	**2.31 (1.68–3.18)**	**< 0.001**
Region							
Center	250 (24.5%)	13.27 ± 5.80	163 (65.2%)	Ref		-	
East	257 (25.2%)	14.14 ± 5.06	158 (61.5%)	0.85 (0.59–1.22)	0.385		
Ouest	252 (24.7%)	13.40 ± 4.99	173 (68.7%)	1.17 (0.81–1.70)	0.411		
South	260 (25.5%)	13.13 ± 4.98	183 (70.4%)	1.27 (0.87–1.84)	0.211		
Area							
Urban	825 (81%)	13.60 ± 5.19	542 (65.7%)	Ref		-	
Rural	194 (19%)	12.98 ± 5.36	135 (69.6%)	1.20 (0.85–1.68)	0.302		
Marital status							
Ever married	307 (30.1%)	13.92 ± 5.92	184 (59.9%)	Ref		Ref	
Never married	712 (69.9%)	13.30 ± 4.88	493 (69.2%)	**1.51 (1.14–1.99)**	**0.004**	1.10 (0.59–2.04)	0.76
Level of education							
Low level	56 (5.5%)	12.20 ± 6.45	37 (66.1%)	Ref		-	
Medium level	110 (10.8%)	13.27 ± 5.88	70 (63.6%)	0.89 (0.46–1.77)	0.757		
High level	853 (83.7%)	13.60 ± 5.03	570 (66.8%)	1.03 (0.58–1.83)	0.908		
House setting							
With family	962 (94.4%)	13.53 ± 5.17	642 (66.7%)	Ref		-	
Alone	57 (5.6%)	12.68 ± 6.04	35 (61.4%)	0.79 (0.46–1.37)	0.408		
Living with someone who has a chronic disease							
No	488 (47.9%)	13.26 ± 5.17	334 (68.4%)	Ref		-	
Yes	531 (52.1%)	13.70 ± 5.26	343 (64.6%)	0.84 (0.65–1.09)	0.194		
Having chronic disease							
No	883 (86.7%)	13.34 ± 5.15	598 (67.7%)	Ref		Ref	
Yes	136 (13.3%)	14.45 ± 5.57	79 (58.1%)	**0.66 (0.46–0.96)**	**0.027**	0.88 (0.56–1.38)	0.579
Job							
Unemployed	144 (14.1%)	12.76 ± 5.86	100 (69.4%)	Ref		Ref	
Healthcare sector	136 (13.3%)	14.66 ± 4.61	84 (61.8%)	0.71 (0.43–1.17)	0.177	0.60 (0.32–1.02)	0.057
Public sector	165 (16.2%)	13.60 ± 5.57	106 (64.2%)	0.79 (0.49–1.27)	0.334	0.80 (0.46–1.40)	0.438
Privat sector	122 (12%)	13.84 ± 6.24	70 (57.4%)	**0.59 (0.36–0.98)**	**0.042**	**0.53 (0.29–0.97)**	**0.038**
Student	364 (35.7%)	13.20 ± 4.61	255 (70.1%)	1.03 (0.67–1.57)	0.892	0.67 (0.39–1.15)	0.147
Others	88 (8.6%)	13.34 ± 4.99	62 (70.5%)	1.05 (0.59–1.87)	0.871	1.07 (0.55–2.06)	0.851
Income							
>100K AD	199 (19.5%)	14.69 ± 5.22	117 (58.8%)	Ref		Ref	
50K−100K AD	347 (34.1%)	13.48 ± 5.02	235 (67.7%)	**1.47 (1.03–2.11)**	**0.036**	1.47 (0.99–2.17)	0.051
<50K AD	473 (46.4%)	12.98 ± 5.29	325 (68.7%)	**1.54 (1.09–2.17)**	**0.014**	1.34 (0.92–1.95)	0.132
Children							
No	763 (74.9%)	13.30 ± 4.96	527 (69.1%)	Ref		Ref	
Yes	256 (25.1%)	14.04 ± 5.92	150 (58.6%)	**0.63 (0.47–0.85)**	**0.002**	0.73 (0.40–1.35)	0.315
Fear of getting the disease							
No	144 (14.1%)	11.12 ± 5.37	116 (80.6%)	Ref		Ref	

(Continued)

TABLE 3 | Continued

Parameter/category	Total (n = 1019)	Engagement score	Non-engagement (Engagement score≤15)				
	N (%)	Mean ± SD	Rate, *N* (%)	Unadjusted OR (95%CI)	P-value	Adjusted OR (95%CI)*	P-value
Got the disease	164 (16.1%)	13.70 ± 4.58	114 (69.5%)	**0.55 (0.32–0.94)**	**0.027**	0.68 (0.38–1.21)	0.19
Yes	711 (69.8%)	13.92 ± 5.21	447 (62.9%)	**0.41 (0.26–0.63)**	**< 0.001**	**0.56 (0.35–0.91)**	**0.018**
Perception of COVID-19 severity							
Null	439 (43.1%)	12.36 ± 5.50	318 (72.4%)	Ref		Ref	
Medium	317 (31.1%)	14.38 ± 4.79	194 (61.2%)	**0.60 (0.44–0.82)**	**0.001**	0.76 (0.52–1.09)	0.134
High	263 (25.8%)	14.30 ± 4.90	165 (62.7%)	**0.64 (0.46–0.89)**	**0.007**	**0.66 (0.47–0.92)**	**0.014**
Health perception							
Below average	131 (12.9%)	14.17 ± 5.67	76 (58.0%)	Ref		Ref	
Good/excellent	888 (87.1%)	13.39 ± 5.15	601 (67.7%)	**1.52 (1.04–2.20)**	**0.03**	1.45 (0.94–2.24)	0.097
Level of Adherence to preventive measures							
High level	435 (42.7%)	15.06 ± 5.24	243 (55.9%)	Ref		Ref	
Medium level	491 (48.2%)	12.78 ± 4.79	352 (71.7%)	**2.00 (1.52–2.63)**	**<0.001**	**2.07 (1.54–2.78)**	**<0.001**
Low adherence	93 (9.1%)	9.86 ± 4.74	82 (88.2%)	**5.89 (3.05–11.36)**	**< 0.001**	**6.93 (3.46–13.87)**	**<0.001**

*95% CI, 95% confidence interval; AD, Algerian dinar; N, number; OR, odds ratio; SD, standard deviation; y, years; *adjusted for age gender marital status having chronic disease job income having children fear from getting the disease perception of severity of the disease health perception and level of adherence to preventive measures. Bold value indicates statistical significance.*

association of vaccine engagement with being married and having children that were found in the unadjusted analysis in the present study. Another potential factor explaining this gender disparity is the belief that COVID-19 is part of a global conspiracy, which was reportedly more common in women, thus explaining the higher vaccine hesitancy of females in some populations (21, 47).

However, past research data showed conflicting results about gender. A global survey including 13,426 individuals in 19 countries with a high COVID-19 burden showed that men were relatively less likely to have a positive attitude toward vaccination than women (48). Another study showed that women in Russia and Germany had higher acceptance rates of the COVID-19 vaccines than men (49). This phenomenon has been named "*the* Covid-19 *gender paradox*" (50). This gender difference can be explained by multidimensional psychological, social, cultural, and environmental influences. Further research may be required to determine the gender-specific factors associated with acceptance or refusal of the vaccine, which would enable designing targeted awareness campaigns with gender-specific messages to enhance the vaccine acceptance rates in both genders.

There is a remarkable similarity between the engagement rates of the general population (35%) and healthcare workers (38%) in the present study, which is an issue of big concern as it may constitute a significant barrier to the national vaccine campaign. Indeed, the practitioner's vaccine hesitancy influences the vaccination attitudes of the patients (51). When providers are unsure of the safety of the vaccine, they are unable to recommend it to the general population. Such an issue should be considered at the critical level by the health authorities, and corrective measures are warranted urgently to increase awareness among health providers. Furthermore, this study showed comparable patterns of safety concerns about the vaccine in the two subgroups, i.e., health workers vs. the general population (75% and 73%, respectively). This indicates the consistency of the popular misconceptions about the COVID-19 vaccine across all categories of the studied population and highlights the need for a comprehensive awareness-raising campaign at the national scale.

Other notable factors of vaccine refusal include fear of the side effects and concern about the efficiency of the vaccines. Similar concerns have been reported in other countries such as Jordan (39, 52) and the USA (52). Arguably, these concerns may be comprehensible, considering the rapid vaccine development process, the novelty of the mRNA technology used in some vaccines, and the public mediatization of the vaccine side effects; all exposing the population to massive misinformation notably in the social media (53, 54). This could be related to the decreasing acceptance rate over time in the MENA region as shown in the systematic review part of the study. Hence there is a crucial need to implement effective strategies to correct the popular misconceptions regarding the vaccine's safety.

This study also highlighted the positive association between the level of adherence to preventive measures and vaccine acceptability. This observation is in accordance with another MENA region study in Kuwait (33), reporting that high adherence to the governmental recommendations was an important predictor for vaccine uptake. Both low adherence to preventive measures and adverse attitudes toward vaccines could reflect adherence to the conspiracy theory, and this was observed among 23.4% of the avoidant group. Conspiracy theories have been associated with vaccine hesitancy as a result of mistrust between the public and the government policymakers (50).

STRENGTHS AND LIMITATIONS

One of the strengths of the present study is the use of a multidimensional model to define vaccine engagement based on a conceptual framework combining perceived vaccine effectiveness and safety with self-declared acceptance and

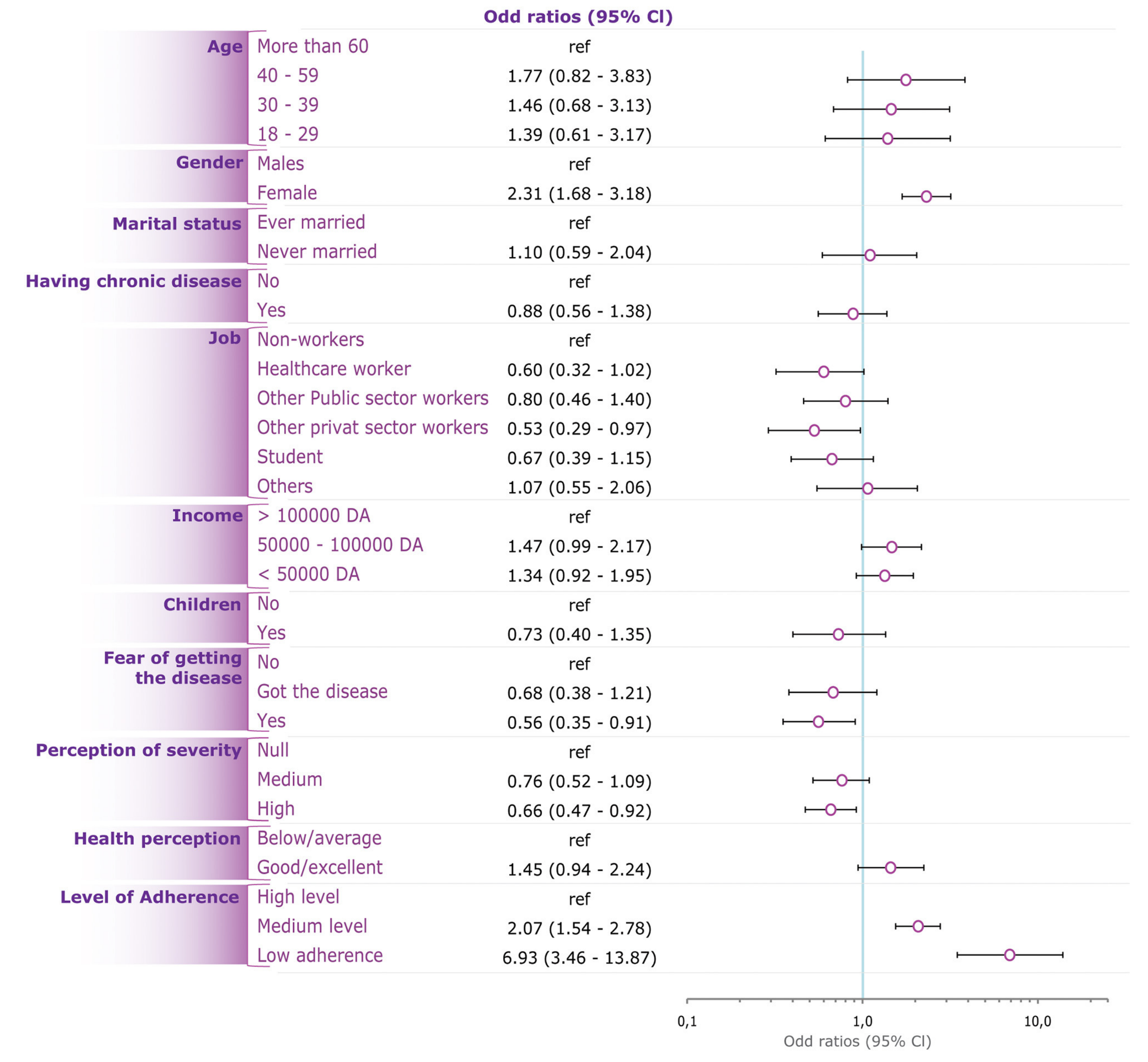


FIGURE 3 | Predictors of nonengagement to COVID-19 vaccine in Algeria.

willingness. This combination is assumed to be more reliable than using self-declared acceptance and willingness, as perceived safety and efficacy are less subjected to social desirability bias. Yet, the scale requires further validation to support this assumption. On the other hand, there are no validated instruments to assess attitudes toward the COVID-19 vaccines, and the relevant studies principally used various formulations of self-declared willingness or preparedness, which is limited by the high risk of negative or positive social desirability bias. Future research is recommended in this regard to design a validated scale to measure vaccine acceptance based on a strong model, which will enhance the quality and comparability of the findings. Another strong point of this study is that participants were equally distributed from the 4 regions of the country, which supports the generalizability of the findings. Further, determinants of vaccine acceptance and avoidance were highlighted for the first time nationwide. Therefore, the findings of this study can have a high impact on health authorities' decisions for the management of vaccination campaigns.

The major limitation of this study is the recruitment method of the participants, which was restricted to those who have access to the internet and an electronic device since the questionnaire was shared online. This probably led to a selection bias, occulting a non-negligible section of the population that may have distinct

TABLE 4 | Characteristics of studies included from the MENA regions.

References	Country	Study Period	Setting/ population	Sampling & recruitment	Sample size	Males, *n* (%)	Older age category, *n* (%)	Acceptance rate	Predictors for acceptance	Predictors for avoidance
Muqattash et al. (32)	United Arab Emirates	04/07/2020 04/08/2020	National, population-based	Snowball sampling, Web-based	1,109	309 (28%)	>45 y, 219 (20%)	75%	NA	NA
AlAwadhi et al. (33)	Kuwait	16/05/2020 31/08/2020	National, population-based	Convenient sampling, Web-based	5,651	1,321 (23%)	>60 y, 382 (7%)	65%	High adherence to recommendations by the government.	Female gender, Younger age, Ever married.
Alabdulla et al. (35)	Qatar	15/10/2020 15/11/2020	National, population-based including HCWs	Convenient sampling, Web-based	7,821	4,648 (59%)	>65 y, 325 (4%)	61%	Ever married, Flu vaccination.	Female gender, Younger age, Self-employment, Safety concerns.
Elhadi et al. (36)	Libya	01/12/2020 18/12/2020	National, population-based including HCWs	Snowball sampling, Web-based	15,087	6,227 (41%)	>50 y, 675 (5%)	61%	Currently infected with COVID-19, Having a friend infected/died from COVID-19.	Younger age, Never married.
Alfageeh et al. (34)	Saudi Arabia	08/12/2020 14/12/2020	National, population-based	Snowball sampling, Web-based	2,137	1,227 (57%)	>60 y, 212 (10%)	48%	Fear from being infected, High income, Flu vaccination.	Female gender.
El-Elimat et al. (39)	Jordan	01/11/2020 01/12/2020	National, population-based including HCWs	Convenient sampling, Web-based	3,100	1,012 (33%)	>35 y, 1,060 (34%)	37%	Flu vaccination.	Female gender, Younger age, Employment, Conspiracy theory, Safety concerns.

characteristics. One of these characteristics is the source of information regarding COVID-19 disease and vaccine, which may be radically different in the subpopulation of internet non-users by reference to internet users. This may result in discrepant opinions and attitudes toward the vaccine by reference to the study population. Unfortunately, no data was collected about sources of information about the vaccines, which would provide an indication about the aforementioned issue. Nevertheless, a study showed that individuals who get information from the internet are less inclined to accept the COVID-19 vaccine than those who get information from healthcare workers (55). Another aspect of the selection bias is the overrepresentation of medical students and healthcare providers, which was probably due to the snowball sampling method and which limits the generalizability of the findings.

CONCLUSION

Two-third of Algerians are likely to be non-engaged for COVID-19 vaccine uptake, making them one of the least accepting public for the voluntary vaccination in the MENA region. This probably provides an explanation for the slow ascension of the vaccination curve, which constitutes a great public health concern. These findings and their interpretation should be taken into consideration by the policymakers to acknowledge and address the adverse attitude about the vaccine, notably among healthcare providers who are the vectors and major contributors of a successful vaccine policy. Vaccine awareness campaigns should be implemented to address the multiple misconceptions and enhance the levels of knowledge and perception both about the disease and the vaccine, by prioritizing target populations and engaging both healthcare workers and the general population.

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/s.

AUTHOR CONTRIBUTIONS

SK, SK-D, FY, ME, and MH were responsible for the idea and study design. SK analyzed the data under the supervision of MH. SK, SK-D, FY, and MH wrote the first draft of the manuscript. SG, JS, and MH critically revised the original draft. All authors collected the data, performed systematic review screening and extraction, interpreted the data, shared in the writing, formatting, and approval of the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.843449/full#supplementary-material

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Analysis of the Transmission of SARS-CoV-2 Delta VOC in Yantai, China, August 2021

Yulou Sun[1†], Yuwei Zhang[2†], Zimo Liu[3†], Xia Li[1], Juan Liu[1], Xinghan Tian[4], Qiao Gao[1], Peihua Niu[5], Hongli Zhai[6], Zhenlu Sun[1,5], Yunlong Tian[1*] and Ji Wang[5,7*]*

[1] Yantai Center for Disease Control and Prevention, Yantai, China, [2] Shandong Center for Disease Control and Prevention, Jinan, China, [3] Electrocardiogram Room, Yantai Yuhuangding Hospital, Yantai, China, [4] Department of Critical Care Medicine, Yantai Yuhuangding Hospital Affiliated to Qingdao University, Yantai, China, [5] National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China, [6] Research Institute of Luye Public Health, Ludong University, Yantai, China, [7] Chinese Field Epidemiology Training Program, Chinese Center for Disease Control and Prevention, Beijing, China

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***Correspondence:**
Zhenlu Sun
sunluyu1007@126.com
Yunlong Tian
174678338@qq.com
Ji Wang
wangji@ivdc.chinacdc.cn

† These authors have contributed equally to this work

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Objective: Starting 31 July 2021, a SARS-CoV-2 outbreak occurred in Yantai, Shandong Province. The investigation showed that this outbreak was closely related to the epidemic at Nanjing Lukou Airport. In view of the fact that there were many people involved in this outbreak and these people had a complex activity area, the transmission route cannot be analyzed by simple epidemiological investigation. Here we combined the SARS-COV-2 whole-genome sequencing with epidemiology to determine the epidemic transmission route of Yantai.

Methods: Thirteen samples of SARS-CoV-2 outbreak cases from 31 July to 4 August 2021 were collected and identified by fluorescence quantitative PCR, then whole-genome deep sequencing based on NGS was performed, and the data were analyzed and processed by biological software.

Results: All sequences were over 29,000 bases in length and all belonged to B.1.617.2, which was the Delta strain. All sequences shared two amino acid deletions and 9 amino acid mutations in Spike protein compared with reference sequence NC_045512.2 (Wuhan virus strain). Compared with the sequence of Lukou Airport Delta strain, the homology was 99.99%. In order to confirm the transmission relationship between patients, we performed a phylogenetic tree analysis. The results showed that patient 1, patient 2, and patient 9 belong to an independent branch, and other patients have a close relationship. Combined with the epidemiological investigation, we speculated that the epidemic of Yantai was transmitted by two routes at the same time. Based on this information, our prevention and control work was carried out in two ways and effectively prevented the further spread of this epidemic.

Keywords: analysis, transmission, SARS-CoV-2 Delta, Yantai, China

INTRODUCTION

SARS-COV-2 is a novel coronavirus first reported in Wuhan, China in December 2019 which caused an epidemic of acute respiratory syndrome (1, 2). Since then, the coronavirus disease 2019 (COVID-19) has spread quickly all over the world causing great casualties and property losses (3, 4). By mid-March 2022, nearly 460 million cases of COVID-19 were diagnosed with over 6 million deaths around the world (https://coronavirus.jhu.edu/map.html). All viruses, including SARS-CoV-2, change over time. Most changes have little to no effect on virus properties, but some changes especially the mutation accumulation may affect the propagation, pathogenicity, performance of vaccines, diagnostic tools, and so on (5). In order to prioritize global monitoring and research, and ultimately inform the ongoing response to the COVID-19 pandemic, the world health organization (WHO) classified important variants into two categories: variants of concern (VOC) and variants of interest (VOI) (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants). VOC means that the Virus strains have a wide range of influence, and data supports it enhancing the transmissibility and detrimental change or reduces the vaccine effectiveness and therapeutic effect. VOI means that the Virus strains are predicted or known to change characteristics, and have been found in many countries with an increasing number of cases over time. Given the continuous evolution of the virus and the constant developments in our understanding of the impacts of variants, these definitions may be periodically adjusted. Currently, there are five designated VOCs (Alpha from the UK, Beta from South Africa, Gamma from Brazil, Delta from India, and Omicron from Multiple countries) and two VOIs (Lambda from Peru and Mu from Colombia). Each strain contains its unique characteristic mutation spectrum and also has the same mutation sites among strains. Alpha, Beta, and Gamma have the same mutation N501Y within the receptor-binding domain (RBD) of the spike protein, which can increase the affinity to human angiotensin-converting enzyme 2 (hACE2) (6, 7). This may play an essential role in the higher transmission of these strains. Beta and Gamma have another shared mutation, E484K, in their spike protein, this mutation can not only enhance the receptor binding affinity but also can escape the neutralization by vaccine-induced humoral immunity or some therapeutic monoclonal antibodies (8–10). Focusing on the mutations of the Delta strain, it hosts L452R T478K P681R mutations in RBD, these can greatly improve the transmission ability and immune system evasion (11, 12). Since April 2021, Delta has expanded rapidly in the world until the emergence of Omicron in December 2021. Omicron contains more than 15 mutations in RBD, these mutations greatly changed the structure of Spike protein, enhanced its binding ability to ACE2, and invalidated many antibody binding sites (13, 14). In addition, Omicron also got rid of the dependence on cellular protease TMPRSS2 and made it reproduce rapidly and massively in airway cells above the lungs that do not express TMPRSS2, which not only increased the viral load but also accelerated the transmission speed of the virus (15, 16). At present, Omicron has almost completely replaced Delta all over the world.

TABLE 1 | Details of patients involved in this study.

Patient no.	Gender	Age	Date of diagnosis	Location
Patient 1	Male	60	2021.07.31	Laishan district, Yantai
Patient 2	Male	62	2021.08.01	YEDA
Patient 3	Female	39	2021.08.02	YEDA
Patient 4	Male	28	2021.08.02	YEDA
Patient 5	Female	38	2021.08.03	YEDA
Patient 6	Male	29	2021.08.03	YEDA
Patient 7	Female	28	2021.08.03	YEDA
Patient 8	Female	26	2021.08.03	YEDA
Patient 9	Female	57	2021.08.03	Laishan district, Yantai
Patient 10	Female	26	2021.08.04	YEDA
Patient 11	Male	25	2021.08.04	YEDA
Patient 12	Female	33	2021.08.04	YEDA
Patient 13	Male	33	2021.08.04	YEDA

China was also troubled by the SARS-COV-2 Delta strain. Since June 2021, it has been found in new outbreaks in Yunnan, Guangdong, and Jiangsu. The outbreak started at Lukou Airport of Nanjing with related epidemics in many provinces and cities. Because of omissions in cleaning and disinfection of an inbound Russian aircraft CA910 which arrived at Lukou Airport in Nanjing from Moscow on July 10, the cleaning staff were infected with SARS-COV-2 and then caused the spread of the infection. The investigation showed that the SARS-COV-2 outbreak in Yantai was also closely related to this source. The first Lukou-related case in Yantai was diagnosed on 31 July 2021 and a total of 13 patients were finally diagnosed in 5 days. It was worth noting that the epidemiological investigation showed that the transmission relationship among the 13 people was complex. So in order to determine the virus strains type and the transmission relationship between cases, we sequenced the whole genomic nucleic acids of these 13 cases based on second-generation high-throughput sequencing technology (NGS), analyzed the gene characteristics and variation of the virus from the molecular level, and traced the source of the virus.

METHODS AND MATERIALS

Sample Collection

Since 31 July 2021, a SARS-CoV-2 outbreak has occurred in Yantai, Shandong Province. As of 4 August, a total of 13 novel coronavirus-positive cases have been detected. Their nasopharyngeal swabs were collected to our laboratory for testing before sending them to an infectious disease hospital for treatment.

SARS-CoV-2 Nucleic Acid Diagnosis

Viral RNA was extracted from 140 μL clinical specimens using a QIAamp viral RNA mini kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. The purified RNA was eluted in a 50 μL elution buffer. Fluorescent qPCR was performed using an *In Vitro* Diagnostic (IVD) reagent (Bioperfectus Technologies, Jiangsu, China) prior to sequencing of the

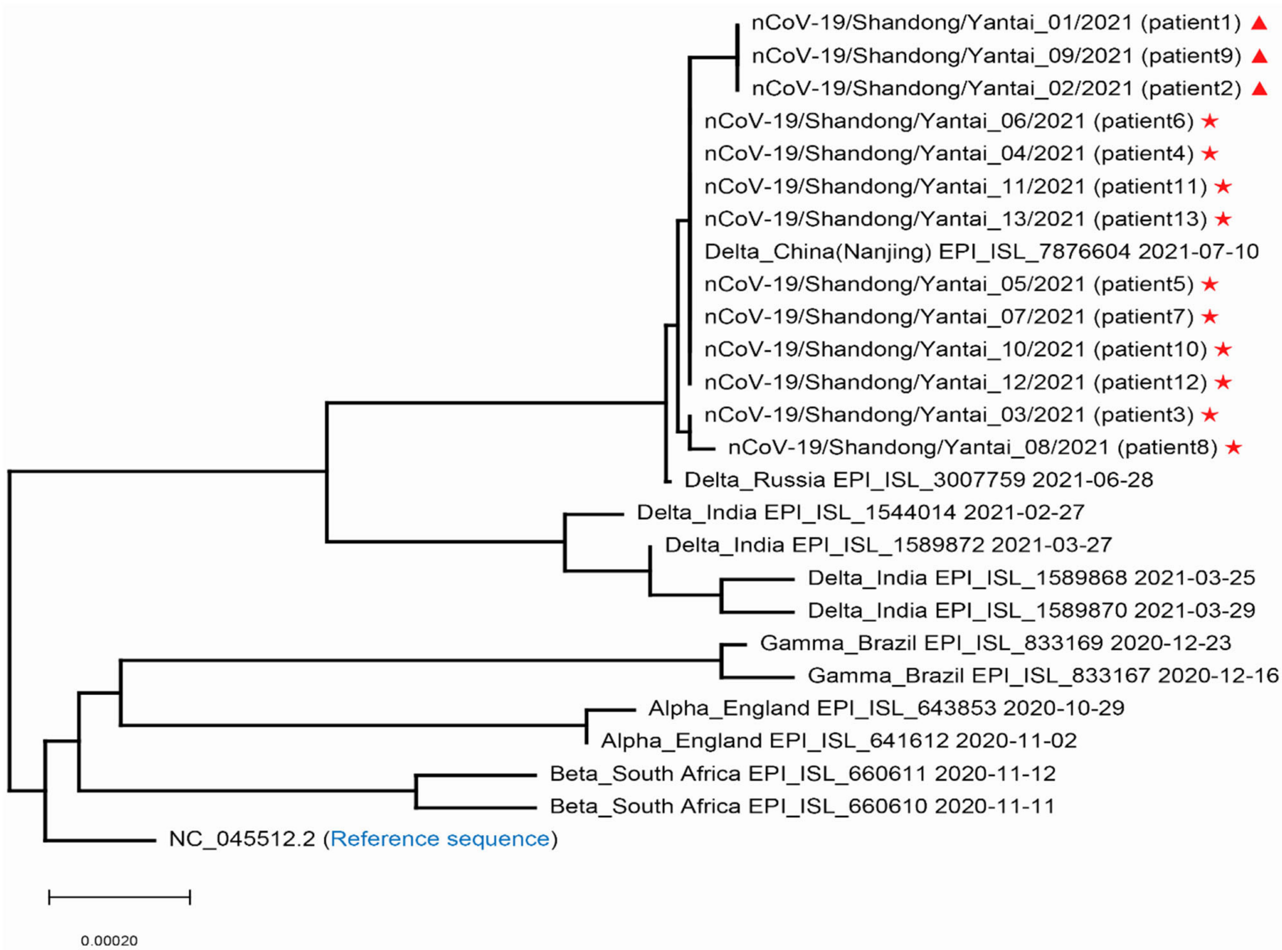

FIGURE 1 | Phylogenetic tree of the SARS-COV-2 sequences in Yantai with other reported sequences. Stars and triangles represent the two transmission routes of COVID-19, respectively in Yantai.

PCR product. Open Reading Frame gene region (ORF1a/b), Nucleocapsid region (N) of SARS-CoV-2, and a positive reference gene were used to evaluate the presence and the quantity of SARS-COV-2. We followed kit instructions with thermocycler protocol: 1 cycle 50°C 10 min; 1 cycle 97°C 1 min; 45 cycles 97°C 5 s; 58°C 30 s with fluorescence reading. The circulation threshold (Ct) detection limit was 40 (350 copies/ml). A Ct value <37 is considered positive. All samples' Ct values were <30, meaning that subsequent sequencing steps could be carried out. All tests were conducted under strict biosafety conditions and standard operating procedures.

Sequencing Strategies

In order to obtain the sequence of SARS-COV-2 specifically, an amplicon-based enrichment method was used for sequencing library preparation. Reverse transcription and amplification steps were performed using ULSEN® 2019-nCoV Whole Genome Kit (Micro-Future, Beijing, China). A measure of 16 μL of viral RNA was reverse-transcribed into the first strand of cDNA and the viral genome was amplified by primer pools A and B. The PCR product was purified with AMPure XP beads (Beckman Coulter, Brea, CA) and diluted to 0.2 ng/μL. Paired-end libraries were generated with Nextera XT DNA Library Preparation Kit (Illumina, San Diego, CA) following the reference guide. Samples were multiplexed, using the Nextera XT index kit (Illumina, San Diego, CA). For the quantification and validation of the library, the Qubit 4.0 Fluorometer system (Life Technologies, Carlsbad, CA) and 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA) were used. Library sequencing was performed on Miseq using MiSeq Reagent Kit v2 (300-cycles; Illumina, San Diego, CA).

Data Analysis

For raw data, we first calculated the quality of sequencing reads by FastQC software (Babraham Institute, Cambridge, UK), and clean data was generated after removing sequencing adapters, reads containing poly-N and low quality reads by trimmomatic software (17). All downstream analysis was based on high-quality clean data. The reference genome

TABLE 2 | Details of all sequences involved in this study.

Virus name	Collection date	Location	Accession ID	Database	Note
hCoV-19/England/QEUH-B12D90/2020	2020.11.02	England	EPI_ISL_641612	GISAID	–
hCoV-19/England/CAMC-B08C45/2020	2020.10.29	England	EPI_ISL_643853	GISAID	
hCoV-19/South Africa/KRISP-EC-K004574/2020	2020.11.11	South Africa	EPI_ISL_660610	GISAID	
hCoV-19/South Africa/KRISP-EC-K004576/2020	2020.11.12	South Africa	EPI_ISL_660611	GISAID	
hCoV-19/India/MH-NCCS-P1162000182735/2021	2021.02.27	India	EPI_ISL_1544014	GISAID	
hCoV-19/India/WB-1931300251103/2021	2021.03.25	India	EPI_ISL_1589868	GISAID	
hCoV-19/India/WB-1931501009078/2021	2021.03.29	India	EPI_ISL_1589870	GISAID	
hCoV-19/India/WB-1931501003695/2021	2021.03.27	India	EPI_ISL_1589872	GISAID	
hCoV-19/Brazil/AM-987/2020	2020.12.16	Brazil	EPI_ISL_833167	GISAID	
hCoV-19/Brazil/AM-989/2020	2020.12.23	Brazil	EPI_ISL_833169	GISAID	
hCoV-19/Russia/MOW-RII-MH27370S/2021	2021.06.28	Russia	EPI_ISL_3007759	GISAID	
hCoV-19/Jiangsu/NJ/2021	2021.07.10	China (Nanjing)	EPI_ISL_7876604	GISAID	
hCoV-19/Shandong/Yantai_01/2021	2021.07.31	Yantai	EPI_ISL_8525417	GISAID	Patient 1
hCoV-19/Shandong/Yantai_02/2021	2021.08.01	Yantai	EPI_ISL_8525418	GISAID	Patient 2
hCoV-19/Shandong/Yantai_03/2021	2021.08.02	Yantai	EPI_ISL_8525419	GISAID	Patient 3
hCoV-19/Shandong/Yantai_04/2021	2021.08.02	Yantai	EPI_ISL_8525420	GISAID	Patient 4
hCoV-19/Shandong/Yantai_05/2021	2021.08.03	Yantai	EPI_ISL_8525421	GISAID	Patient 5
hCoV-19/Shandong/Yantai_06/2021	2021.08.03	Yantai	EPI_ISL_8525422	GISAID	Patient 6
hCoV-19/Shandong/Yantai_07/2021	2021.08.03	Yantai	EPI_ISL_8525423	GISAID	Patient 7
hCoV-19/Shandong/Yantai_08/2021	2021.08.03	Yantai	EPI_ISL_8525424	GISAID	Patient 8
hCoV-19/Shandong/Yantai_09/2021	2021.08.03	Yantai	EPI_ISL_8525425	GISAID	Patient 9
hCoV-19/Shandong/Yantai_10/2021	2021.08.04	Yantai	EPI_ISL_8525426	GISAID	Patient 10
hCoV-19/Shandong/Yantai_11/2021	2021.08.04	Yantai	EPI_ISL_8525427	GISAID	Patient 11
hCoV-19/Shandong/Yantai_12/2021	2021.08.04	Yantai	EPI_ISL_8525428	GISAID	Patient 12
hCoV-19/Shandong/Yantai_13/2021	2021.08.04	Yantai	EPI_ISL_8525429	GISAID	Patient 13
SARS-CoV-2	2019.12	China	NC_045512.2	NCBI	Reference

(NC_045512.2) was downloaded directly from NCBI (National Center for Biotechnology Information). Paired-end clean reads were aligned to the reference genome using BWA-MEM v0.7.17 (18). Mapped reads were sorted by name using sambamba v0.6.8 (19). PCR duplications were processed by GATK (Genome Analysis Toolkit) (20) v4.2.0.0. The full length of virus sequences were obtained by ivar v1.3.1 (21), sequencing depth <3, and uncovered areas were replaced with "N." For clade assignment and mutation calling, we imported all sequences into Nextclade (https://clades.nextstrain.org/tree) and the web-application Phylogenetic Assignment of Named Global Outbreak Lineages (pangolin: https://pangolin.cog-uk.io/). The full-length SARS-CoV-2 genome sequences were aligned using ClustalW integrated in the MEGA X. The neighbor-joining (NJ) phylogenetic tree was constructed by the program MEGA X using the Kimura two-parameter model and 1,000 bootstrap samplings.

RESULTS

Epidemiological History Survey

Patient 1, a native of Laishan District, Yantai, was transferred by plane to Nanjing Lukou Airport on 15 July 2021. He was confirmed as the first positive case of the novel coronavirus outbreak in Yantai on 31 July 2020. Patient 2, a migrant worker in YEDA, was a close contact of patient 1, who was diagnosed with a common case of COVID-19 on 1 August 2021. Patient3, a worker of a beauty salon in YEDA, transshipped at Nanjing Lukou Airport by plane on July 19, 2021. She returned to Yantai on July 22 and was confirmed to be infected with novel coronavirus on August 2. Patient 4, Patient 5, Patient 6, Patient 7, Patient 8, Patient 10, Patient 11, and Patient 13 were all employees of a beauty salon in YEDA and were close contacts of Patient 3. Patient 9 was the wife and close contact of Patient 1. Patient 12 was a close contact of Patient 4 (**Table 1**).

Nucleic Acid Test Results

Nasopharyngeal swabs were collected from all 13 patients, viral RNA was extracted from a 140 μL sample using a QIAamp viral RNA mini kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. The purified RNA was eluted in a 50 μL elution buffer. Before sequencing, an *In Vitro* Diagnostic (IVD) reagent (Bioperfectus Technologies, Jiangsu, China) applying fluorescent PCR technology was used. Internal quality control was evaluated using a group of positive (confirmed case RNA) and negative (DEPC H_2O) controls. Results showed that two specific targets (ORF1ab, N gene) of SARS-CoV-2 from 13 cases, standard kit, and positive internal

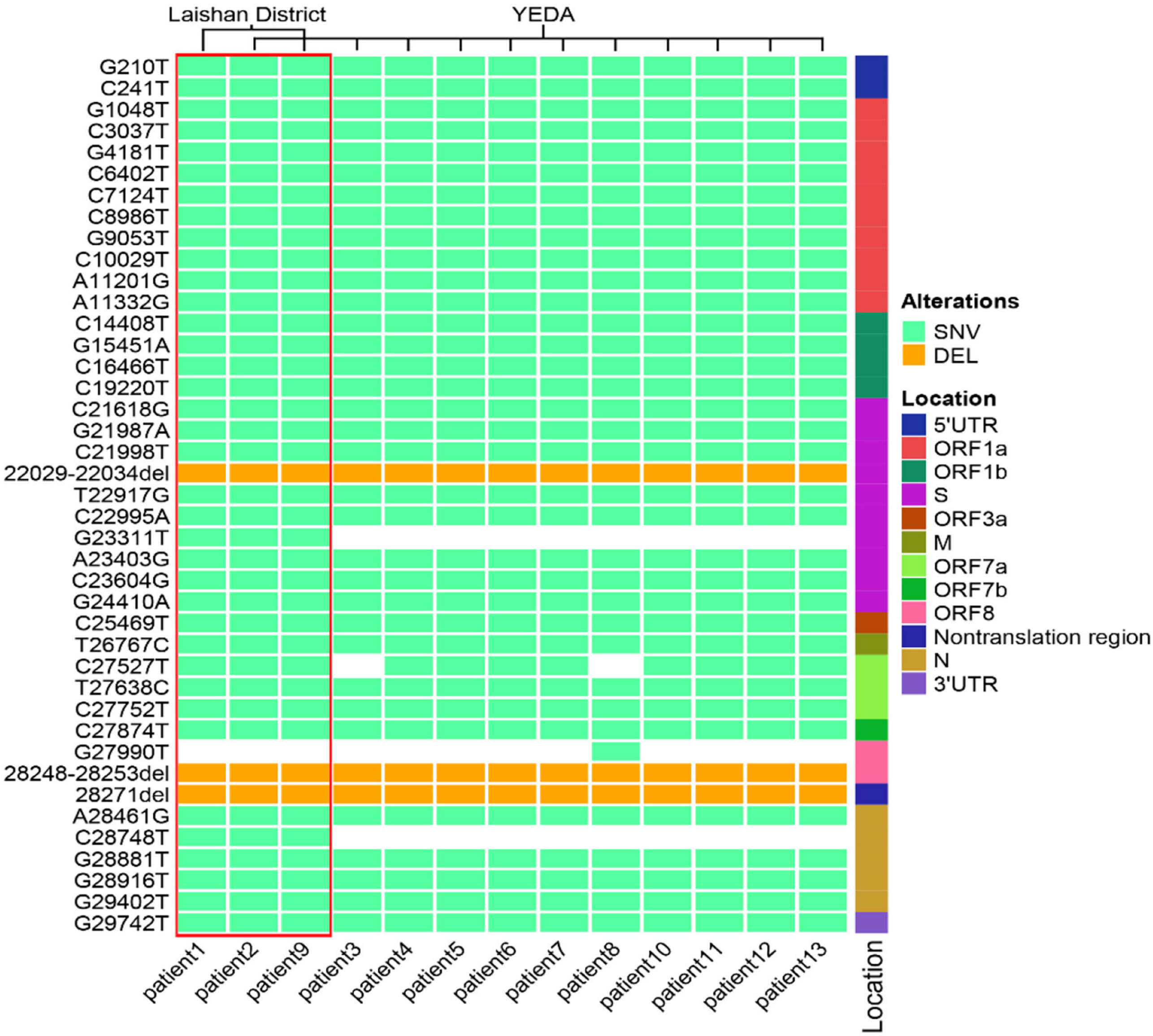

FIGURE 2 | The mutation spectrum of 13 SARS-COV-2 sequences in Yantai. These mutation sites are based on the alignment between the whole genome sequence of the virus and the reference genome. All sites were sorted according to their positions in the genome. The location represents the position of the mutation site in the genome. The pale green box represents SNV, the orange box represents DEL and the white box represents no mutation at this site. The red box contains three patients within the same transmission route.

quality control were positive, and an ideal logarithmic curve was obtained.

Next-Generation Sequencing Results

NGS was used to complete the whole genome sequencing of 13 cases, and a total of 13 novel coronavirus genome sequences were obtained. The fastA sequences of the whole genome were assembled successfully, all of which were over 29,000 bases in length. Through the web-application pangolin, we got the information that the novel coronavirus genome sequences of the above cases all belong to branch B.1.617.2 (Delta) strain.

Homology Analysis and Gene Traceability Analysis

In order to confirm the close relationship of the epidemic between Yantai and Nanjing Lukou Airport, we aligned our sequences with one SARS-COV-2 sequence from the confirmed case (EPI ISL 7876604) in CA910, and the homology was 99.99%. Due to the fact that the CA910 took off from Moscow, we also aligned our sequences with all SARS-COV-2 sequences from Russia from 20 June to 20 July from the GISAID database. One sequence (EPI_ISL_3007759) collected from Moscow on June 28 2021 was highly homologous with our sequence.

This evidence could support that the Yantai epidemic belongs to the transmission chain of the Lukou epidemic. To infer the transmission relationship between all patients, we built a Neighbor-Joining phylogenetic tree based on the whole SARS-COV-2 genome of 13 sequences in Yantai and 12 genomes available on GISAID including the sequence from Russia, and the reference sequence download from NCBI (https://www.ncbi.nlm.nih.gov/sars-cov-2/; **Figure 1**). Details of all sequences were shown in **Table 2**. The result showed that patient 1, patient 2, and patient 9 belong to an independent branch, and other patients have a close relationship. Combined with the epidemiological investigation, we speculated that the epidemic in Yantai was transmitted by two routes at the same time. To confirm this speculation, we analyzed their mutation information (**Figure 2**). A total of 41 mutations were found in the 13 sequences compared to the reference sequence (NC_045512.2). The mutation spectrum of patient 1, patient 2, and patient 9 were the same and included two specific mutations (G23311T in Spike protein, C28748T in N protein), it could be concluded that they belong to the same route and that patient 1 was the source of transmission. There were some differences in the mutations of others, patient 3 had the least number of mutations and had been to Lukou Airport. So patient 3 was the source of transmission of another route, and mutations occurred during passage. Compared with patient 3, patient 8 carried a unique mutation G27990T in ORF8 protein and no other patients had this mutation, which showed that the virus carried by patient 8 had not spread again. Compared with patient 3 and patient 8, patient 4, patient 5, patient 6, patient 7, patient 10, patient 11, patient 12, and patient 13 had the same mutation C27527T in ORF7a protein, we can make sure that the virus had spread between these patients, but we cannot determine the order of transmission.

DISCUSSION

Delta VOC was first identified in October 2020 and has become a major variant globally since April 2021. According to WHO research, the transmission rate of the Delta virus has increased by nearly 100% compared to other strains not listed as "of concern," and a recent study of the transmission dynamics of the Delta variant virus that caused the COVID-19 outbreak in Guangdong, China, also suggests that it is twice as infectious as previous pandemic strains (22). The Delta variant also spread faster than other strains. In the past, the incubation period of the Novel Coronavirus has been 5–6 days, and that of the Novel Coronavirus Delta variant is 4 days. The passage interval used to be 4 or 5 days, but now it is about 3 days (23, 24).

Thirteen cases of this outbreak, caused by a Delta variant in Yantai have been locally transmitted. During the study period, the local government implemented an epidemiological follow-up, and we sequenced all confirmed patients. This provides an opportunity for our study to understand its transmission characteristics.

In this outbreak, we found that patient 1 has been to YEDA and infected one close contact, there may be track crossing with other cases in YEDA. So only investigating the track of the action could not determine the transmission relationship of this epidemic. At this time, whole-genome sequence information may provide evidence for genotyping and phylogenetic analysis which help us to resolve this difference (25, 26), of course, this must also be based on a certain basis: their sequences must have enough differences. Fortunately, the virus transmitted this time meets this prerequisite. Through sequence analysis, we determined that this epidemic situation had two transmission routes (**Figure 1**) and obtained the mutation spectrum (**Figure 2**) of each virus. Based on this information, the prevention and control work was carried out in two ways immediately and simultaneously. By the end of this epidemic, there were only 13 cases, which was a great achievement for a city with 3 million people. Like other similar studies, it fully illustrates the importance of rapid virus genome analysis in epidemic prevention and control (27–30).

As SARS-CoV-2 continues to spread around the world, the dynamics of virus evolution and mutation are still changing, and new viruses are constantly acquiring new mutations in their genomes. Although some mutations provide the virus with the advantage of resisting human immune response, these mutations may lead to changes in pathogenicity and virulence (31). Therefore, future prevention and control work should strengthen screening of close contacts, investigation of infection sources, investigation of clusters of outbreaks, and active detection of people in high-risk areas.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here: GISAID, the accession numbers can be found in the **Supplementary Material**.

ETHICS STATEMENT

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YS: data curation, investigation, and writing original draft preparation. YZ: data curation, formal analysis, investigation, and resources. ZL: formal analysis, investigation, and methodology. XL and JL: data curation, methodology, and resources. XT, QG, PN, and ZH: data curation and investigation. ZS: methodology, data curation, writing original draft preparation, writing review and editing, and project administration. YT and JW: methodology, data curation, writing review and editing, and project administration. All authors have read and agreed to the published version of the manuscript.

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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.2022.842719/full#supplementary-material

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Assessment of COVID-19 Vaccine Acceptance and Reluctance Among Staff Working in Public Healthcare Settings of Saudi Arabia: A Multicenter Study

Muhammad Bilal Maqsood [1,2,3], ***Md. Ashraful Islam*** [4], ***Ali Al Qarni*** [1,2,5], ***Zeb-un-Nisa*** [6], ***Azfar Athar Ishaqui*** [1,2,3,7]*, ***Naif Khalaf Alharbi*** [1,2,3], ***Murtaja Almukhamel*** [8], ***Mohammad Akbar Hossain*** [9], ***Nayyra Fatani*** [10], ***Ahmad Jamal Mahrous*** [11], ***Muhammad Al Arab*** [1,2,3], ***Fahad Sami Abdulaziz Alfehaid*** [12] ***and Zahida Akbar*** [1,2,13]

[1] King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [2] King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [3] Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia, [4] Department of Pharmacy Practice, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, [5] Department of Medicine, King Abdulaziz Hospital, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia, [6] Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan, [7] Department of Pharmacy, Iqra University, Karachi, Pakistan, [8] College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, [9] Department of Pharmacology and Toxicology, Al Qunfudah Medical College, Umm Al Qura University, Al Qunfudah, Saudi Arabia, [10] Department of Pharmacy Practice, College of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia, [11] Department of Clinical Pharmacy, College of Pharmacy, Umm Al Qura University, Makkah, Saudi Arabia, [12] Department of Pharmacy, Prince Sultan Cardiac Center, Ministry of Health, Al Hofuf, Saudi Arabia, [13] Department of Obstetric and Gynaecology, King Abdulaziz Hospital, National Guard Health Authority, Jeddah, Saudi Arabia

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****Correspondence:***
Azfar Athar Ishaqui
azfar.hd@hotmail.com

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Objective: The study aimed to evaluate the novel coronavirus disease 2019 (COVID-19) vaccination acceptance and reluctance among staff working in Saudi healthcare facilities.

Methods: A cross-sectional study was conducted during April – May 2021, among healthcare workers in five public hospitals under the National Guards Health Association located in Alahsa, Dammam, Jeddah, Madinah, and Riyadh. The study used a questionnaire in English language, which was distributed through official email communication among healthcare staff currently working at study venues. The data was analyzed using IBM SPSS v23. An ethical approval was obtained.

Results: A total of 1,031 responses were recorded. Most of the staff had both doses of COVID-19 vaccine (89%). The mean score for vaccine acceptance on a scale of 1 (strongly disagree) to 5 (strongly agree) was 3.55 ± 1.6. The mean score for vaccine reluctance on the same scale was 2.71 ± 1.05. Most participants mentioned safety (76.9%) and efficacy (56.3%) as vaccine concerns and believed that COVID-19 vaccine may not be effective because of changes in virus strain (55.5%). The variables of gender and nationality significantly affected vaccine acceptance, while age, gender, nationality, and profession significantly affected vaccine reluctance ($p < 0.05$).

Conclusion: Most healthcare staff were vaccinated, and a high acceptance for COVID-19 vaccination was reported. Several demographic factors affected the vaccine acceptance and reluctance.

Keywords: COVID-19, COVID-19 vaccine, vaccine hesitancy, vaccine acceptance, Saudi Arabia

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) pandemic has spread globally and infected millions across the globe, while many have lost their lives due to this infection (1). The world is in the midst of COVID-19 pandemic that is still evolving in terms of its infectiousness and transmissibility. Several new variants of the virus that have high transmission and capability to spread are reported in the scientific literature (2, 3). Besides, the daily reporting of new cases and deaths attributable to COVID-19 is a common occurrence in the news media these days. This has propagated a sense of fear and anxiety among Saudi healthcare workers (4–6).

The emphasis and extensive coverage of COVID-19 in the media and the possibility of early availability of vaccine are unique in this pandemic (1). Besides, the disease has adversely affected the global economy owing to restrictions with regards to social interaction, work, and travel (7). Most of the countries already have strategies to respond to the pandemic crisis, including restrictions on social and large gatherings, travel bans, hand hygiene, and use of face mask. Significant improvement has been observed because of these measures. However, such strategies are not sustainable, and this requires a permanent solution such as medications or vaccines. Efforts are already being made for vaccine development. Therefore, the availability of a COVID-19 vaccine has heightened public excitement (1). It could be said that there is an expectation to return to a normal life post pandemic.

It is important to assess the reaction of healthcare workers toward a novel COVID-19 vaccine as it becomes available. The evaluation of the intent and observed behavior is essential to predict how the recovery from pandemic would take shape. Several studies have been conducted, which strived to report vaccine acceptance among healthcare staff. A study in Indonesia reported that healthcare professionals were more likely to accept a vaccine for COVID-19 (8). In Saudi Arabia, a study reported that >60% of the participants indicated their interest in receiving a COVID-19 vaccine, should it become available (9). However, the study was conducted among the general public and did not analyze the responses from a healthcare subject group specifically.

This study was conducted during the time when the vaccines against the viral infection were approved and prioritized for healthcare staff (10). At the time of this study, the first wave had passed and it was the beginning of the second wave. The healthcare staff were either in the process of receiving a vaccine or had received it. However, receiving vaccination may not be reflective of an individual's acceptance or reluctance as there may be other factors that shape an individual's perception about the vaccine. Such factors may include an individual agreeing to receive a vaccine as a requirement of a purpose such as essential travel during the pandemic. Moreover, some individuals may agree to receive a vaccine as they may believe that it is helpful; however, their confidence may depend on its safety and effectiveness. Therefore, it is important to report the confidence, i.e., acceptance and reluctance in a vaccine for COVID-19, among healthcare staff working in Saudi healthcare settings, as it would not only predict the shape of post-pandemic recovery but also highlight how this confidence would translate into public acceptance in future as healthcare professionals play a pivotal role in providing education and promoting awareness among patients and the general public.

METHODS

Study Aim

The study strived to document whether the healthcare staff were willing to get vaccinated against COVID-19 disease, and/or report if there was any reluctance to vaccinate. The confidence of the staff was measured through documentation of three traits: the tendency toward registration for a vaccine, the acceptance of a vaccine, and the reluctance toward the same. Therefore, the study aimed to evaluate the confidence of healthcare workers toward COVID-19 vaccination.

Study Design, Duration, and Venue

This was a cross-sectional study conducted over 2 months, i.e., April – May 2021, at five hospitals under the Ministry of National Guard Health Affairs (MNGHA), across five cities of Saudi Arabia. It included the Imam Abdulrahman Al Faisal Hospital in Dammam, King Abdul Aziz Medical City in Riyadh, Prince Mohammad Bin Abdul Aziz Hospital in Madinah, King Abdul Aziz Hospital in Al-Ahsa, and King Abdul Aziz Medical City in Jeddah. All were tertiary care facilities.

Study Participants and Eligibility Criteria

The target participants for the study were healthcare staff working at the afore-mentioned venues. The staff who were employed in the above mentioned hospitals and deemed eligible for COVID-19 vaccination as per the Saudi health regulator's COVID-19 vaccination guidelines at the time of study were included. Participants who did not provide consent to participate were not included.

Sampling Strategy and Sample Size Calculation

The convenience sampling technique was used to collect data from the participants. Participants who had their contact emails available in the list containing organizational emails were contacted. The venue consisted of five public hospitals located in five cities across different regions of the country. It included all the workers of these hospitals. The sample size was calculated using a sample size calculator (11). The margin of error was considered at 3%, while the confidence level was kept at 95%. The required sample size was 1,014. Since the data was collected online, the aim was to gather data more than the required sample size to account for any unforeseen circumstance such as incomplete surveys. An error rate of 10% was included in the final sample. The final sample size was 1,127. The survey analyzed 1,031 complete responses.

Research Instrument

The research instrument used in this study was a questionnaire. It was developed after review of relevant literature (12–16).

Additionally, opinions from practicing healthcare professionals in Saudi healthcare settings were also considered in creating questions. The questionnaire consisted of four sections. The first section was the socio-demographic section that contained questions related to age, gender, marital status, education, nationality, profession, work experience, and workplace. The number of items in this section was 8. The second section contained items related to registration for a vaccine and vaccination status. The number of items in this section was 5. The third section was related to vaccine acceptance and contained 5 items. The last section contained items related to reluctance and concerns and had 8 items.

Mean scores for the acceptance and reluctance toward COVID-19 vaccine were calculated. Items related to vaccine acceptance included belief about importance of vaccine to address the COVID-19, acknowledging the pandemic as a serious health issue in the country, confidence in the accuracy of a vaccine, willingness to get vaccinated upon availability of a COVID-19 vaccine, and willingness to vaccinate family members upon availability of a COVID-19 vaccine. Items related to vaccine reluctance included reluctance to vaccinate, concerns about the possible adverse effects, and concerns about the rushed pace of vaccine development overlooking potential adverse effects. All items were designed as Likert scale from 1 to 5, where 1 meant strongly disagree while 5 meant strongly agree. A mean score was calculated from these items. Some items were dichotomous, i.e., contained a Yes/No response, and were not included in scoring.

The questionnaire was available in English language as it was the primary means of communication among the employees at the study venues. The questionnaire was also piloted on 15 participants before the actual study. Healthcare professionals, academicians, and students participated in the pilot study. The instrument was piloted on 7 pharmacists, 3 medical practitioners, 3 academicians, and 2 pharmacy students. All participants, except students, had at least 3 years of work experience. No difficulty in understanding of the questions was observed. The pilot data was not included in the actual study.

Data Collection

Data for the study was collected from the staff using the questionnaire. The survey was encoded by the data management section of the institute using Lime Survey platform, in a weblink, and was distributed *via* email through the corporate communication office of MNGHA. Several email reminders were sent later using the same staff list to increase the response rate to achieve the desired sample size. The data collected was anonymous, and the respondents could not be identified from their responses.

Data Analysis and Management

Data analysis was done through IBM SPSS program version 23. The descriptive statistics such as mean, median, and standard deviation (SD) were used for reporting continuous data, while frequency (%) and sample counts (N) were used to report categorical data. The variables of "vaccine acceptance" and "vaccine reluctance" were the dependent variables. Simple and multiple linear regression analyses were employed to report the significance predictors of vaccine confidence. The level of significance was 5%.

The data was without any personal identifiers, and the data file was password protected. It was sent through official communication and stored in a password-protected computer. Any hardcopies created during analysis were securely disposed.

Ethics Approval and Consent

The study was approved by the Institutional Review Board at the King Abdullah International Medical Research Center (KAIMRC), Saudi Arabia, on 10th April, 2021. The study number was NRA21A/015/03 and the memo reference number was IRBC/0804/21. The approval was applicable to all healthcare facilities. The questionnaire was filled through an email link sent through official communication. The survey was accessible to participants after they reviewed the study consent section and agreed to participate voluntarily.

RESULTS

A total of 1,031 responses were analyzed. Most of the staff were aged between 41–50 years ($N = 409$, 39.7%) and had an experience between 10 and 15 years ($N = 244$, 23.7%). Most were females ($N = 750$, 72.7%), non-Saudi ($N = 747$, 72.5%), married ($N = 668$, 64.8%), and had a bachelor's degree ($N = 751$, 72.8%). More than half were nurses ($N = 681$, 66.1%) (**Table 1**).

The majority ($N = 935$, 90.7%) registered themselves on the web application for vaccination, while more than half ($N = 697$, 67.6%) strongly agreed that they were willing to register immediately upon announcement. Slightly more than a third of participants ($N = 337$, 32.7%) registered themselves on the web application between 1 and 3 months. Majority had taken an influenza vaccine ($N = 811$, 78.7%) and both doses of COVID-19 vaccine at the time of data collection ($N = 918$, 89%) (**Table 2**).

For the participant's view of vaccine acceptance, the mean score was 3.55 (3.45–3.65 for 95% confidence interval [CI], 1.60 SD). The Cronbach's alpha value of the items was 0.979 that highlighted an acceptable reliability. The mean score for several items related to the COVID-19 vaccine acceptance are mentioned in **Table 3**.

For the participant's view of vaccine reluctance, the average mean score of the three items related to the COVID-19 vaccine reluctance was 2.71 (2.65–2.78 for 95% CI, 1.05 SD). The Cronbach's alpha value of the items was 0.715 that highlighted an acceptable reliability. The mean score for several items related to the COVID-19 vaccine acceptance are mentioned in **Table 4**.

Further, most participants mentioned safety ($N = 700$, 76.9%) and efficacy ($N = 580$, 56.3%) as vaccine concerns. Most participants sought additional information regarding COVID-19 vaccine, such as compatibility with health conditions ($N = 529$, 51.3%), and safety and reliability of vaccine ($N = 660$, 64%). Slightly more than half of the participants believed that COVID-19 vaccine may not be effective because of changes in virus strain ($N = 572$, 55.5%) (**Table 5**).

The model for COVID-19 vaccine acceptance revealed that gender and nationality were significant predictors after adjusting

TABLE 1 | Demographic characteristics of study participants (N = 1,031).

Characteristics	Frequency (N)	Percent (%)
Age		
20–30	166	16.1
31–40	399	38.7
41–50	409	39.7
>50	57	5.5
Gender		
Male	281	27.3
Female	750	72.7
Marital Status		
Single	312	30.3
Married	668	64.8
Divorced	38	3.7
Widowed	13	1.3
Education level		
Bachelor	751	72.8
Masters	110	10.7
Doctorate	170	16.5
Nationality		
Saudi	284	27.5
Non-Saudi	747	72.5
Occupation		
Doctor	293	28.4
Nurse	681	66.1
Pharmacists	4	0.4
Allied Health	40	3.9
Support Staff	13	1.3
Work experience (years)		
1–5	167	16.2
6–10	223	21.6
11–15	244	23.7
16–20	171	16.6
>20	226	21.9
Healthcare facility		
Imam Abdulrahman Al Faisal Hospital	32	3.1
King Abdul Aziz Medical City	628	60.9
Prince Mohammad Bin Abdul Aziz Hospital	60	5.8
King Abdul Aziz Hospital	137	13.3
King Abdul Aziz Medical City	174	16.9

TABLE 2 | Response distribution for vaccine registration and vaccination items (N = 1,031).

Items and response	Frequency	Percent
I have registered myself for COVID-19 vaccination at "Sehaty or MNG-HA" Application*		
No	96	9.3
Yes	935	90.7
I was willing to register for vaccination immediately when it was announced		
Strongly disagree	47	4.6
Somewhat disagree	48	4.7
Neither agree nor disagree	79	7.7
Somewhat agree	160	15.5
Strongly agree	697	67.6
Timing to register for vaccination when it was announced		
Less than 1 month	330	32
1–3 M	337	32.7
4–6 M	175	17
7–9 M	45	4.3
More than 9 M	144	14
I have taken Influenza vaccine in last 12 months		
No	220	21.3
Yes	811	78.7
I have taken first dose of COVID-19 vaccine		
No	35	3.4
Yes	996	96.6
I have taken both doses of vaccine**		
No	113	11
Yes	918	89

*At the time of survey.
**No represents one dose taken and/or no dose taken.

TABLE 3 | Novel coronavirus disease 2019 (COVID-19) vaccine acceptance among staff (N = 1,031).

Items	Mean (95% CI of Mean)	SD
I believe that vaccine is important to combat the COVID-19 pandemic	3.60 (3.50, 3.71)	1.70
I think that COVID-19 pandemic is a serious health condition in Saudi Arabia	3.60 (3.50, 3.71)	1.71
I am confident about accuracy of COVID-19 vaccine.	3.42 (3.33, 3.51)	1.52
I am willing to get vaccinated immediately upon availability of COVID-19 vaccine	3.57 (3.46, 3.67)	1.70
I will vaccinate my children/spouse/family members if vaccine is available immediately	3.55 (3.44, 3.65)	1.71

other variables. Males reported higher likelihood mean score for acceptance. The acceptance score increased by 0.78 ($p < 0.05$) when other factors are adjusted. Besides, on comparison based on nationality, i.e., Saudi vs. non-Saudi, the likelihood score for acceptance decreased by 0.154 for Saudi citizen ($p < 0.05$), provided other variables are considered. The variables of bachelor of education, and all professions except allied health were found significant in simple regression analysis only. All other variables such as level of education, marital status, profession, and work experience were non-significant when adjusted for demographic characteristics of participants (**Table 6**).

Simple regression revealed that except for the master level of education, all variables including participants' age,

TABLE 4 | COVID-19 vaccine reluctance among staff ($N = 1,031$).

Items	Mean (95% CI of Mean)	SD
I am reluctant to get COVID-19 vaccine	1.80 (1.73, 1.88)	1.28
I am worried about possible side effects of a vaccine for myself	3.21 (3.13, 3.30)	1.35
I am worried that the rushed pace of testing the new COVID-19 vaccine may have failed to detect potential side effects or dangers	3.12 (3.04, 3.21)	1.34

TABLE 5 | COVID-19 vaccine concerns among staff ($N = 1,031$).

Concerns	Responses	
	Yes (N & %)	No (N & %)
I have following specific concerns(s) about the vaccine		
Safety (e.g., Side effects)	700 (76.9)	331 (32.1)
Efficacy	580 (56.3)	451 (43.7)
Newness, including not wanting to be the first to get the vaccine	352 (34.1)	679 (65.9)
Vaccine contents	383 (37.1)	648 (62.9)
No concerns	200 (19.4)	831 (80.6)
I need additional information about vaccine for my satisfaction		
Compatibility with personal health conditions (e.g., allergies, comorbid condition	529 (51.3)	502 (48.7)
Recommendation from doctor or officials	280 (27.2)	751 (72.8)
Timing regarding state of pandemic, personal immunity	406 (39.4)	625 (60.6)
Safety and reliability of vaccine	660 (64)	371 (36)
I do not need additional information	233 (22.6)	798 (77.4)
I believe that COVID-19 vaccine is not effective because		
Change in virus strain	572 (55.5)	459 (44.5)
Hastiness in vaccine development	140 (13.6)	891 (86.4)
Rush in Vaccine testing process	277 (26.9)	754 (73.1)
Less information available about safety of vaccine	313 (30.4)	718 (69.6)
All of above	268 (26)	763 (74)

nationality, marital status, bachelor and doctorate levels of education, professions (physician, nurse, and allied health), and work experience were significantly associated with reluctance toward COVID-19 vaccine. The multiple model for COVID-19 vaccine reluctance revealed that for a change in age group from $\leq$ 40 years to $>$ 40 years, the reluctance score increased by 0.094 ($p < 0.05$), provided other variables are constant. Besides, considering gender, compared to females, the reluctance score increased by 0.079 ($p < 0.05$) for males, when other factors are considered. Further, while considering the nationality of participants, the reluctance score increased by 0.070 ($p < 0.05$) for Saudi participants compared to non-Saudis, when adjusted for participant's demographics. Moreover, for profession, the reluctance score decreased to 0.108 ($p < 0.05$) for physicians when compared to non-physicians, when all other demographic factors are considered. On the contrary, the reluctance score increased by 0.072 ($p < 0.05$) for allied health profession compared to others while adjusting for participant's demographics (**Table 7**).

DISCUSSION

It could be argued that vaccines are perhaps among the strongest measures that could help mitigate the risk of the COVID-19 infection and its resultant impact on the daily lives. Vaccination against the viral infection could help reduce its spread, thereby reducing the likelihood of reversing the preventive measures that impact daily life. This large-scale multicenter study was conducted to document the confidence of staff working at healthcare facilities of Saudi Arabia, regarding vaccination against COVID-19 infection.

It was observed that most of the staff were quite positive toward vaccination, as more than 90% mentioned that they registered themselves for vaccination through the web application as soon as it became available. At the time of data collection, almost 90% of the respondents had taken their second dose. In this context, a study among healthcare workers in the US reported that out of every 20 participants surveyed, 3 were found to be hesitant (17). On the other hand, another study in the same population in Germany reported a vaccine acceptance of 91% (18).

Secondly, the respondents showed good acceptance of COVID-19 vaccine, as the average mean score for the items regarding the same was 3.55 out of 5. In this context, a study among healthcare workers in the neighboring country of the UAE reported that vaccine acceptance was high (>89%) (19). Similar finding was reported from the same population in Kuwait (20). The staff shared their opinion that vaccine was important in addressing the pandemic, and acknowledged it as a serious issue in the country. Several studies conducted among the general population of Saudi Arabia reported an increased readiness to vaccinate, and most participants held positive perceptions about the vaccines. However, a sizeable portion of the population also showed their reluctance with concerns regarding safety (21). Another study conducted among a small sample of healthcare workers in Saudi Arabia highlighted that 50% were willing to receive a vaccine, out of which roughly 49% seemed willing to receive it immediately upon availability (22). Another study reported an acceptance of roughly 65% (23). However, the timeline of data collection for both studies was up to December 2020. Our study has been relatively recent and highlights that this acceptance greatly increased and literally doubled in the following year. Such an occurrence shows the increase in confidence of healthcare staff toward vaccination.

The Organization for Economic Cooperation and Development (OECD) mentions that public trust in vaccines against COVID-19 is as important as the effectiveness of the

TABLE 6 | Model for COVID-19 vaccine acceptance among staff ($N = 1,031$).

Characteristics	Simple Regression		Multiple Regression		
	Coefficient (β)	*p*-value	Coefficient (β)	*p*-value	VIF
Age (in year)					
≤40 vs. >40	−0.013	0.679	–	–	–
Gender					
Male vs. Female	0.122	<0.001	0.078	0.041	1.55
Nationality					
Saudi vs. Non-Saudi	−0.175	<0.001	−0.154	<0.001	1.11
Marital status					
Single vs. Married	0.049	0.114	–	–	–
Bachelor education					
Yes vs. No	0.141	<0.001	0.076	0.111	2.41
Masters' education					
Yes vs. No	−0.045	0.147	–	–	–
Doctorate education					
Yes vs. No	−0.131	<0.001	−0.024	0.609	2.39
Physician (Profession)					
Yes vs. No	−0.127	<0.001	0.026	0.573	2.34
Nurse (Profession)					
Yes vs. No	0.132	<0.001	*	*	*
Allied Health (Profession)					
Yes vs. No	−0.023	0.453	–	–	–
Work Experience (in years)					
≤15 vs. >15	0.010	0.757	–	–	–

Removed from model due to Multicollinearity problem, Multiple regression model applied. Model fitness tested by: ANOVA ($F = 10.078$, $p = <0.001$); $R^2 = 0.047$ and adjusted $R^2 = 0.042$.

vaccines, and the actions of the governments to increase this trust could be a determinant for their success (24). According to published sources, Saudi health authorities approved the use of vaccine for preventing COVID-19 as early as December 2020 and prioritized geriatrics and healthcare workers to receive the vaccine (25). Later, two more vaccines were approved for use (23). Moreover, the health authority launched the web applicaton to register for receiving a vaccine. The receipients were able to book a date as early as 24 h (26). Such measures were pivotal in increasing the uptake of vaccines by the residents. Hence, these might be the reasons as to why there was an increase in acceptance compared to previous studies. However, this change also points to the fact that such opinions toward vaccination have been largely fluid and may not be consistent. Therefore, it is imperative that such measures are continued to ensure that acceptance remains consistent or improves further.

Further, it was reported that the average mean score for reluctance toward a COVID-19 vaccine was 2.71 out of 5. Although it was low, and given the fact that 90% of the participants received a vaccine, it still cannot be ignored. A high mean score >3 was observed for the statement regarding worry about adverse effects of vaccine. This apprehension was also reported by participants in previous studies (21, 23). Moreover, another statement with a high mean score for reluctance >3 was about the failure to detect dangerous adverse effects due to the rushed pace of vaccine development. This occurrence was also witnessed as health regulators found rare adverse effects such as blood disorders and myocarditis as a consequence of receiving COVID-19 vaccines (27, 28). To this end, a study in Qatar reported that a small proportion of healthcare workers, roughly 13%, had vaccine hesitency (29).

An important finding was that more than half of the participants were of the view that the vaccine may not remain effective owing to the mutations that occur in a circulating virus. The healthcare workers in Qatar also had doubts over vaccine's protection (29). According to the World Health Organization (WHO), the currently available vaccines may not become completely ineffective in the face of emerging variants and would continue to offer reasonable protection against these new variants. However, it is imperative that measures are taken to reduce the spread so as to reduce the likelihood of the virus to mutate into a new variant (30).

There is a massive drive for vaccination in MNGHA hospitals. The organization had a dedicated vaccination center in each hospital for staff at the time of writing. Therefore, vaccine related information is readily availabile and accessible. The availability of vaccine is ensured within the hospital. This study had a limitation. It was not possible to estimate the response rate and at the same time, considering the online nature of study, the

TABLE 7 | Model for COVID-19 vaccine reluctance among healthcare staff (*N* = 1,031).

Characteristics	Simple Regression		Multiple Regression		
	Coefficient (β)	*p*-value	Coefficient (β)	*p*-value	VIF
Age (in year)					
≤40 vs. >40	0.130	<0.001	0.094	0.045	2.73
Gender					
Male vs. Female	0.139	<0.001	0.079	0.041	1.60
Nationality					
Saudi vs. Non-Saudi	0.062	0.048	0.070	0.044	1.28
Marital status					
Single vs. Married	0.086	0.006	0.027	0.421	1.17
Bachelor level of Education					
Yes vs. No	0.085	0.006	−0.047	0.338	2.56
Masters level of Education					
Yes vs. No	−0.013	0.665	—	—	—
Doctorate level of Education					
Yes vs. No	−0.091	0.003	−0.021	0.664	2.40
Physician (occupation)					
Yes vs. No	−0.150	<0.001	−0.108	0.031	2.67
Nurse (occupation)					
Yes vs. No	0.096	0.002	*	*	*
Allied Health (occupation)					
Yes vs. No	0.098	0.002	0.072	0.030	1.18
Work Experience (in year)					
≤15 vs. >15	0.094	0.003	−0.014	0.763	2.18

Removed from model due to Multicollinearity problem. Multiple regression model applied. Model fitness tested by: ANOVA ($F = 5.935$, $p = <0.001$); $R^2 = 0.050$ and adjusted $R^2 = 0.041$.

response is usually low. Several email reminders were sent to overcome the issue of a low response rate. We estimate that our response rate was lower than 70%.

CONCLUSION

The findings of this study reveal that most participants were vaccinated and expressed confidence in COVID-19 vaccination. Some of the apprehensions such as adverse effects and effectiveness of vaccines on variants of COVID-19 virus were genuine and were true in retrospection. Several demographic factors affected the vaccine acceptance and reluctance.

DATA AVAILABILITY STATEMENT

The datasets presented in this article would be available from corresponding author upon suitable request. Requests to access the datasets should be directed to AL, azfar.hd@hotmail.com.

AUTHOR CONTRIBUTIONS

MM: conceptualization, interpretation and writing—original draft, revision, and editing. MI: conceptualization, methodology, analysis, validation and writing—review original draft, revision, and editing. AA: conceptualization, interpretation and writing—original draft, revision, and editing, proposal review, ethics review process, critical review of manuscript, and feedback. ZN: writing, critical review of manuscript, revision, and feedback. NA: methodology, writing, critical review of manuscript, and feedback. MA: writing, results, critical review of manuscript, and feedback. MH and AM: conceptualization, methodology and writing—review, and editing. NF: conceptualization, interpretation, critical feedback, and editing. MAA and FA: proposal review, ethics review process, critical review of manuscript, and feedback. ZA: conceptualization, interpretation, methodology, results, and writing—original draft and editing. All authors agreed on the final version for submission.

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MINI REVIEW
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COVID-19 Vaccine Hesitancy in Pakistan: A Mini Review of the Published Discourse

Sumaira Khalid[1]*, *Bilal Ahmed Usmani*[1] *and Sameen Siddiqi*[2]

[1] *Epidemiology and Biostatistics Section, Community Health Sciences, Aga Khan University, Karachi, Pakistan,* [2] *Health Policy and Management Section, Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan*

This minireview provides a summary of the main findings, features, as well as limitations and gaps in the current epidemiologic research on COVID-19 vaccine hesitancy (VH) in Pakistani population. For this purpose, data on VH studies were extracted from January 2020 to October 2021, using a systematic review and meta-analysis approach. Literature review and other narrative studies were excluded. There exists a significant heterogeneity in the reported vaccine hesitancy in the population (pooled estimates from random-effects meta-analysis: 35% (95% CI, 28–43%). However, none of the co-variables included in the studies explained the observed variance/heterogeneity in the moderator analysis models. In this minireview and critical appraisal of current VH research, we conclude that an in-depth analysis of COVID-19 vaccine hesitancy in a representative sample of Pakistani population is crucial to measure the magnitude of VH as well to explore and identify the determinants of VH in Pakistani population. This is an important step toward informing intervention and policy design and to address this issue at its root cause. To this end, focused, methodologically robust and hypothesis-driven VH research is needed using a wide range of co-variables to support a detailed coverage of the individual and environmental level VH attributes.

Keywords: COVID-19, vaccine hesistancy, population health, meta-analysis, review

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****Correspondence:***
Sumaira Khalid
sumaira.khalid@aku.edu

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The COVID-19 pandemic witnessed a surge in community health research (CHR) in Pakistan on a range of topics concerning the infection, its spread, and the potential implications for health policy and interventions. Early research focused on exploring knowledge, attitudes, and practices pertaining to prescribed preventive measures and estimation of the changing burden of COVID-19 infections in the population. After the arrival of COVID-19 vaccine, the discourse, however, shifted toward the uptake and hesitancy of vaccine in the Pakistani population. Vaccine hesitancy (VH), as defined by the WHO, is a complex and context-specific concept revolving around three main pillars: complacency, confidence, and convenience. VH is not a novice concept in Pakistan's healthcare landscape; therefore, considering the historic polio vaccination challenges, the number of CHR studies exploring COVID-19 vaccine hesitancy and acceptance, and the effect of the government's vaccine mandate in Pakistan has risen exceedingly.

Vaccine hesitancy-community health research bears implications on much larger levels including public health measures, future research directions, and policy design and implementation. VH-CHR serves three major goals: (1) measures the magnitude of the VH issue, (2) explores and identifies the determinants of the VH issue, and (3) offers an action-oriented narrative, cognizant of the rich context and features of VH in the population, to inform public health messaging, interventions, prospective research, policy design, and implementation (1–3). We suggest that the existing VH-CHR in Pakistan falls short of all the three goals, and despite the increasing number, the overall findings from individual VH studies remain inconclusive, especially in estimating (1) VH magnitude across different population subgroups, (2) determinants of different VH proportions across subgroups (e.g., small vs. large provinces), and (3) influential features and areas for a long-term action plan.

To capture a holistic account of the published VH-CHR in Pakistan, a total of 323 studies were extracted using the systematic review and meta-analysis approach, starting from January 2020 to October 2021. Of the 323 studies on COVID-19 vaccination, 72 were selected for abstract screening, 19 for full-text screening, yielding 10 eligible studies (i.e., original epidemiologic research articles) that addressed VH in Pakistani populations including 9 cross-sectional survey studies (4–12) and 1 quasi experiment-based study (13). One of the eligible studies did not report VH proportion as their primary outcome and was excluded from quantitative analysis. Assuming a significant level of heterogeneity across the studies, a random-effects meta-analysis (RMA) model was used to summarize the findings of the included studies.

ANALYSIS OF MAIN FINDINGS

Figure 1 condenses findings from the RMA model using a forest plot of the weighted VH proportions (WVPs) of the included VH studies and the overall VH proportion (pooled estimate) derived from the meta-analysis, i.e., 35% (95% CI: 29–43%, $p < 0.0001$). Only two studies' WVPs exceeded the measured pooled estimate, while 6 other WVPs were at or below the pooled estimate. Test for heterogeneity (I^2) was 98% (95% CI: 95–99, $p < 0.0001$), indicating a statistically significant presence of variation/heterogeneity across WVPs. To identify the co-variables explaining the observed variance across VH proportions, meta-regression moderator analyses were conducted on available covariates, namely, age, sex, region, study type (online vs. mixed method), and study period (**Table 1**). **Table 1** shows that none of the covariables were significant and that their contribution to explaining the observed variance/heterogeneity was unremarkable and statistically insignificant (explained by Q statistics, and *p*-values). The majority of study respondents were from Punjab province ($n = 6$) and to assess the difference in VH proportions for Punjab vs. Sindh province, a subgroup analysis was performed (**Figure 2**). The pooled VH estimate for Punjab studies (36%, 95% CI: 28–45) was higher than both the overall pooled estimate and that for Sindh (33%, 95% CI: 25–43). Test for heterogeneity was significant for the Punjab subgroup (Punjab ($n = 6$), $I^2 = 98.75\%$, Q = 400.49), while for Sindh, despite a high I^2 (93.67%, Q = 15.81; *p*-values < 0.01), it remained inconclusive on account of small subgroup size ($n = 2$). The difference across provinces was found to be statistically insignificant in the moderator analysis (Q = 0.22, *p*-value = 0.64).

Vaccine hesitancy research is crucial to provide in-depth analysis and insight into the population and environmental level determinants of the increasingly important VH issue in the country. The overall finding of relatively low vaccine hesitancy vs. vaccine acceptability in the general population (pooled estimates, respectively, 35 vs. 65%) suffers from a high degree of bias, mainly inherited from research design, underlying framework, selection and sampling, and coverage of covariates. For example, the exclusively self-administered online-based design of the studies resulted in the recruitment of a disproportionately younger study sample (aged between 18 and 30 years, an average of 23 years). This rendered "age," a potential predictor for VH in any population, an unproductive covariate. The resulting under representation of middle-aged and older adults in the current VH-CHR compromised our understanding of VH determinants and other correlates in the middle-aged and older population subgroups. Similarly, the majority of the study participants were University students, unmarried, female, had access to computers, and belonged to the middle and upper-middle socioeconomic groups. It would be exceedingly helpful to explore the relationships between rurality, ethnicity, and VH; however, the majority of the studies drew data from predominantly urban regions of Punjab and Sindh, leading to a glaring under-representation of smaller, dominantly rural provinces (e.g., Khyber Pukhtunwa, Balochistan, and Gigit-Baldistan). Similarly, those married and those with children make an important population in which to explore VH. The representation of these subgroups was highly under-whelming in current VH studies.

Similarly, other major drivers of VH, such as lower education, poor healthcare access, perceived health status, quality of life, unemployment, and homelessness, remained under-explored. Lastly, as alluded above, the frequently used self-administered online cross-sectional survey design has led to oversimplification and binarization of VH, an issue deeply rooted in ethnocultural, religious, and socioeconomic complexities.

Table 2 summarizes the major themes of the included VH studies. These themes stem from three fundamental yet intersecting elements: (1) conspiracy and religious beliefs, (2) education on COVID-19 and vaccine safety and efficacy, and (3) lack of trust. Although some of the findings suggest that the government's COVID-19 vaccine mandate might have helped in getting people vaccinated, research indicates that it is not a stand-alone driver of vaccine acceptance and compliance in the population. The repulsion of the deep-seated VH behavior and related concerns in the population would take a detailed multilevel analysis aimed at identifying the modifiable factors of VH in the individual (e.g., age, sex, educational attainment, employment type/status, and access to healthcare/insurance) and environmental (e.g., rurality, healthcare infrastructure, healthcare inequities, and public health policies) levels. For example, the demographic attributes of those with insufficient knowledge of efficacy would likely be different than those of believers in natural immunity dogma. Similarly, a subgroup that believes that a vaccine is perhaps not widely available or is

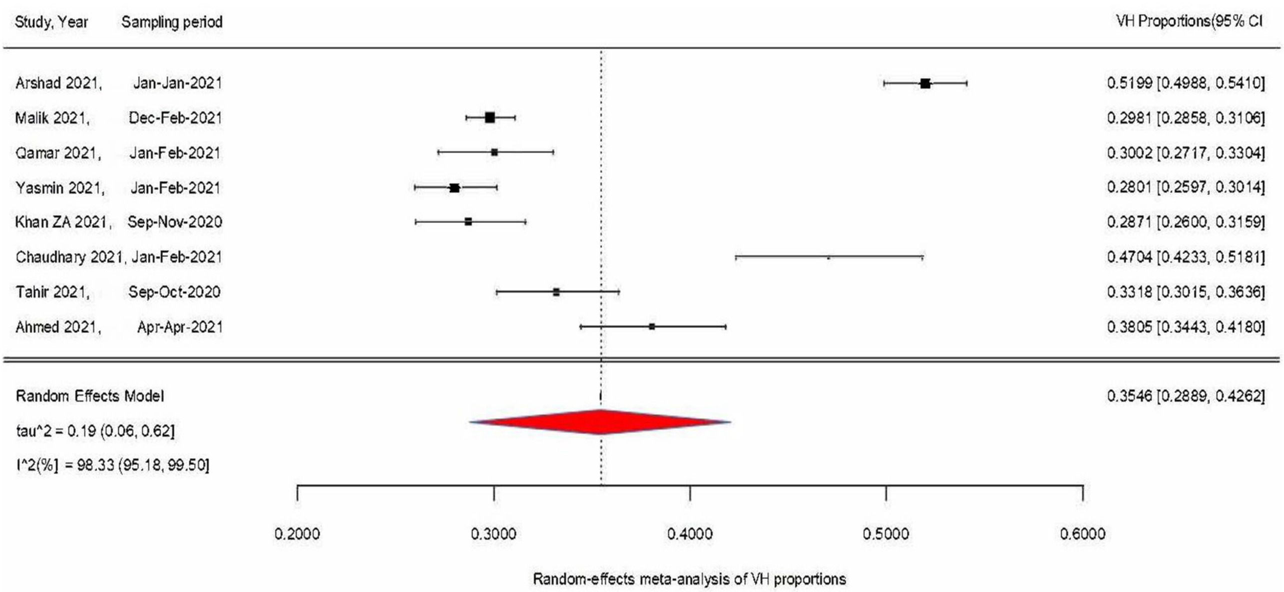

FIGURE 1 | Meta-analysis of vaccine hesitancy proportions (Jan 2020 to Oct 2021).

TABLE 1 | Meta-regression analysis: test for moderators.

Moderator	Estimate, *P*-value	*Q*, *P*-value
Age in Yrs.		1.4736, 0.9612
Mean 23–30	0.0073, 0.6729	
Majority sex		1.2030, 0.5480
Female vs. NA	0.0843, 0.5657	
Male vs. NA	−0.0417, 0.7662	
Study period		1.3606, 0.9286
Sep to Oct-2020	0.0302, 0.9014	
Sep to Nov-2020	0.0600, 0.8039	
Dec to Feb-2021	0.0534, 0.8311	
Jan to Jan-2021	−0.0913, 0.6315	
Jan to Feb-2021	0.0191, 0.9226	
Apr to Apr-2021	Reference	
Study type		0.0120, 0.9130
Online Vs. mixed	−0.0147, 0.9130	

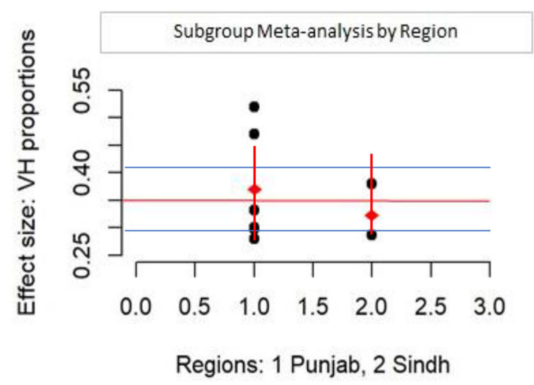

FIGURE 2 | Subgroup analysis by dominating region.

TABLE 2 | Qualitative summary of the findings from VH studies ($N = 9$).

Major themes	*N* (%)
Conspiracy beliefs/religious beliefs	3 (33)
Vaccine unavailability	2 (22)
Non-healthcare workers/care providers	2 (22)
Insufficient knowledge on efficacy and effectiveness	4 (44)
Toxicity/adverse effects/side-effects	3 (33)
Denial vs. perceived fear of COVID	2 (22)
Natural immunity dogma	2 (22)

available at a high cost might differ in features from a subgroup that believes the vaccine is toxic or ineffective. Identification of those differentiating features, which could come either from the individual or environmental level or both, is imperative for the purpose of targeted intervention and informed policy changes.

In addition to the aforementioned methodological gaps, the conceptual framework of current VH-CHR has largely been drawn on the acute VH models (i.e. short-term and reactive vs. long-term and proactive VH models) for example (1) reinforcement of vaccine mandate, (2) fear-based public health messaging, (3) calling on other non-public health bodies for engagement e.g., print, live, and online media, and (4) calling on direct care providers and healthcare practitioners to take the lead. Therefore, the current VH-CHR discourse is dominated by the notion of approximating acute VH models (points 1–4, above) as some panacea for the ingrained VH issue in Pakistan. This undermines the need for a proactive strategy that is necessary for developing long-term, sustainable, and multisectoral public health efforts. One solution could be to balance the narrative by incorporating acute and long-term factors, e.g., the momentum and advocacy of the government-imposed punitive measures and mandates could be balanced out by making inroads in quality research aimed at identifying modifiable determinants, barriers, and facilitators of VH in different ethno sectoral subgroups in Pakistan to arrive at dependable long-term solutions.

The ideological framework could also use principles of compassion and empowerment, elements that form the very crux of public health practice, by adjusting the tone and framing of the current VH-CHR away from public blaming (14). In part, this can be achieved by identifying and acknowledging the public's VH beliefs and concerns and by attempting to explore the prodromal factors rooted in the system and environmental levels.

For example, only one study included in our thematic analysis (**Table 2**) had discussed VH in the context of mistrust that was generated by frequently changing narratives of international public health agencies (13). Similarly, the phase-wise vaccine distribution and its performance in flattening the epidemic curve remain understudied in the context of the Pakistani population, a relatively young population suffering from drastic healthcare inequities. Evidence is scarce but nevertheless exists, e.g., a recent modeling study evaluated the health impact and cost-effectiveness of COVID-19 vaccine distribution in Sindh; their models demonstrated that prioritizing vaccination for elders ($\geq$65 years) could only be effective in populations with high proportions of elders or in places where the vaccination had a significantly high impact on curbing the transmission of the pathogen (15).

Long-standing VH-CHR in other countries informs that majority of individual-level VH determinants are close correlates of environmental-level factors. Countries with a strong public health infrastructure were able to address the arising VH in their populations at a much faster rate. In Pakistan, the historic lack of public health leadership remains a huge environmental-level effect mediator of VH in the nation. The resulting void is consequently providing a fertile ground for breeding theories of fear, conspiracy, and mistrust in the nation. In addition to VH, other public health challenges facing Pakistan, e.g., the alarmingly rising antibiotic pan-resistance, is also in part due to the lack of strong health infrastructure, causing unregulated clinical and dispensing practices. By mid-century, the burden of non-communicable diseases will rise inexplicably and be fuelled by an increasingly aging population. Coupled with the emergence of novel communicable diseases, it is imperative that Pakistan's major health agencies do not solely rely on policies that are born out of acute necessity and, hence, die out when the necessity goes away. In the past and during the ongoing pandemic, independent health institutions and international organizations have gathered and have partnered with government agencies to form a consortium for addressing major public health issues at hand. However, such efforts were short-lived and, perhaps because of a lack of ownership, did not translate into full-scale, long-term, and dependable solutions. We argue that in addition to addressing deep-seated public health challenges, strong public health infrastructure in the country will also foster the quality of CHR activities by (1) streamlining and sustaining public health programs and research activities, (2) resourcing and allocating large funds to high-priority and under-explored areas, and (3) provisioning early career researchers with sufficient funds to support capacity building and training activities in public health institutions nationwide.

Recent systematic and scoping reviews on COVID-19 VH and its determinants in other countries have indicated that despite low vaccine acceptance rates among Middle Eastern, African, and certain European countries (16), VH determinants and their contextual factors vary widely within and across different populations (17, 18). For example, a comprehensive review on determinants of VH in high-income countries has reported female sex, younger age, ethnic minority, and lower educational attainment to be associated with increased VH in addition to lack of trust, history of a flu shot, and absence of any chronic conditions; this may very well indicate possibilities of interactions and effect modification between different VH covariates (17). In this study, we have attempted to summarize the current, most updated VH-CHR, and its strengths and limitations. The major strength of our study is the use of rigorous systematic review and meta-analysis methodology to summarize the extant research on this topic. There are some limitations, however, that remained in our study. For example, the quality of individual studies included in our meta-analytic model could not be adequately assessed using a standard tool such as the Newcastle-Ottawa Scale for assessing the quality of observational studies in meta-analyses. The overall quality of the included studies was not very high, and the number of parameters was very limited. The application of meta-regression for moderator analysis did not yield any substantial findings for this very reason. In the future, we would like to extend this study by including studies from other countries with a socioeconomic profile similar to that of Pakistan. Other limitations include small sample size and a lack of detailed thematic analysis. Furthermore, we recommend that the existing VH-CHR narrative be revisited to increase its coverage, functionality, and rigor. This can be achieved by employing a mixed-methods research approach and by taking into account the diverse demographic features and contours of the Pakistani population. In addition to using better sampling techniques, a larger and representative sample size, and better coverage of covariates, we also recommend future studies on VH to use validated ethnographic and cross-cultural research models to undertake high-quality research with a substantial value for the public health practice and policy in Pakistan.

AUTHOR CONTRIBUTIONS

SK: conception of the study, drafting and revision of the work, analysis and visualization, final approval, and agreeing to the accuracy of the work. BU and SS: critical revision of the work, final approval, and agreeing to the accuracy of the work. All authors have read and approved the final manuscript.

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Ready for Vaccination? COVID-19 Vaccination Willingness of Older People in Austria

Lukas Richter[1]*, *Stephan Schreml*[2] *and Theresa Heidinger*[3]

[1] Department of Social Sciences, St. Pölten University of Applied Sciences, St. Pölten, Austria, [2] Department of Socioeconomics, Vienna University of Economics and Business, Vienna, Austria, [3] Department of Gerontology and Health Research, Karl Landsteiner University of Health Sciences, Krems an der Donau, Austria

In spite of findings highlighting higher health risk from infection compared to younger people, a certain percentage of older people in Austria still lack a valid vaccination certificate. The current gaps in vaccination coverage in countries such as Austria are likely to be in large part due to vaccination refusal and pose or will pose problems for the health system and consequently for all of society should the initial findings on Omicron coronavirus infectivity prove true. Surprisingly, only a few studies around the globe explicitly address older people's COVID-19 vaccination willingness. The present work therefore intends to contribute to this field by identifying factors associated with the decision for or against a vaccination among the older population in Austria. Data collected between late 2020 and early 2021 via the cross-national panel study Survey of Health, Aging and Retirement in Europe (SHARE) are used to perform multinomial logistic regression to analyse differences between COVID-19 vaccination supporters, undecided persons and rejectors. The results show that persons exhibiting a low risk assessment toward COVID-19, less health protection behaviors, lower education and belonging to households with financial burdens are significantly more likely to refuse vaccination or be ambivalent. Although multimorbidity reduces risk of vaccination refusal, poor subjective health was significantly related to a higher risk of refusing vaccination. The results point to the importance of addressing the factors related to refusal. Only by understanding these factors will it be possible to increase vaccination rates and thus minimize other restrictive measures.

Keywords: COVID-19, vaccination willingness, Austria, older people, vaccine hesitancy

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***Correspondence:**
Lukas Richter
lukas.richter@fhstp.ac.at

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INTRODUCTION

Nearly 260 million confirmed infections and five million fatalities from or with COVID-19 (1), as well as estimations from the World Health Organization that another 700,000 people could die from COVID-19 by spring 2022 in the European region alone (2) are the grim results of the SARS-CoV-2 pandemic by the end of 2021. In Austria nearly 1.1 million infections and 12,000 deaths were recorded by November 2021 (3). At completion of this paper, the country has undergone multiple lockdowns, in order to relieve the health care system with the fourth nationwide lockdown starting at the end of November 2021 (4), even though the first COVID-19 vaccinations had already been administered on Dec. 27, 2020 (5) and have been freely available to all people in Austria for several months (6).

Aim

Scientifically, vaccinations are indisputable as an effective means of combating infectious diseases (7) and, in the best case, have a reducing effect on infection, disease and transmission. Based on meta-analyses, COVID-19 vaccines have been shown to be highly effective in reducing infection and preventing severe disease progression (8, 9), additionally recent evidence suggests that transmission probability is reduced in vaccinated individuals (10). However, effective the vaccines may be, the desired consequence of this measures will only be achieved if there is an appropriate vaccination rate (11) and necessary amount of willingness in the population to get vaccinated. To achieve herd immunity, at least theoretically, recent estimates (based on data from Spain) suggest a good upper threshold of 70% for the ancestral variant, while the value for the delta variant is around 90% (12). However, it must be noted that these values vary according to multiple factors (12, 13), and that, even if the thresholds are reached, herd immunity does not constitute a panacea against the virus but requires adaptive and proactive measures.

Studies show that the COVID-19 vaccination acceptance rates at European (14) and at international level (15) varies significantly between countries. A recent review shows that of 114 countries, the acceptance rate is below 60% in 42 countries, whereby the situation is particularly diverse in Europe: At the beginning of 2021, the acceptance rate was 89% in Norway, 55% in Austria, and 47% in Hungary (16). As of December 7, 2021 (last check by the authors) 71.8% of the total population in Austria has had at least one COVID-19 vaccination and 67.6% has an active vaccination certificate (17). Even though the rapid increase of infections as of autumn 2021, followed by restrictions on unvaccinated persons and finally entering the fourth general lockdown as well as the multitude of public debates and subsequent announcement of a nationwide vaccination requirement starting in February 2022 (18) contributed to a slight increase in the coverage rate, which had been largely stagnant from August to November 2021 (17, 19), coverage rates continue to disappoint. It is noteworthy that even a certain percentage of older people in Austria continue to lack a valid vaccination certificate—18% among 55–64 year olds, 14% among 65–74 year olds, 10% among 75–84 year olds, and 13% among those 85 years and older (17)–in spite of findings highlighting higher health risk from infection for older persons as compared to younger people due to age-related physiological changes and multiple age-related comorbid conditions (20, 21). A large number of studies have demonstrated an age-related increase in health risk associated with COVID-19 infection (22, 23), which is reflected in more severe courses of disease and an increased risk of mortality (24, 25). This led many nations to prioritize their older population for vaccination at the advent of COVID-19 vaccines.

The current gaps in vaccination coverage in countries such as Austria are likely to be largely due to vaccination refusal despite availability of the vaccine (26), which poses health, economic, and ultimately social problems for society. The aim of this paper is to identify factors associated with the decision for or against COVID-19 vaccination among the older population using data of Austrian citizens.

State of Research and Hypotheses

A growing body of scientific work on the topic of COVID-19 vaccination willingness can be identified which has already led to several literature reviews (27–31). For Austria, the authors are aware of four internationally published papers (32–35) to date. Surprisingly, only a few studies worldwide explicitly address older people (36–44). Current data availability is likely to play a role here, as the second SHARE Corona Survey data—which includes data on vaccination willingness—for example, are not yet available for scientific analysis, although initial results have already been published (36). Therefore, the present work is intended to expand the knowledge on this important group, which we currently know little about.

Rather than presenting a rundown of the full state of research, the most important results, as per the authors, are highlighted, which are used to formulate hypotheses and will then be empirically tested. Results of studies on COVID-19 vaccination willingness among older adults and literature reviews will be addressed. Studies dealing with the vaccination willingness of specific groups such as parents in relation to their children (45), adolescents (32) or healthcare workers (46) are excluded.

Important factors for the willingness to receive a COVID-19 vaccination were identified as the individual *risk assessment* of a COVID-19 infection or illness on one hand (28, 29, 37–39) and *past health protection behaviors*, such as having gotten an influenza vaccination in the past, on the other hand (28, 29, 37, 40). On a theoretical level, this can be explained by Protection Motivation Theory (47). Thus, willingness to be vaccinated becomes less likely when an infection is perceived as unlikely to occur or as posing a negligible threat to health or if the recommended protective action (in this case vaccination), is perceived as ineffective or even harmful in its own right (48). With regard to *health status*, it has been shown that pre-existing illnesses or a poor subjective health status are associated with a lower rate of vaccination refusal (29, 36, 37, 49). Perceived vulnerability associated with health status (43) and the anticipated risk of infection to health (39) can be used as arguments in this context. Among the socioeconomic factors, *financially disadvantaged* individuals were shown to be more likely to refuse vaccination (28, 29, 36, 42). *Higher education level* (28, 29, 31, 37, 40, 42) and *older age* (27–29, 31, 36, 40–42) have been found to be positively associated with vaccination acceptance. In addition, differences between genders surfaced in multiple studies: men were less likely to refuse vaccination as compared to women (27, 28, 31, 36, 37, 41, 42); however, a recent Italian study came to the opposite conclusion for older people (40). Despite these individual findings, meta-analyses also reveal divergent impacts of socioeconomic factors (27–30) depending, among other things, on the surveyed groups, sociocultural factors and different measurement methods. This emphasizes the

TABLE 1 | Operationalization.

Variable		Manifestation	Distribution	Share Dataset
Vaccination willingness		0 "supporter"	0 = 55%	W8C19SAT
		1 "undecided"	1 = 22,5%	
		2 "rejector"	2 = 22,5%	
Individual risk assessment	Risk of catching COVID-19	1 "very/low risk"	1 = 66%	W8C19SAT
		2 "medium risk"	2 = 28 %	
		3 "very/high risk"	3 = 6%	
	Risk to one's own health	1 "not/a bit dangerous"	1 = 16%	W8C19SAT
		2 moderately dangerous"	2 = 30%	
		3 "quite/very dangerous"	3 = 54%	
Health risk reduction	Currently social contact reduction	0 "yes"	0 = 94%	W8C19SAT
		1 "no"	1 = 6%	
	Influenza vaccination in 2019	0 "yes"	0 = 26%	W8C19SAT
		1 "no"	1 = 74%	
Health condition	Subjective health	1 "excellent/very good"	1 = 32%	W8C19SAT; W8,
		2 "good"	2 = 43%	
		3 "fair/poor"	3 = 25%	
	Multimorbidity	0 "2+ chronic diseases"	0 = 49%	MW8, W7, W6, W5, W4
		1 "none/one chronic disease"	1 = 51%	
Autonomy	Autonomy 3-items scale	1 (low)−18 (high).	M = 10,59 SD = 2,08	W8C19SAT
Sociodemographic variables	Highest formal education	ISCED 97 classification from 0 (no formal education)−6 (high formal education)	M = 3,39 SD = 1,29	W8C19SAT, MW8, W7, W6, W5, W4 W2, W1
	Able to make ends meet	0 "fairly/easily"	0 = 90%	W8C19SAT, MW8
		1 "with great/some difficulties"	1 = 10%	
	Age	1 "<65"	1 = 19%	W8C19SAT
		2 "65–79"	2 = 57%	
		3 "80+"	3 = 24%	
	Gender	0 "female"	0 = 61%	W8C19SAT
		1 "male"	1 = 39%	

ISCED 97, International Standard Classification of Education Version 1997; M, mean; SD, standard deviation.

importance of further study on the issue, especially among older people. Based on the presented state of research the following hypotheses can be formulated:

- H_1: The lower the risk assessment, the higher the risk of refusing vaccination.
- H_2: The less health protection behavior is shown, the higher the risk of refusing vaccination.
- H_3: The better the health status, the higher the risk of refusing vaccination.
- H_4: The lower the level of education and the worse the financial situation, the higher the risk of refusing vaccination.

Furthermore, a relationship between the degree of autonomy and the willingness be vaccinated is suspected, as it had been shown that perceiving vaccination as a social norm in a persons' circle of friends and family positively influenced the acceptance of vaccination (50). Under such conditions, it can be assumed that a high degree of individual autonomy is required (51) to refuse vaccination.

H_5: The higher the level of perceived autonomy, the higher the risk of refusing vaccination.

METHODS

To test the hypotheses, data from the cross-national panel study Survey of Health, Aging and Retirement in Europe (SHARE) are used which includes data on persons aged 50 years and older living in the general population: Wave 8—COVID-19 Survey 1—Special Survey Austria (W8C19SAT) Release version: 1.0.0 (52) conducted from November 2020 to January 2021 in Austria via CATI serves were used as the main data source. In addition, data were imported from the main wave 8 survey (MW8) as well as from previous waves to minimize missing values (W7-W1). **Table 1** shows the variables, their origin and distribution, whereby the values surveyed at the closest timepoint to the observation period (mainly W8C19SAT) were used for analyses.

Sample Description

A total sample of $n = 2{,}522$ respondents in Austria serves as basis for analyses. 61% of the sample are women, the average age of the respondents is $M = 72$, 67 years ($SD = 8$, 54 years); 33% live alone, 56% in a two-person, and 11% in a three-or more-person household. 20% of the respondents have low (ISCED 0-2), 51% moderate (ISCED 3-4) and 29% have high formal education (ISCED 5-6). The more highly educated group is overrepresented, overall, the distribution structure can be described as sufficient; see **Table 1**.

Operationalization

The dependent variable is nominally coded and differentiates between respondents who, during the survey period, (0) could imagine getting vaccinated against COVID-19 should such a vaccine be made available to them (55% hereafter referred to as "supporters"), (1) were undecided (22.5% "undecided"), and (2) were planning to refuse vaccination (22.5% "rejectors").

Independent variables are divided into five dimensions—individual risk assessment, health protection behaviors, health condition, autonomy, and sociodemographic variables. For individual risk assessment, respondents were asked how threatening an infection with the SARS-CoV-2 virus would be (threat of virus) and how high they would estimate the probability of infection with the virus to their own person (probability of infection). Both items were measured using a 5-point rating scale and were grouped into three levels for analysis (see **Table 1**). For the dimension of health protection behaviors, a question on whether social contact had been reduced and another assessing whether the respondent had partaken in a vaccination against influenza in 2019 were included, these were answered with 0 "yes" and 1 "no". Health condition is measured by subjective health assessment and multimorbidity. Multimorbidity is based on a longer list of questions (e.g., diabetes or high blood sugar etc.) and is coded as 0 "2+ chronic diseases" and 1 "none/one chronic disease". This is due to the consideration that in comparison to persons with multimorbidity (reference group), the chance of belonging to the group of rejectors should increase for persons with no or only one chronic disease. Autonomy is measured using the subscale of the Psychological Well-being Scale of Ryff & Keyes (51) which calculates an additive index from 1 to 18 (low to high autonomy). According to Ryff & Keyes (51) a person with high scores should be independent and resists social pressure.

In addition, sociodemographic variables are included in the analyses. Education is classed into the International Standard Classification of Education (ISCED) for international comparability in SHARE [for more information, see the release guide of wave 8, see (52)]. For analyses, the variable ISCED97—0 = no formal education to 6 = high educational attainment—is used. Since ISCED data were largely unavailable at the time of the analysis in wave 8, this information had to be imported from previous survey waves. Financial situation is depicted using a question on the extent of difficulty for a household to make ends meet in a month; the 4-point scale was summarized in 0 "fairly/easily" and 1 "with great/some difficulties". Age is coded as 1 "< 65", 2 "65–79" and 3 "80+", gender as 0 "female" 1 "male".

Statistical Analysis

Data analysis was conducted using IBM SPSS 27 and unweighted data was used for analysis. To test the hypothesized associations multinomial logistic regression (a method that generalizes logistic regression to multiclass problems) was performed to analyse all three groups (supporters, undecided and rejectors) together. For the statistical model, the category "supporter" was chosen as the reference category in the dependent variable; accordingly, the effects of the independent variables are to be considered in relation to the reference group. In order to check the goodness of fit, independent logical regression models were additionally calculated—among others, the values of the area under the receiver operating characteristic curve (ROC AUC) are shown below.

RESULTS

For statistical requirements linearity was assessed using the Box and Tidwell (53) procedure and all metric variables were found to follow linearity to the logit. Goodness of fit for both independent models—supporters vs. undecided [Nagelkerke's $R^2 = 0.132$ Hosmer–Lemeshow test (8) = 2,703; $p = 0.952$ and ROC AUC = 0.696] and supporters vs. rejectors [Nagelkerke's $R^2 = 0.273$ Hosmer–Lemeshow test (8) = 2.730; $p = 0.950$ and ROC AUC = 0.777] are deemed acceptable. Consequently, the multinomial logistic regression with 2116 respondents was calculated [$X^2(30) = 440.238$, $p = 0.001$]. Pearson's chi-square test [$X^2(3380) = 3419.328$, $p = 0.314$] and deviance chi-square [$X^2(3380) = 3062.774$, $p = 1.00$] indicate a good fit and Nagelkerke's $R^2 = 0.218$ is deemed acceptable.

Table 2 shows the results of the multinomial logistic regression. Factors significantly associated with being in the group of undecided persons were found to be classification of risk of catching SARS-CoV-2 virus as moderate (odds ratio or OR 1.765), not having participated in the influenza vaccination in 2019 (OR 3.473), not having any or only one chronic disease(s) (OR 1.362) and reporting financial difficulties (OR 2.308). Being in very good health (OR 0.665), having a higher level of education (OR 0.843) and belonging to the 65–79 age group (OR 0.686) led to a reduction of probability to identify as undecided and a higher likelihood to be classed as a supporter of vaccination.

Persons were more likely to be classed as rejectors as compared to supporters if they assess the threat posed by COVID-19 as moderate (OR 1.664), or low (OR 2.591), did not currently reduce their social contacts (OR 2.083), did not get vaccinated against influenza in 2019 (OR 9.459), reported no or one chronic disease (OR 1.549) and had financial difficulties (OR 3.267). Like the comparison undecided/ supporters, a very good state of health (OR 0.525), higher level of education (OR 0.826) and belonging to the age group 65–79 (OR 0.724) lead to a reduction in likelihood to be part of the rejector group.

It is apparent, that the structure of *supporters vs. undecided* and *supporters vs. rejectors* is similar, with autonomy, health status and socioeconomic variables showing particularly striking similarity across both comparisons. Slight differences in individual risk assessment and health protection behavior can be observed: While undecided persons and supporters do not differentiate along the assessment of threat posed by COVID-19, the probability of being undecided increases when the own risk of infection is assessed as low. The reverse is true when comparing supporters and rejectors: while there is no differentiation along the assessment of own risk of infection,

TABLE 2 | Multinomial logistic regression vaccination willingness (supporter vs. undecided and supporter vs. refuser).

		Undecided				Refuser			
Dimension	**Variable**	**Odds Ratio**	**95% CI**		***p***	**Odds Ratio**	**95% CI**		***p***
Individual risk assessment	Risk of catching Corona (ref. very/high risk)								
	Moderate risk	**1.765**	1.024	3.042	0.041	1.076	0.631	1.834	0.788
	Very/low risk	1.477	0.870	2.506	0.148	1.211	0.728	2.013	0.461
	Dangerous for your health (ref. quite/very dangerous)								
	Moderately dangerous	1.192	0.912	1.559	0.198	**1.664**	1.258	2.202	0.000
	Not/a bit dangerous	1.223	0.851	1.757	0.276	**2.591**	1.853	3.623	0.000
Health defense behavior	Currently social contact reduction (ref. yes)								
	No	1.153	0.677	1.965	0.600	**2.083**	1.318	3.293	0.002
	Influenza vaccination in 2019 (ref. Yes)								
	No	**3.473**	2.589	4.660	0.000	**9.459**	6.235	14.348	0.000
Autonomy	1 (low autonomy)−18 (high autonomy)	0.973	0.922	1.027	0.316	1.033	0.977	1.092	0.255
Health condition	Subjective health (ref. fair/poor)								
	Good	1.025	0.759	1.384	0.872	0.798	0.585	1.089	0.155
	Very good/excellent	**0.665**	0.468	0.945	0.023	**0.525**	0.369	0.748	0.000
	Multimorbidity (ref. 2+ chronic diseases)								
	None/one chronic disease	**1.362**	1.067	1.739	0.013	**1.549**	1.205	1.991	0.001
Sociodemographic variables	ISCED 97 classification: 0 (no formal education)−6 (high formal education)	**0.843**	0.767	0.926	0.000	**0.826**	0.749	0.911	0.000
	Able to make ends meet (ref. fairly/easily)								
	With great/some difficulties	**2.308**	1.537	3.467	0.000	**3.267**	2.204	4.845	0.000
	Age (ref. 80+)								
	65–79	**0.686**	0.517	0.912	0.009	**0.724**	0.532	0.983	0.039
	<65	0.720	0.497	1.042	0.082	0.921	0.634	1.338	0.666
	Gender (ref. female)								
	Male	0.865	0.682	1.096	0.230	0.990	0.779	1.259	0.935
	X^2/df/*p*	440.438/30/0.001							
	Nagelkerkes R^2	0.218							
	N	2,116							
	Pearson's Chi^2/deviance Chi^2	3,419.328, $p = 0.314$/3,062.774, $p = 1.00$							

Values marked in bold are significant.

the probability of belonging to the group rejecting a vaccination increases when threat of a COVID-19 infection is assessed as lower. Correspondingly, as the threat of the virus is estimated as less severe, social contact reduction is seen less often in this group as compared to supporters. Results of the comparison of supporters vs. rejectors are discussed in more detail below.

DISCUSSION

Focussing on the first two dimensions (health risk assessment and health protection behaviors) it seems clear that a low perception of threat posed by the virus, lack of prior (influenza vaccination) and current (reduction of social contact) health protection behaviors increase the risk of being classed among the persons rejecting a COVID-19 vaccination. All of these factors thus indicate underestimation of risk and, according to the Protection Motivation Theory (47), make willingness to get vaccinated less probable. Therefore, H_1 and H_2 can be largely confirmed based on the data, with the notable limitation that supporters and rejectors do not differ in respect to the estimated risk of COVID-19 illness (probability of catching COVID-19). Based on Protection Motivation Theory it follows that it is not the perceived risk of getting infected with the virus, but rather the perceived consequences of such an infection for one's own health (severity of expected health problems), which fundamentally differentiates between these two groups. Conclusively, previous results are confirmed (29, 37).

The unexpected result concerning health status, which contradicts expectations set out in H_3, must be considered as problematic: assessment of health status as good or fair reduces the risk of rejecting the vaccine by a factor of 0.53, i.e., a negative health assessment lead to a higher probability of refusing vaccination among older respondents. Not only do rejectors show a higher predisposition for infection due to their comparative lack of health protection behaviors but may also have an increased risk for severe courses of illness due to their poorer health status. Results using SHARE data from the summer of 2021 also showed an association between negative assessment of health status and more frequent refusal of vaccination in Bulgaria, Estonia, Latvia and Slovenia whereas no significant correlation has been found in other countries (36). However, as the second variable depicting health status (multimorbidity) followed the hypothesized direction (multimorbidity patients were less likely to reject the vaccination), H_3 cannot be fully rejected.

H_5 must be rejected based on the empirical analysis: Autonomy does not seem to be related to the decision to be vaccinated. At first glance, this may seem surprising, as the image of the "autonomous rejectors" is often perpetuated by the media. It is likely, that especially in the beginning of vaccination debates, both camps contained a broad cross-section of people with a high and low degree of autonomy. Further studies should examine this aspect, as the group of rejectors is or has become smaller probably due to increasing social pressure.

Hypothesis H_4 can be confirmed by the present study and thus supports many of the international findings (28, 29, 36, 42). In short, the higher the level of education and the better the financial means, the lower the risk of refusing Covid-19 vaccination. In addition, gender has no influence, which is also confirmed by another study (36) for Austria, and the age group 65–79 years has a lower risk of refusing vaccination as compared to the oldest old (80+ years). Comparing our used data of the special SHARE survey Austria with the results of the second SHARE Corona Survey (36), a clear reduction of the group of "undecided" persons between the two survey time points—about 8 months apart—can be found, however the block of rejectors remained relatively strong in summer 2021 with 15% (in contrast to 22.5% in the end of 2020/early 2021).

As a limitation, it must be noted that the study presented only a fraction of variables, which is reflected in the level of Nagelkerke's R^2. In particular, the exploration of the motivations for and against vaccination of the older population against the socioeconomic background could provide further insights. In view of the different acceptance rates in Europe, caution is required when generalizing the results also because the situation is currently undergoing rapid change. Further analysis is needed to better understand the remaining core of rejectors.

CONCLUSION

This study points to the importance of understanding reasons for vaccination rejection. Only by understanding these factors it will be possible to increase vaccination rates and thus minimize other restrictive measures put in place to stop the pandemic spread. It seems particularly alarming that people with a poor subjectively health assessment had a higher risk of being among the refusers, and that socioeconomic status plays a considerable role. The question of how these groups can be activated for health measures, which has been raised before and will continue to be asked, will play an important part in the management, and hopefully the end of this health crisis. At least in Austria, the pandemic has proven once again that social inequalities become manifest in health behavior and, arguably, in health inequalities.

DATA AVAILABILITY STATEMENT

This paper uses data from SHARE Waves 1, 2, 4, 5, 6, 7 and 8 (DOIs: 10.6103/SHARE.w1.800, 10.6103/SHARE.w2.800, 10.6103/SHARE.w4.800, 10.6103/SHARE.w5.800, 10.6103/SHARE.w6.800, 10.6103/SHARE.w7.800, 10.6103/SHARE.w8.800, 10.6103/SHARE.w8ca.800), see Börsch-Supan et al. (2013) for methodological details.

AUTHOR CONTRIBUTIONS

LR was the primary author of this manuscript. Analysis and writing were done in collaboration with SS and TH. All authors contributed to the article and approved the submitted version.

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COVID-19 Pandemic Impact on Cardiometabolic Markers in Adults in Chongqing, China: A Retrospective Cohort Study

Zhongxiang He[1], *Yong Zhang*[1,2], *XiaoYang Xu*[1], *Ying Mei*[1], *Jamal Rahmani*[3], *Shaikh Sanjid Seraj*[4] *and XiaoYa Qi*[1]*

[1] Department of Health Management, The Second Hospital Affiliated With Chongqing Medical University, Chongqing, China, [2] School of Public Health and Health Management, Chongqing Medical University, Chongqing, China, [3] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4] Walsall Manor Hospital, Walsall Healthcare NHS Trust, Walsall, United Kingdom

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***Correspondence:**
XiaoYa Qi
2766922286@qq.com

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The influx of COVID-19 infection and government-enforced lockdowns and social isolation changed people's lifestyles. Concerns regarding the health impact of the COVID-19 pandemic due to the new sedentary lifestyle. This study aims to investigate the impact of the COVID-19 pandemic on cardiovascular health factors. A retrospective observational study was conducted using historical medical records. The cohort consisted of healthy adults (without chronic non-communicable diseases) over 18 years of age who have undertaken a health examination at the Chongqing Medical University from 2019 to 2020. The analysis of covariance (ANCOVA) test was used to compare variables between 2019 and 2020. The effect of exposure time to COVID-19 on cardiometabolic markers was analyzed using multiple linear regression models. 29,773 participants took part in this study. The average age was 42.5 ± 13.44 years at baseline, and the average follow-up period was 12.7 ± 2.8 months. Analysis showed that weight, BMI, waist circumference, hip circumference, WHR, fasting blood glucose, TG, LDL, uric acid, and liver enzymes increased significantly during the COVID-19 pandemic ($P < 0.05$). This study showed evidence that the COVID-19 pandemic and its control measures negatively impacted cardiometabolic profiles.

Keywords: COVID-19, cardiometabolic profiles, obesity, sedentary lifestyle, lockdown

INTRODUCTION

More than 200 million confirmed cases and more than 5 million deaths have been estimated to be caused by COVID-19 at the end of 2021 (1).

China has taken strict measures to prevent COVID-19 from spreading in the community, including city lockdowns, quarantines, social-distance orders, stay-at-home orders, and travel restrictions (2, 3). Government-enforced social isolation encouraged people to reduce unnecessary activities such as working, studying, shopping, and entertainment. In a bid to accommodate this lifestyle change, online activities have replaced daily routine activities (4).

Furthermore, COVID-19 has raised significant concerns about its impact on health and wellbeing (4). However, the specific health impacts of social isolation policies on the general population have remained unclear. This study aims to examine the impacts of the COVID-19 pandemic on cardiometabolic health, through a retrospective cohort that took physical examinations between 2019 and 2021.

MATERIALS AND METHODS

Study Design

A retrospective cohort study was conducted using historical medical records to compare the COVID-19 pandemic impact on cardiometabolic markers (comparing cardiometabolic markers before the outbreak of COVID-19 with 1 year after the start of the outbreak). This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University and conducted on the principles of the Helsinki Declaration (No. 2020-252).

Participants

Adults (without non-communicable diseases) aged 18 years and over underwent medical examinations at the Second Affiliated Hospital of Chongqing Medical University in 2019 and 2020. Medical check-up records from January 2019 to December 2020 were retrieved from the hospital information system (HIS). As the Medical Health Center was almost closed from February to March 2020 due to the COVID-19 outbreak in China, those who had health examinations before April were also excluded from the analysis.

Data Collection

The anthropometric data (weight, height, and waist and hip circumferences) and blood pressure were measured by trained staff following standard procedures. Bodyweight (kg) and height (cm) were measured in light clothing and without shoes using calibrated digital scales and stadiometers. Body mass index (BMI) was calculated as the weights and heights of participants. Waist and hip circumferences were measured in centimeters with a soft tape scale while participants were standing and wearing no heavy outer garments. Waist circumference (WC) was measured at the level of the umbilicus, and hip circumference was measured at the level of the greater trochanters. Waist-to-hip ratio (WHR) was computed as WC divided by hip circumference. An Omron digital monitor was used for the automated measurement of blood pressure and heart rate.

In this study, blood samples were collected *via* venesection between 7:30 am and 12:00 am after the participant had fasted at least 12 h prior. All blood samples were used to perform biochemical analyses using standard laboratory procedures. These analyses included plasma glucose (mmol/L), glycated hemoglobin (HbA1c, %), high-density lipoprotein cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), total serum cholesterol (TC, mmol/L), triglyceride (TG, mmol/L) levels, plasma uric acid (μmol/L), aspartate aminotransferase (IU/L), and alanine aminotransferase (IU/L).

Data Analysis

Continuous variables are presented as means ± *SD*s and categorical variables are described with frequency and

TABLE 1 | Characteristics of participants at baseline of 2019.

Variables	*N*	Mean ± SD	Male		Female	
			N	Mean ± SD	*N*	Mean ± SD
Age (year)	29,973	42.50 ± 13.44	16,821	42.00 ± 13.11	13,152	43.15 ± 13.81
Height (cm)	29,973	164.58 ± 8.21	16,821	169.59 ± 6.11	13,152	158.16 ± 5.68
Weight (kg)	29,973	63.93 ± 11.89	16,821	70.61 ± 10.25	13,152	55.38 ± 7.61
BMI (kg/m^2)	29,973	23.52 ± 3.26	16,821	24.53 ± 3.13	13,152	22.15 ± 2.94
Waist (cm)	27,271	80.24 ± 9.95	15,385	85.15 ± 8.30	11,886	73.89 ± 8.17
Hip (cm)	27,265	93.78 ± 6.32	15,381	96.11 ± 5.69	11,884	90.77 ± 5.81
Waist hip ratio	27,265	0.85 ± 0.07	15,381	0.89 ± 0.06	11,884	0.81 ± 0.06
SBP (mmHg)	29,938	120.01 ± 16.68	16,814	123.69 ± 15.55	13,124	115.31 ± 16.88
DBP (mmHg)	29,938	73.05 ± 11.12	16,814	76.06 ± 11.09	13,124	69.21 ± 9.86
FBG (mmo/L)	25,793	5.02 ± 1.07	14,699	5.11 ± 1.22	11,094	4.89 ± 0.81
HbA1c (%)	31,53	5.77 ± 0.89	1,890	5.81 ± 0.96	1,263	5.71 ± 0.77
TC (mmo/L)	27,895	4.96 ± 0.91	15,990	4.94 ± 0.90	11,905	4.98 ± 0.91
TG (mmo/L)	27,896	1.61 ± 1.44	15,990	1.89 ± 1.72	11,906	1.23 ± 0.78
HDL (mmo/L)	22,043	1.37 ± 0.31	12,105	1.28 ± 0.27	9,938	1.49 ± 0.31
LDL (mmo/L)	22,043	2.49 ± 0.67	12,105	2.57 ± 0.67	9,938	2.39 ± 0.66
UA (μmol/L)	28,175	349.62 ± 93.45	16,029	398.03 ± 82.99	12,146	285.73 ± 63.20
AST (IU/L)	26,835	21.77 ± 12.36	15,389	23.49 ± 14.47	11,446	19.46 ± 8.21
ALT (IU/L)	29,251	24.44 ± 25.32	16,602	30.00 ± 30.79	12,649	17.15 ± 12.01

BMI, body mass index; WHR, waist to hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fast blood glucose; HbA1c, hemoglobin A1c; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

TABLE 2 | Paired difference of cardiometabolic markers between 2019 and 2020.

Variables	*N*	Paired difference	SD	*P* value*	*P* value#
Weight	29,973	0.40	2.71	<0.001	<0.001
BMI	29,973	0.15	0.99	<0.001	<0.001
Waist	15,112	0.24	5.77	<0.001	<0.001
Hip	15,109	0.27	4.52	<0.001	<0.001
WHR	15,109	<0.0012	0.05	0.671	0.04
SBP	29,921	0.67	12.93	<0.001	0.06
DBP	29,922	−0.15	9.24	0.005	0.01
Glu	24,794	0.02	0.71	<0.001	0.007
HbA1c	1,224	0.04	0.57	0.008	0.08
TC	26,311	0.02	0.68	<0.001	0.73
TG	26,312	0.03	1.26	<0.001	<0.001
HDL	20,295	−0.02	0.22	<0.001	<0.001
LDL	20,295	0.30	0.50	<0.001	<0.001
UA	27,220	10.33	55.07	<0.001	0.002
AST	25,669	0.01	15.10	0.910	<0.001
ALT	28,565	0.17	28.73	0.311	<0.001

*P-value calculated with paired samples test.

#P-value calculated with ANCOVA and the weight, BMI, waist, hip, and WHR adjusted for age and sex and other outcomes adjusted for age, sex, and BMI.

BMI, body mass index; WHR, waist to hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fast blood glucose; HbA1c, hemoglobin A1c; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

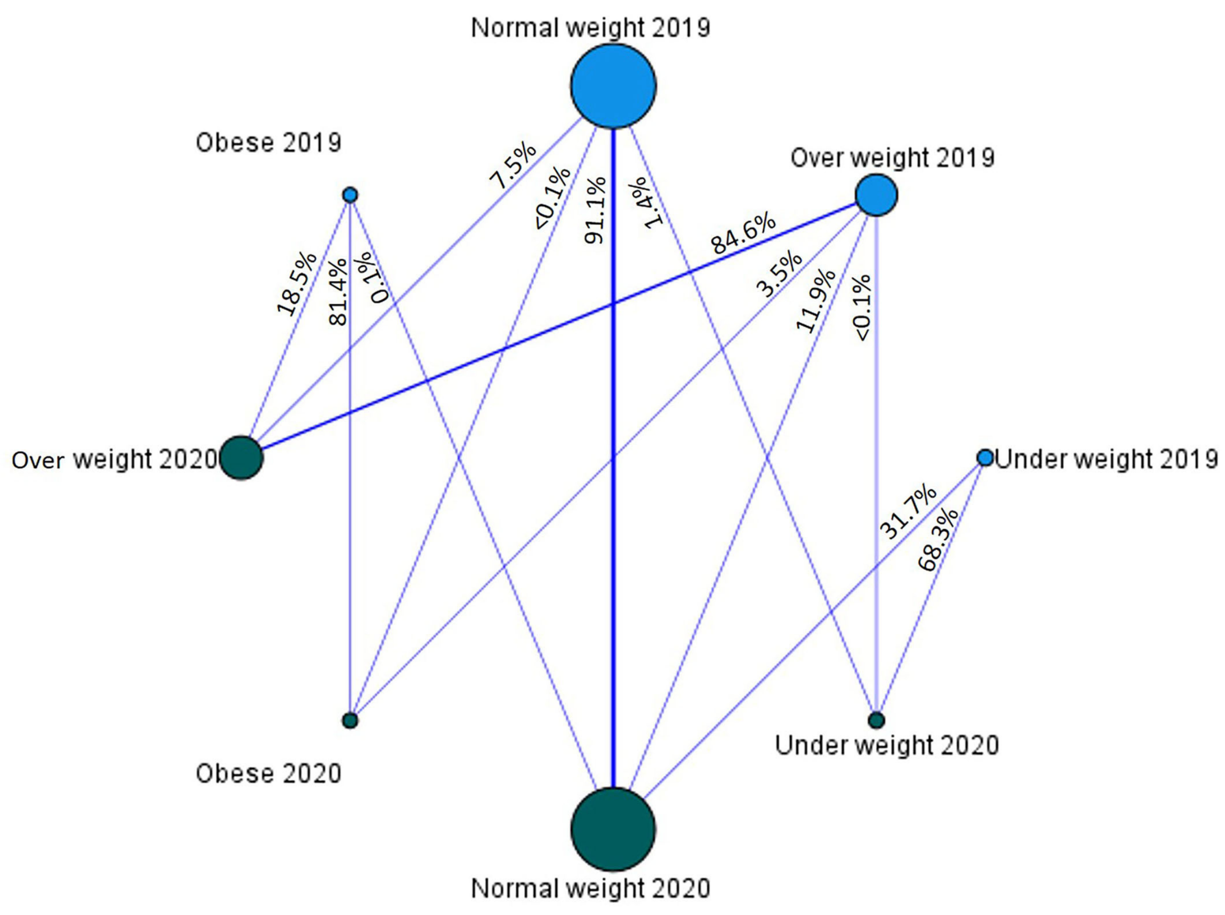

FIGURE 1 | The flow graph of BMI categories between 2019 to 2020 (*P* value < 0.001).

percentages. Mean paired differences of each participant were compared with zero. The *P*-value was assessed using the Independent sample *t*-test for quantitative variables and the chi-square test for qualitative variables. The paired t-test was used to compare variables between 2019 and 2020 in raw conditions, and the analysis of covariance (ANCOVA) test was used to compare variables between 2019 and 2020 by adjusting covariates. A multiple linear regression model was used to evaluate the association between exposure time of the COVID-19 pandemic and cardiometabolic markers (after adjustment for age, gender, and height). Statistical significance was set at $p < 0.05$. All analyses were performed with the SPSS 26 statistical software package (SPSS Inc, Chicago, IL, USA).

RESULTS

Characteristics of the Established Retrospective Cohort

A total of 327,879 records (129,046 in 2019 and 198,833 in 2020) were retrieved, and 31,788 persons with the matched ID number in 2019 and 2020 were selected. After excluding those with age <18 and those with missing or outlier data, 29,773 participants were included in the study. In this cohort, 16,821 (56.12% of the total) participants were men, and the mean age of participants was 42.5 ± 13.44 years and the mean follow-up time was 12.7 ± 2.8 months. Other characteristics and baseline measurements in 2019 are presented in **Table 1**.

COVID-19 Pandemic and Cardiometabolic Markers

The paired differences in cardiometabolic markers in the same person between 2020 and 2019 are presented in **Table 2**. The raw data showed that weight, BMI, waist circumference, and hip circumference, systolic blood pressure, fasting blood glucose, HbA1c, blood lipids (HDL decreased), uric acid increased ($P < 0.05$) in this cohort due to exposure to COVID-19 pandemic; no significant change was observed for the two liver enzymes ($P > 0.05$). Unlike ALT and AST ($P > 0.05$), the adjusted analysis showed that weight, BMI, waist circumference, hip circumference, WHR, fasting blood glucose, TG, LDL, uric acid, and liver enzymes increased ($P < 0.05$), whereas HDL levels decreased significantly ($P < 0.05$) in this cohort due to exposure to COVID-19 pandemic.

The BMI category flow graph between 2019 and 2020 is provided in **Figure 1**. It showed that 7.5% and <1% of the normal-weight people in 2019 followed to overweight and obese categories in 2020, respectively. Furthermore, 3.5% of overweight people in 2019 flowed to the obese category in 2020.

The Duration of COVID-19 Pandemic Exposure and Cardiometabolic Markers

Duration of exposure to COVID-19 was measured in months. Multiple linear regression analysis was performed to test the relationship between exposure duration and cardiometabolic markers. Results showed that exposure was positively associated with weight, BMI, systolic blood pressure, and uric acid ($P < 0.05$), while as negatively related to changes in HDL and AST ($P < 0.05$), with no effects on the waist, DBP, TG, and ALT ($P > 0.05$) (**Table 3**).

TABLE 3 | Multiple linear regression analysis exposure length of COVID-19 and paired changes of cardiometabolic markers.

Variables	*B**	SD	*P* value
Weight	0.125	0.008	<0.001
BMI	0.046	0.003	<0.001
Waist	0.005	0.025	0.854
Hip	0.070	0.019	<0.001
WHR	−0.001	0.001	0.011
SBP	0.349	0.038	<0.001
DBP	−0.047	0.027	0.078
FBG	0.008	0.002	0.001
HbA1c	0.034	0.009	<0.001
TC	0.033	0.002	<0.001
TG	−0.007	0.005	0.113
HDL	−0.007	0.001	<0.001
LDL	0.059	0.002	<0.001
UA	0.681	0.175	<0.001
AST	−0.122	0.048	0.010
ALT	−0.142	0.087	0.104

B: adjusted regression coefficient of exposure length of COVID-19 and cardiometabolic markers. Sex, age, and height were adjusted.*
BMI, body mass index; WHR, waist to hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fast blood glucose; HbA1c, hemoglobin A1c; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Impact of COVID-19 Pandemic Exposure on Cardiometabolic Markers According to Gender

Figure 2 provides a percent chance of cardiometabolic markers according to sex difference in 2020 rather than 2019. The weight, BMI, waist, hip, WHR, and other outcomes were adjusted for age and sex. These results showed that weight, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) increased in females more than in males ($P < 0.05$) during pandemic exposure, but WHR, TC, and TG were higher in males compared to female ($P < 0.05$).

COVID-19 Pandemic Exposure to Cardiometabolic Markers According to BMI Categories

Figure 3 provided a percent change in cardiometabolic markers according to BMI categories in 2020 rather than 2019. The weight, BMI, waist, hip, and WHR are adjusted for age and sex, and other outcomes are adjusted for age, sex, and BMI. These results showed that the increase in weight, BMI, waist, hip, WHR, SBP, AST, and ALT are highest in lower BMI categories compared to those with higher BMI ($P < 0.05$). Whereas the rise in fasting blood glucose is more significant in participants with higher BMI compared to those with lower BMI ($P < 0.05$).

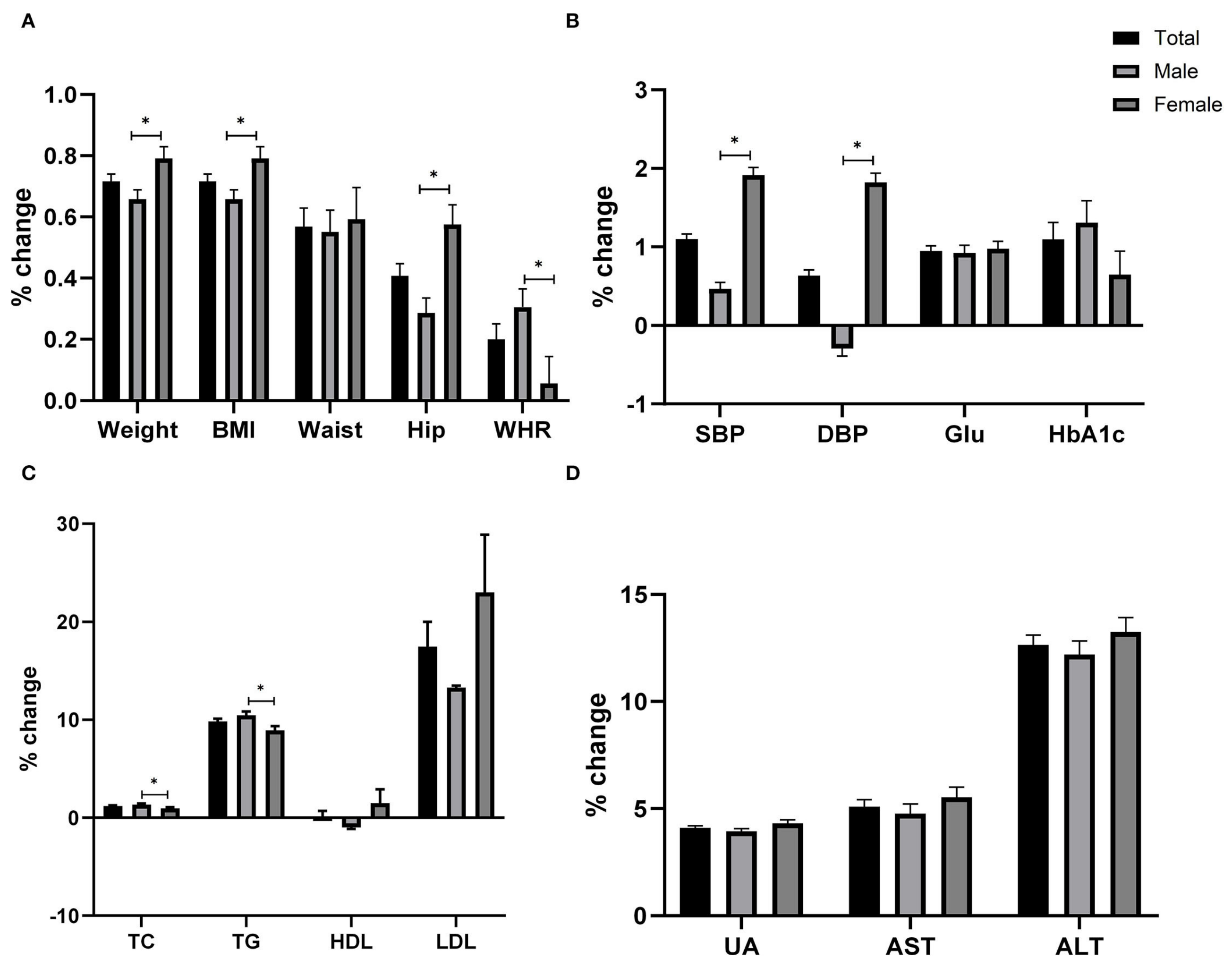

FIGURE 2 | Covid-19 pandemic exposure on cardiometabolic indexes according to sex difference.

Age Subgroup Analysis of COVID-19 Pandemic Exposure on Cardiometabolic Markers

Results showed that pandemic exposure increased weight, waist circumference, and hip circumference in the youngest age groups ($P < 0.05$). However, SBP, fasting blood sugar, HDL, and uric acid in the oldest age group deteriorated more significantly ($P < 0.05$) (**Table 4**).

DISCUSSION

To control the spread of COVID-19, governments pursued lockdown measures to curtail social mobility. Its true cost on cardiovascular and metabolic health remains unclear despite the plethora of literature examining the health impact of the pandemic (5).

In the present study, we established a retrospective cohort with 29,773 participants and compared the cardiometabolic markers before the outbreak of COVID-19 with 1 year after the start of the outbreak. Results showed that there were significant weight increases, waist circumference, hip circumference, blood pressure, fasting blood glucose, lipids, and uric acid in this cohort during the first year of COVID-19 pandemic exposure, which suggested that the pandemic may have worsened the risk of developing cardiovascular and metabolic diseases among the general population.

The adverse effects of social isolation and change in lifestyle brought about by pandemic exposure may have contributed to worsening cardiometabolic markers. In the first outbreak, China experienced a 3-month-long national lockdown to break the chain of transmission in the community (6). After lifting the national lockdown, all kinds of social activities were discouraged, and stay-at-home lifestyles were promoted. Studies examining behaviors in the Chinese population have shown that more time was spent on electronic screens in preschool children (7), in youths (8), increased snack intake, reduced physical activity, and sleep duration in adults (9–11). Physical activity

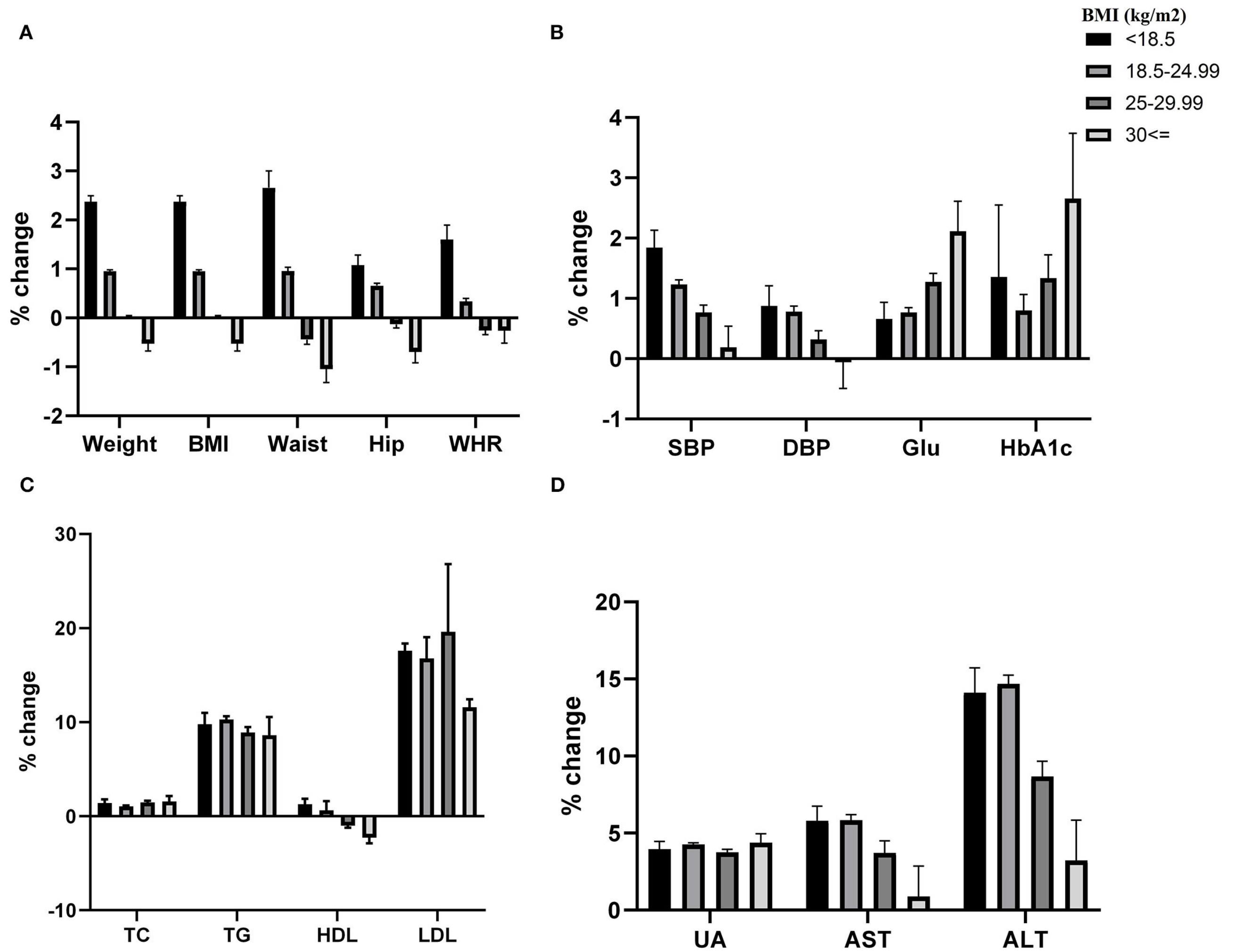

FIGURE 3 | Covid-19 pandemic exposure on cardiometabolic indexes according to BMI categories. Table provided Adjusted *P* value between different levels of BMI to each variable.

is an essential factor in physical and mental health (12) and is strongly recommended for health and wellbeing (13). Therefore, reduced physical activity during the pandemic can explain the worsening metabolic health indicators examined in this study. Furthermore, the COVID-19 pandemic also reduced the availability of healthy and fresh foods (14), contributing to the worsening of cardiometabolic markers in our study. Other studies also indicated that during the pandemic, people suffered economic pressure and mental health problems (15), which may reversely reduce the quality of food and lead to the deterioration of cardiometabolic parameters.

The findings of our study are consistent with the other two published longitudinal studies (16, 17). In our study, the average follow-up interval was over 12 months. Additionally, we examined the association between COVID-19 pandemic exposure time and changes in cardiometabolic markers, which confirms the results of other studies with more reliability.

In this present study, an age subgroup analysis explored the impact of COVID-19 on different age groups. Results showed that weight gain-related parameters were worse in the younger group than in the older groups. Metabolic indexes such as SBP, fasting blood glucose, and uric acid was worse in the older groups. This may be due to older adults being predisposed to cardiovascular and metabolic diseases.

The main advantage of this study is the large sample size and longitudinal cohort design, which can provide robustness and reliability. The limitations of this study include this study population originating from one center, which may introduce selective bias. Secondly, due to the lack of social and economic information, such as education, occupation, and income, it is impossible to estimate the effects of these confounding factors. Lastly, behavior and emotional data were unavailable in this study, such as diet and exercise. Therefore, we cannot provide a direct explanation for our findings. One of the other limitations of this study is maturation bias. Maturation bias occurs when

TABLE 4 | Paired cardiometabolic markers differences between 2020 and 2019 in different age groups (year in 2020).

Variables	18 ≤ year of age < 40			40 ≤ year of age < 60			≥ 60 year of age		
	N	**Mean ± SD**	***P***	***N***	**Mean ± SD**	***P***	***N***	**Mean ± SD**	***P****
Weight	15,173	0.61 ± 2.94	< 0.001	11,124	0.25 ± 2.45	< 0.001	3,676	0.01 ± 2.42	0.838
BMI	15,173	0.22 ± 1.06	< 0.001	11,124	0.10 ± 0.91	< 0.001	3,676	0.004 ± 0.94	0.787
Waist	7,698	0.37 ± 5.94	< 0.001	5,743	0.22 ± 5.49	0.002	1,671	−0.28 ± 5.89	0.053
Hip	7,698	0.33 ± 4.71	< 0.001	5,740	0.32 4.24	< 0.001	1,671	−0.13 ± 4.58	0.242
WHR	7,698	0.001 ± 0.05	0.079	5,740	<0.0014 ± 0.05	0.508	1,671	−0.001 ± 0.06	0.246
SBP	15,156	0.02 ± 11.73	0.797	11,103	1.05 ± 13.31	< 0.001	3,662	2.20 ± 15.97	< 0.001
DBP	15,157	−0.22 ± 8.70	0.002	11,103	0.10 ± 9.49	0.273	3,662	−0.61 ± 10.51	< 0.001
FBG	12,352	0.01 ± 0.52	0.017	9,451	0.03 ± 0.77	0.001	2,991	0.06 ± 1.11	0.003
HbA1c	173	−0.09 ± 0.76	0.117	782	0.08 ± 0.52	< 0.001	269	0.01 ± 0.54	0.745
TC	12,855	0.00 ± 0.16	0.474	10,056	0.05 ± 0.71	< 0.001	3,400	0.01 ± 0.82	0.316
TG	12,855	0.03 ± 1.15	0.001	10,057	0.03 ± 1.45	0.022	3,400	0.03 ± 1.03	0.057
HDL	7,9s46	−0.01 ± 0.22	< 0.001	9,080	−0.02 ± 0.22	< 0.001	3,269	−0.05 ± 0.23	< 0.001
LDL	7,946	0.31 ± 0.43	< 0.001	9,080	0.31 ± 0.51	< 0.001	3,269	0.26 ± 0.62	< 0.001
UA	13,496	9.96 ± 55.45	< 0.001	10,378	9.28 ± 53.4	< 0.001	3,346	15.11 ± 58.32	< 0.001
AST	13,142	0.04 ± 15.35	0.777	9,544	−0.05 ± 11.46	0.690	2,983	0.07 ± 22.47	0.858
ALT	14,624	0.27 ± 28.78	0.252	10,580	−0.05 ± 31.57	0.861	3,361	0.45 ± 16.58	0.117

*Compared with zero.

BMI, body mass index; WHR, waist to hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fast blood glucose; HbA1c, hemoglobin A1c; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

natural changes over time, like increasing age, may influence the study outcomes.

In conclusion, this study showed that the COVID-19 pandemic and its control measures significantly negatively impacted cardiometabolic profiles, especially in older adults. The result of this study may help promote a healthier lifestyle to cope with the unwanted effects of COVID-19 pandemic measures.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University and conducted in accordance with the Principles of the Helsinki Declaration (No. 2020-252). Written informed consent was not provided because patient consent was waived due to the fact that this was a retrospective observational study, and anonymized databases provided by the health authorities were used.

AUTHOR CONTRIBUTIONS

XQ and ZH: conceptualization. ZH, YZ, and XX: methodology, formal analysis, writing-original draft, writing-review, and editing. YM and JR: software and data curation. SS: visualization. All authors have read and agreed to the published version of the manuscript.

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SYSTEMATIC REVIEW
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Knowledge, Attitudes, and Practices Toward the Prevention of COVID-19 in Bangladesh: A Systematic Review and Meta-Analysis

Ahsan Raquib[1], Radwan Raquib[1,2], Safayet Jamil[3], Ahmed Hossain[4,5†], Firoj al-Mamun[1,6,7†] and Mohammed A. Mamun[1,6,7,8†]*

[1] CHINTA Research Bangladesh, Dhaka, Bangladesh, [2] Faculty of Veterinary, Animal and Biomedical Sciences, Sylhet Agricultural University, Sylhet, Bangladesh, [3] Department of Pharmacy, Khwaja Yunus Ali University, Sirajgonj, Bangladesh, [4] Department of Public Health, North South University, Dhaka, Bangladesh, [5] Global Health Institute, North South University, Dhaka, Bangladesh, [6] Department of Public Health and Informatics, Jahangirnagar University, Dhaka, Bangladesh, [7] Department of Public Health, University of South Asia, Dhaka, Bangladesh, [8] Department of Public Health, Daffodil International University, Dhaka, Bangladesh

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Md Hasinur Rahaman Khan, University of Dhaka, Bangladesh

****Correspondence:***
Mohammed A. Mamun
mamunphi46@gmail.com

†ORCID:
Ahmed Hossain
orcid.org/0000-0003-4575-1273
Firoj al-Mamun
orcid.org/0000-0003-4611-9624
Mohammed A. Mamun
orcid.org/0000-0002-1728-8966

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Background: Numerous studies on knowledge, attitude, and practice (KAP) about the prevention of COVID-19 infections are available in Bangladeshi contexts, with results that vary significantly. However, no earlier attempt has been made to analyze the available COVID-19 KAP studies in Bangladesh, which is incorporated in this meta-analysis for the first time.

Methods: Following the PRISMA guidelines, articles relevant to COVID-19 KAP that were conducted among the Bangladeshi population were found in databases such as PubMed, Scopus, CINAHL, Google Scholar, and ResearchGate. Random-effect meta-analysis was used to generate a pooled prevalence of knowledge, attitude, and practice level toward the prevention of COVID-19 infection.

Results: This review included 18 articles that were published between March 2020 and November 2021. Overall, 89.87% (95% CI: 67.71–97.40) understood about COVID-19 symptoms, 92.09% (95% CI: 84.32–96.18) knew about how it spreads, and 79.51% (95% CI: 59.38–91.15) knew about how to treat it. The public's perception of controlling COVID-19 is mixed, with only 44.16% (95% CI: 35.74–52.93) and 60.28% (95% CI: 49.22–70.38) believing the country would win the struggle against the pandemic and the infection will be successfully controlled, respectively. Although overall COVID-19 preventative practice was good, subgroup analysis found that men had a poor practice toward controlling the infection. The practice of avoiding crowded places (70.15%) and maintaining social distance (77.17%) was found to be satisfactory in institution-based studies.

Conclusion: The findings of this study revealed that the Bangladeshi population had a good awareness of COVID-19 symptoms, treatment, attitudes, and behaviors. The findings of this study are likely to aid Bangladeshi governments and policymakers in putting evidence into action by identifying gaps and emphasizing the importance of educating the less informed public about COVID-19 transmission.

Keywords: COVID-19 knowledge, COVID-19 preventive behaviors, knowledge, attitudes, practice (KAP), pandemic, systematic review and meta-analysis

INTRODUCTION

The COVID-19 pandemic caused by the SARS-CoV-2 virus has become the most public health concern affecting all aspects of life (1). The first case of COVID-19 was diagnosed in Wuhan, China, in late December 2019 (2, 3), by a patient with unexplained pneumonia etiology (4). However, as of November 22, 2021, approximately 258 million people are reported to be infected with the virus globally, whereas 5.15 million lost their lives. The World Health Organization declared it a pandemic due to its devastating effects on all aspects of health and the quality of life (5). The first COVID-19 case diagnosis in Bangladesh was reported on March 8, 2020 (6, 7). The country has been alleged to have poor healthcare facilities and skilled manpower to tackle any health emergencies. This situation worsened during the pandemic due to the overwhelming number of cases (8). As of November 22, 2021, 1.57 million Bangladeshi people have been tested positive for the virus, and the number of mortalities is 28,000. However, to mitigate the virus's rapid transmission, approaches to medication or therapeutic such as social movement restriction, lockdown, and quarantine have been imposed (9).

The impact of COVID-19 is severe among these people with chronic medical conditions such as diabetes, cancer, heart disease, and circulatory disorders, although general people are not escaping from the stressful situation created by the pandemic (10). Consequently, unwanted fear, panic, and worry related to being infected with the virus, loss of beloved ones, and economic crisis occur, whereas people have been reported at a higher risk of issues such as common mental health problems (i.e., depression, anxiety, and stress) and poor physical health along with inflammatory diseases (5, 11). Nearly half of the Bangladeshi people have been reported suffering from mental health problems (higher than the prevalence rates of mental disorders during the normal period), as estimated by a recent meta-analysis of the studies conducted during the COVID-19 pandemic (12). However, Bangladesh, like other countries, has implemented various safety precautions to mitigate the transmission, including pedestrianizing flow, confining them at home, allowing them to work from home, increasing awareness, disseminating information, closing schools, and providing other public assistance (13, 14).

It is said that public response to a disease is determined by knowledge and understanding of its etiology, signs and symptoms, treatment, and even prevention, which are expressed by their attitudes and practices toward the diseases (15, 16). The risk of disease-related adverse outcomes in a population increases if negative attitudes and practices are not possibly measured for modification. Therefore, assessing public understanding, perception, and experience related to COVID-19 is essential to visualize their preparedness for the pandemic (15, 16). This helps government and health authorities determine how to adopt the programs to control the outbreak. Therefore, many studies have been conducted to assess Bangladesh's knowledge, attitudes, and practice (KAP) toward COVID-19, but there is a lack of evidence generated from a systematic evaluation.

Given the nature of the COVID-19 pandemic, regular update of scientific literature is essential for initiating empirical evidence on interventions and strategies to tackle the COVID-19 pandemic more conveniently. For this purpose, a comprehensive and timely updated systematic evaluation of existing evidence is highly needed, whereas a few systematic review and meta-analysis has been published on the KAP of COVID-19 (15, 17–19). Notwithstanding, region- or country-based systematic reviews lack; for instance, Ethiopia (17, 20) and the United States (20) have reported publishing country-based systematic reviews on the KAP of COVID-19. Furthermore, knowledge and public perception being culture-based, interventions should focus on the data from the respective culture. Despite the global evidence, it is hard to achieve any policy directions and implement them due to cultural sensitivity. As a result, in order to better grasp the KAP for COVID-19 prevention in Bangladesh, a systematic review and meta-analysis is undertaken herein to better comprehend the infection's control.

METHODS

Search Strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol was used as a guideline for performing the present systematic review. To identify relevant studies for including in this review, a systematic literature search was conducted on the relevant databases like PubMed, Scopus, CINAHL, and Google Scholar between July 1, 2021, and July 10, 2021. In addition, random searches were done in ResearchGate to include missing literature. The search strategy included keywords in the combination of (i) knowledge OR attitude OR perception OR practice, (ii) corona virus OR novel coronavirus OR COVID-19 OR severe acute respiratory syndrome (iii) Bangladesh.

Eligibility Criteria

For inclusion of the literature, the following criteria were applied to the retrieved studies (i) being a cross-sectional observation study, (ii) having full-text access, (iii) being concerned with any of the KAP of COVID-19 related questions (**Supplementary File**), (iv) being published in a peer-reviewed journal in English, (iv) being conducted between March 2020 and November 2021, and (v) being conducted among Bangladeshi residents. In addition, literature like editorial, letter to the editor, commentary, perspective, preprint, and articles that failed to

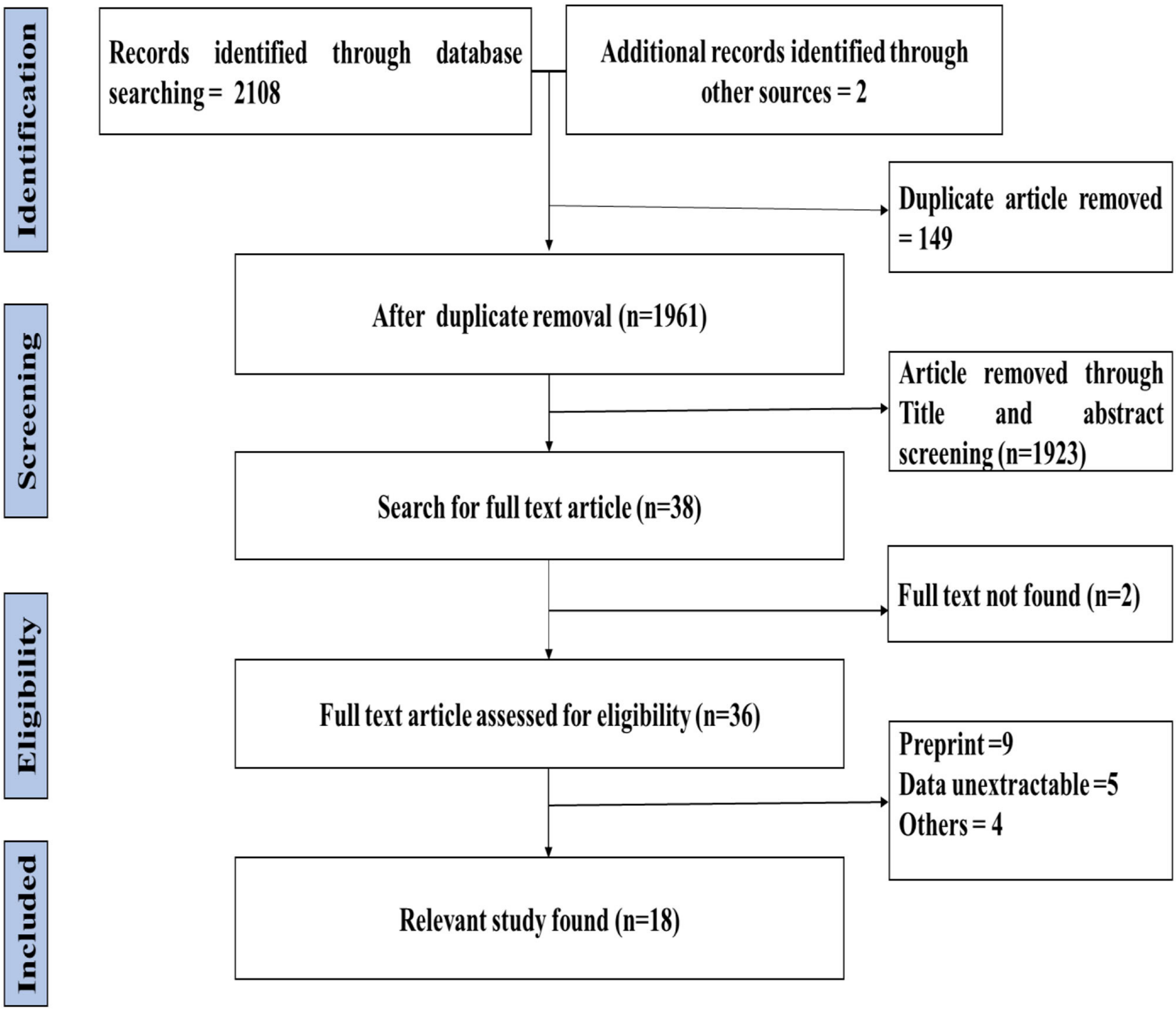

FIGURE 1 | PRISMA flow diagram of literature search and study selection.

fulfill the aforementioned eligibility criteria were eliminated from this study.

Study Selection

To remove duplicate studies, articles ($N = 2{,}110$) retrieved from the database searches were exported to reference manager Zotero and Excel 2013. After carefully removing duplicate articles ($n = 149$), the title and abstracts of the remaining 1,923 studies were screened for pertinent studies, followed by a freely accessible study selection and relevant study selection based on eligibility criteria. Through title and abstract screening, 36 articles were left for full-text reading, and based on the eligible criteria, 18 articles were finally selected to be included in this review (**Figure 1**).

Quality Assessment

Risk of Bias Tool (RoBT) that was developed by Hoy et al. (21) was used to assess the risk of bias of all the included studies in this review. This assessment evaluated 10 items in which external validity (items one to four) and internal validity (items five to ten) were measured (**Supplementary File**). Each item of RoBT is scored "0" (risk of bias absent) or "1" (risk of bias present), where 10 is the highest score reflecting a greater risk of bias. However, based on the RoBT score, studies were classified as low risk (0–3), moderate risk (4–6), and high risk (7–10).

Data Extraction

From the eligible studies, the following information was retrieved in an excel file: first author, sample collection date, publication year, participant's characteristics (age, sex, education level, and

TABLE 1 | Demographic characteristics of the participants.

References	Study design	Participants	Mean age of participants	Sampling date	Focus group	Risk of Bias	Quality score	Questionnaire administration
Rahman et al. (22)	CBCS	616 (male: 58.44%)	Not mentioned	Mid of May to end of May 2020	General people	Low	2	SAOB
Hossain et al. (31)	IBCS	378 (male: 32.54%)	17.03 (±0.17)	August 7 to August 18 2020	Students	Low	3	SAOB
Pervez et al. (23)	CBCS	315 (male: 54.92%)	26.54 (± 3.05)	May 1 to May 25, 2020	Urban people	Low	3	SAOB
Ahmed et al. (32)	IBCS	200 (male: 66%)	22 (± 2.09)	July 3 2020 to July 15 2020	Public university students	Low	3	SAOB
Roy et al. (33)	IBCS	110 (male: 77.27%)	Not mentioned	June 2020	Sub Assistant Agriculture Officers	Moderate	4	Face-to-face interviews
Akram et al. (34)	IBCS	139 (male: 75.54%)	30.1 (±6.1)	April and May 2020	Healthcare workers	Low	3	Not mentioned
Rahman et al. (2)	IBCS	952 (male: 49.58%)	15–30	Not mentioned	Public university students	Low	2	SAOB
Hossain et al. (24)	CBCS	1,861 (male: 64.54%, third gender: 0.81%)	Not mentioned	March 19 to April 15, 2020	General people	Low	3	Not mentioned
Rahman et al. (25)	CBCS	1,520 (male: 62.17%)	30.1 (± 6.1)	March 15 to April 15,2020	General people	Low	2	Online based
Islam et al. (26)	CBCS	406 (male: 53.20%)	44.9 (±12.1)	August and September 2020	Slum dwellers	Low	3	Face to face interview
Anwar et al. (9)	CBCS	1,869 (male: 00%)	29.55 (±12.01)	Not mentioned	Adult women	Low	3	Telephone, online, or in-person interviews
Hossain et al. (27)	CBCS	1,056 (male: 63.26%)	31.6 (±10.56)	May 10 to May 16 May 2020	Adult population	Low	1	SAOB
Paul et al. (28)	CBCS	1,589 (male: 60.48%)	Not mentioned	March 22 to March 28, 2020	General people	Low	2	SAOB
Hossain et al. (8)	CBCS	2,157 (male: 54.06%)	13–90	April 4 to May 2, 2020	General people	Low	2	SAOB
Ahmed et al. (29)	CBCS	1,222 (male: 61.37%)	30.77 (±12.1)	June 27 to July 20, 2020	General people	Moderate	4	Face to face interviews and Online-based
Ferdous et al. (6)	CBCS	2,017 (male: 59.79%)	12–64	March 29 to April 20, 2020	General people	Low	2	SAOB
Wadood et al. (1)	IBCS	305 (male: 74.17%)	20.66 (±1.78)	March 11 to March 19, 2020	Students	Moderate	4	Face to face interview
Ahmad et al. (30)	CBCS	517 (male: 36.94%)	Not mentioned	April 15 to April 30, 2020	Medical students and their family members	Low	3	Online based

IBCS, Institutional-based cross-sectional study; CBCS, Community-based cross-sectional study; SAOB, Self-administered online-based.

TABLE 2 | Pooled prevalence of knowledge about COVID-19 among Bangladeshi residents.

Knowledge about COVID-19		No of study	Sample size	Percentage, (%)	95% CI	I^2 (%)	*p*-Value	Eggers test
COVID-19 symptoms								
Fever		6	3,802	93.54	90.54–95.63	90.6	<0.01	0.30
	Male	3	521	89.64	86.71–91.98	15.7	0.31	
	Female	3	400	91.93	86.52–95.29	65.8	0.05	
Dry cough		6	3,802	85.54	77.73–90.93	96.0	<0.01	0.86
	Male	3	521	82.05	77.37–85.94	61.3	0.08	
	Female	3	400	77.14	68.48–83.99	79.6	<0.01	
Respiratory sign		6	3,802	85.97	69.89–94.18	98.8	<0.01	0.42
	Male	3	521	79.36	55.29–92.28	97.3	<0.01	
	Female	3	400	88.61	42.69–98.78	97.8	<0.01	
Weakness		5	3,497	49.28	27.75–71.08	98.7	<0.01	0.56
	Male	3	521	46.12	20.47–74.00	98.1	<0.01	
	Female	3	400	33.14	7.24–75.89	97.7	<0.01	
Diarrhea		6	3,802	39.24	19.10–63.85	99.0	<0.01	0.23
	Male	3	521	37.24	13.60–69.12	97.9	<0.01	
	Female	3	400	26.26	4.98–70.77	97.0	<0.01	
Headache		3	1,676	56.23	49.80–62.46	89.5	<0.01	0.23
Sore throat		4	3,287	72.84	42.73–90.60	99.4	<0.01	0.17
Overall symptoms		9	8,017	89.87	67.71–97.40	98.9	<0.01	0.50
COVID-19 transmission								
Spread through respiratory droplet		10	8,533	92.09	84.32–96.18	99.1	<0.01	<0.01
	Male	3	1554	85.67	65.11–95.04	95.6	<0.01	
	Female	3	1,069	85.69	61.45–95.74	94.7	<0.01	
COVID-19 treatment								
No-specific treatment available		11	11,634	79.51	59.38–91.15	98.1	<0.01	0.41
	Male	1	1,206	80.18	77.84–82.34			
	Female	2	2,624	82.36	80.85–83.77	0.00	0.38	

occupation), focus group, study design, number of participants, and percentage of positive answers on each selected KAP (knowledge, attitude, and practice) questions.

Data Analysis

R studio version 4.1.0 was used to perform a meta-analysis of the data exported from an Excel spreadsheet. I^2 (%) statistics were applied for the evaluation of study heterogeneity, where 25, 50, and 75% represented low, moderate, and severe heterogeneity, respectively. A random-effect model was employed to conduct the meta-analysis because of high heterogeneity, and the results were presented in forest plots. Additional subgroup analysis was conducted for study design and gender. Publication bias assessment was visualized by funnel plot and for rigorous assumptions egger's regression test was performed.

RESULTS

Characteristics of the Included Studies

General Description of the Included Studies

All the selected studies ($n = 18$) comprised a total of 16,443 participants, where 8,523, 7,885, and 15 participants were male, female, and others, respectively, with a sample size range from 110 to 2,157. Twelve studies (6, 8, 9, 22–30) employed a community-based cross-sectional study design, and the other six (1, 2, 31–34) used an institutional-based cross-sectional study design. Among the included studies, 11 were published in 2020, and seven were published in 2021 (**Table 1**).

Measurement Used in the Included Studies

Knowledge of COVID-19 was assessed by the domains of (i) symptoms (fever, dry cough, respiratory signs, weakness, diarrhea, headache, and sore throat), (ii) transmission (spread through respiratory droplet), and (iii) treatment (no specific treatment is available), whereas those items were responded using "Yes/No/Don't know," or "True/False/Not sure" scheme in the included studies. In case of practices related to COVID-19 (wash hands regularly, maintain social distance, avoid the crowded place, and always wear a mask when going outside) and attitudes concerning COVID-19 (COVID-19 pandemic will be successfully controlled, and Bangladesh can win the battle against the COVID-19 pandemic), the included studies collected response using "Yes/No/Don't know" or "Strongly agree/Agree/Neutral/Disagree/Strongly disagree" items. The responses of "Yes," "True," or "Strongly agree/Agree" are considered positive responses for analysis herein.

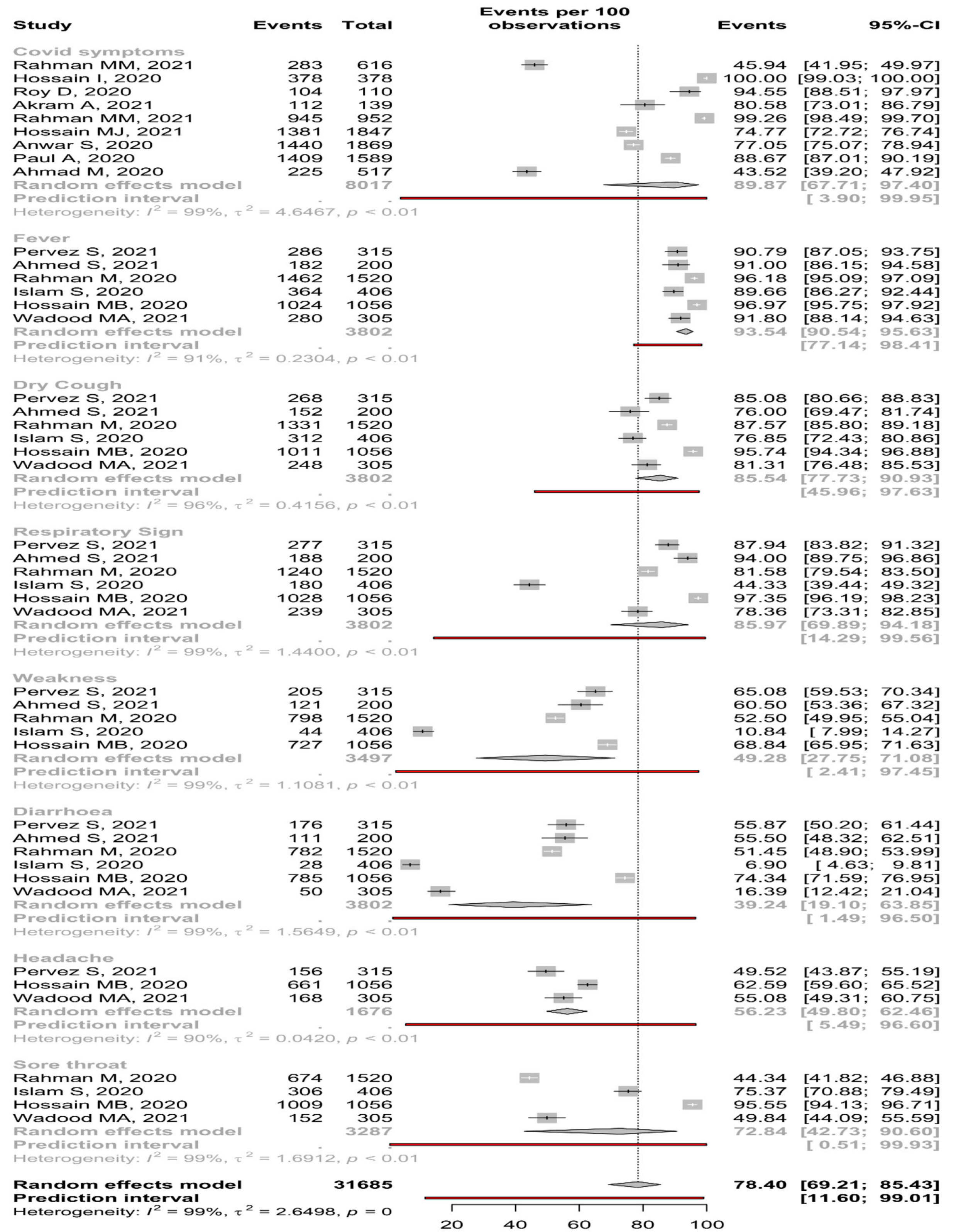

FIGURE 2 | Knowledge about COVID-19 symptoms among Bangladeshi residents.

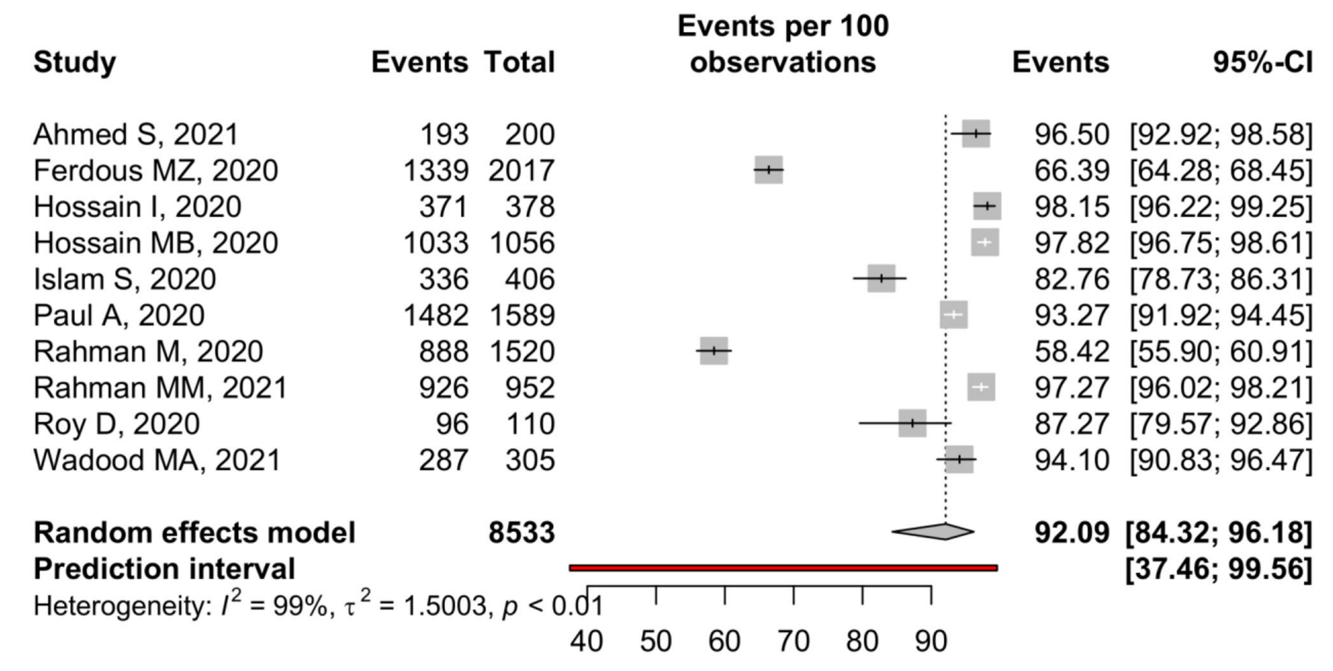

FIGURE 3 | Knowledge about COVID-19 transmission among Bangladeshi residents.

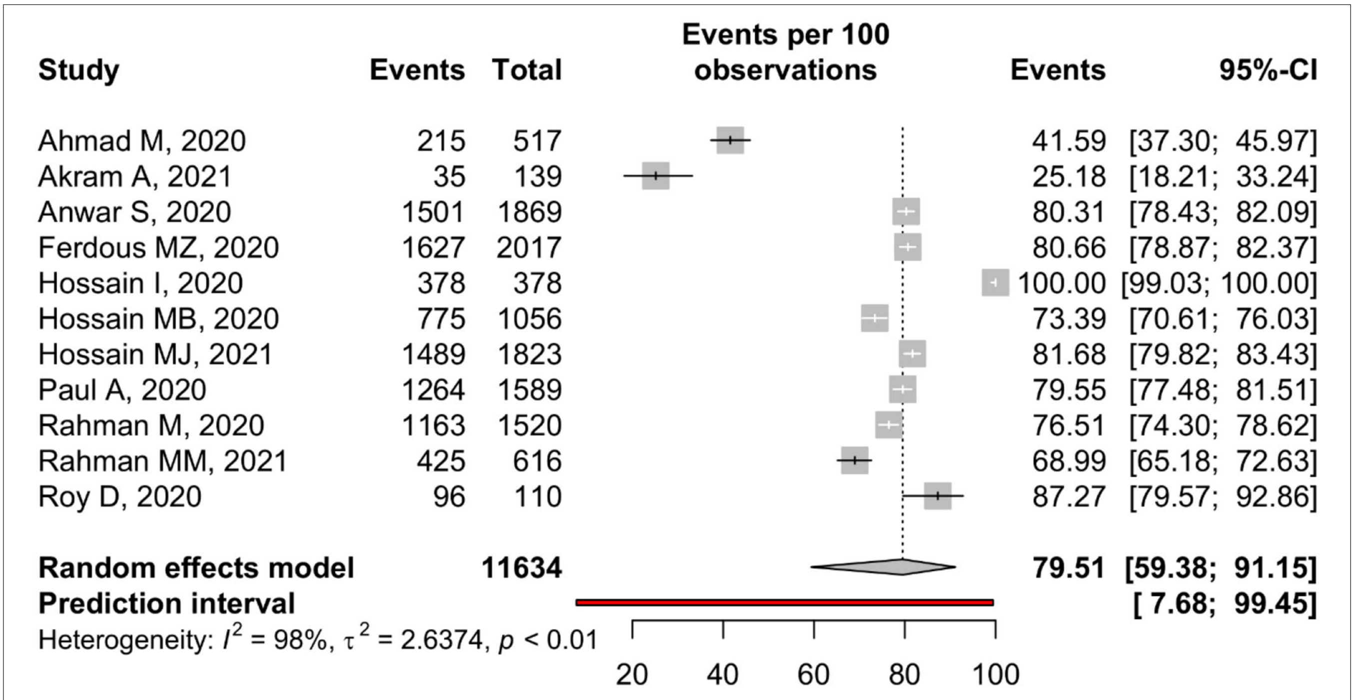

FIGURE 4 | Knowledge about COVID-19 treatments among Bangladeshi residents.

Knowledge About COVID-19 Symptoms

Nine studies reported about overall knowledge of participants about COVID-19 symptoms, where 89.87% (95%, CI: 67.71–97.40%) participants had positive knowledge. In addition, six studies reported knowledge of fever, dry cough, and respiratory signs, where 93.54, 85.54, and 85.97% positive knowledge was encountered. Conversely, the lowest percentage of participants' knowledge was on diarrhea (39.24%, 95%

TABLE 3 | Pooled prevalence of attitude toward COVID-19 among Bangladeshi residents.

Attitudes toward COVID-19	No of study	Sample size	Percentage, (%)	95% CI	I^2 (%)	*p*-value	Eggers test
COVID-19 will be successfully controlled	5	5,696	60.28	49.22–70.38	98.1	<0.01	0.72
Bangladesh can win the battle against the COVID-19	5	5,648	44.16	35.74–52.93	88.7	<0.01	0.37
Male	1	1,166	41.77	38.97–44.62			
Female	2	2,804	40.91	39.10–42.74	0.00	0.36	

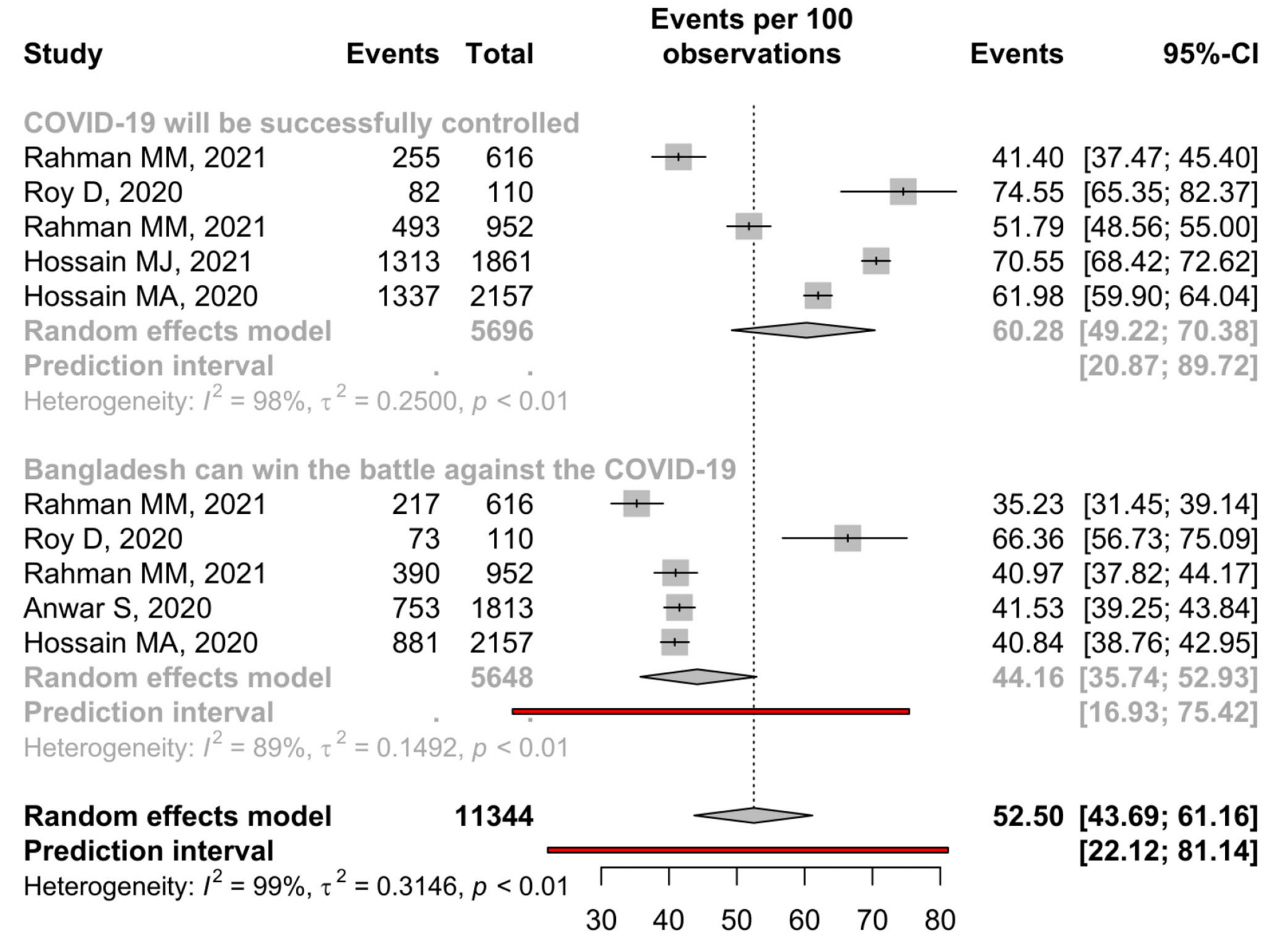

FIGURE 5 | Attitude toward COVID-19 among Bangladeshi residents.

CI: 19.10–63.85%) (**Table 2**). The forest is presented in **Figure 2**.

The subgroup meta-analysis of COVID-19 symptoms reveals that participants of the community-based studies had higher knowledge about fever, dry cough, diarrhea, headache, and sore throat than institution-based studies. In the case of gender, the male had higher knowledge of fever, dry cough, weakness, and diarrhea (**Supplementary Material**).

Knowledge About COVID-19 Transmission

Only 10 studies reported transmission, and random-effect meta-analysis estimated 92.09% (95% CI: 84.32–96.18%) participants were aware of the fact that COVID-19 can transmit through respiratory droplets. A substantial amount of study heterogeneity was identified (I^2 = 99.1%), where Eggers tests showed a small-study effect (**Table 2**). The forest is presented in **Figure 3**.

In the subgroup analysis of gender, it was found that males (85.67%, 95% CI: 65.11–95.04%) and females (85.69%, 95% CI: 61.45–95.74%) had the almost same level of knowledge of COVID-19 transmission. Appropriate knowledge of transmission was estimated as 85.82 % (95%, CI: 66.41–94.88%) in CBCS and 95.82% (95%, CI: 92.50–97.70%) in IBCS (**Supplementary Material**).

TABLE 4 | Pooled prevalence of practice about COVID-19 among Bangladeshi residents.

Practice of COVID-19	No of study	Sample size	Percentage, (%)	95% CI	I^2 (%)	*P*-value	Eggers test
Wash hand regularly	12	9,299	93.79	87.21–97.10	96.8	<0.01	0.09
Male	3	1,554	91.30	78.96–96.71	96.0	<0.01	
Female	3	1,069	90.53	75.53–96>74	98.0	<0.01	
Maintain social distance	9	7,016	83.46	72.99–90.41	99.0	<0.01	0.17
Male	3	1,554	87.13	85.37–88.71	27.7	0.25	
Female	3	1,069	91.93	83.60–96.22	94.3	<0.01	
Avoid crowded place	9	8385	91.18	74.54–97.34	97.4	<0.01	0.17
Male	1	1,166	70.15	67.46–72.71			
Female	1	991	81.53	78.99–83.83			
Always wear mask when go outside	12	11,316	89.22	79.20–94.74	98.2	<0.01	0.08
Male	3	1,514	90.54	80.39–95.71	88.0	<0.01	
Female	3	1,249	85.19	75.85–91.33	87.2	<0.01	

Knowledge About COVID-19 Treatment

Eleven studies reported the treatment of COVID-19, and 79.51% (95%, CI: 59.38–91.15%) of participants know that COVID-19 has no specific treatment. A substantial amount of study heterogeneity was identified ($I^2 = 98.1\%$), whereas a small-study effect was absent based on the Eggers test ($p = 0.41$) (**Table 2**). The forest is presented in **Figure 4**.

Participants of IBCS (95.84%, 95% CI: 11.58–99.98%) had better knowledge of COVID-19 treatment than the participants of CBCS (74.01%, 95% CI: 65.83–80.80%). Higher percentage of female (82.36%, 95% CI: 80.85–83.77%) knew about the unavailability of specific treatment of COVID-19 than male (80.18%, 95% CI: 77.84–82.34%) (**Supplementary Material**).

Attitude Toward COVID-19

Five studies reported attitudes toward the control of COVID-19, and 60.28% (95%, CI: 49.22–70.38%) hold a positive attitude toward it (**Table 3**). In addition, three community-based and two institutional-based studies assessed this attitude among people with an estimated positive attitude of 58.47 and 63.06%, respectively (**Supplementary Material**). The forest is presented in **Figure 5**.

Only 44.16% of people believe Bangladesh can win the battle against COVID-19, and males (41.77%) and females (40.91%) hold almost similar levels of positive attitude toward this (**Table 3**). In contrast, participants of institutional-based studies (53.12%) had a better attitude than the participants of community-based studies (39.71%) (**Supplementary Material**).

Practice of COVID-19

Only 12 studies reported handwashing practice; random-effect meta-analysis estimated 93.79% (95%, CI: 87.21–97.10%) participants regularly do this practice. A substantial amount of study heterogeneity was identified ($I^2 = 96.8\%$), whereas no small-study effect was found based on the Eggers tests ($p = 0.09$) (**Table 4**). The forest is presented in **Figure 6**. Male (91.30%, CI: 78.96–96.71%) and participants of IBCS (96.17%, CI: 85.54–99.07%) used to do this practice more frequently than female (90.53%, CI: 75.53–96.74%) and participants of CBCS (91.71%, CI: 81.28–96.57%) (**Supplementary Material**).

Nine studies reported about maintaining social distance, and only 83.46 % (95%, CI: 72.99–90.41%) participants found to do this practice (**Table 4**). The forest is presented in **Figure 6**. Female (91.93%, CI: 83.60–96.22%) and participants of CBCS (87.29%, CI: 75.28–93.94%) used to do this practice more frequently than male (87.13% CI: 85.37–88.71%) and participants of IBCS (77.17%, CI: 59.92–88.43%) (**Supplementary Material**).

Random-effect meta-analysis revealed 91.18 % (95% CI: 74.54–97.34%, $p < 0.01$) participants avoid crowded place. A substantial amount of study heterogeneity was identified ($I^2 = 97.4\%$). In the Eggers tests, no small-study effect was found ($p = 0.17$) (**Table 4**). The forest is presented in **Figure 6**. About 91.86 % and 92.10% of participants of CBCS and IBCS avoid crowded places, respectively (**Supplementary Material**).

About 89.22% (95% CI: 79.20–94.74%) participants from 12 reported studies always wear mask during going outside (**Table 4**). The forest is presented in **Figure 6**. Male (90.54%, CI: 80.39–95.71%) and participants of IBCS (93.78%, CI: 65.43–99.18%) used to do this practice more frequently than female (85.19%, CI: 75.85–91.33%) and participants of CBCS (86.40%, CI: 78.03–91.91%) (**Supplementary Material**).

DISCUSSION

This systematic review and meta-analysis evaluated participants' overall knowledge of COVID-19 symptoms, transmission, treatment, and attitudes toward successfully controlling the COVID-19 pandemic. In addition, the COVID-19 control practices such as hand washing, wearing a mask, avoiding crowded places, and maintaining social distance were also evaluated in this study. The study included 18 articles, 12 of which used a community-based cross-sectional study design and six of which used an institutional-based cross-sectional study design.

Overall, a significant portion of the participants had knowledge about COVID-19 symptoms (89.87%, CI: 67.71–97.40%), whereas the symptoms like fever, dry cough, and

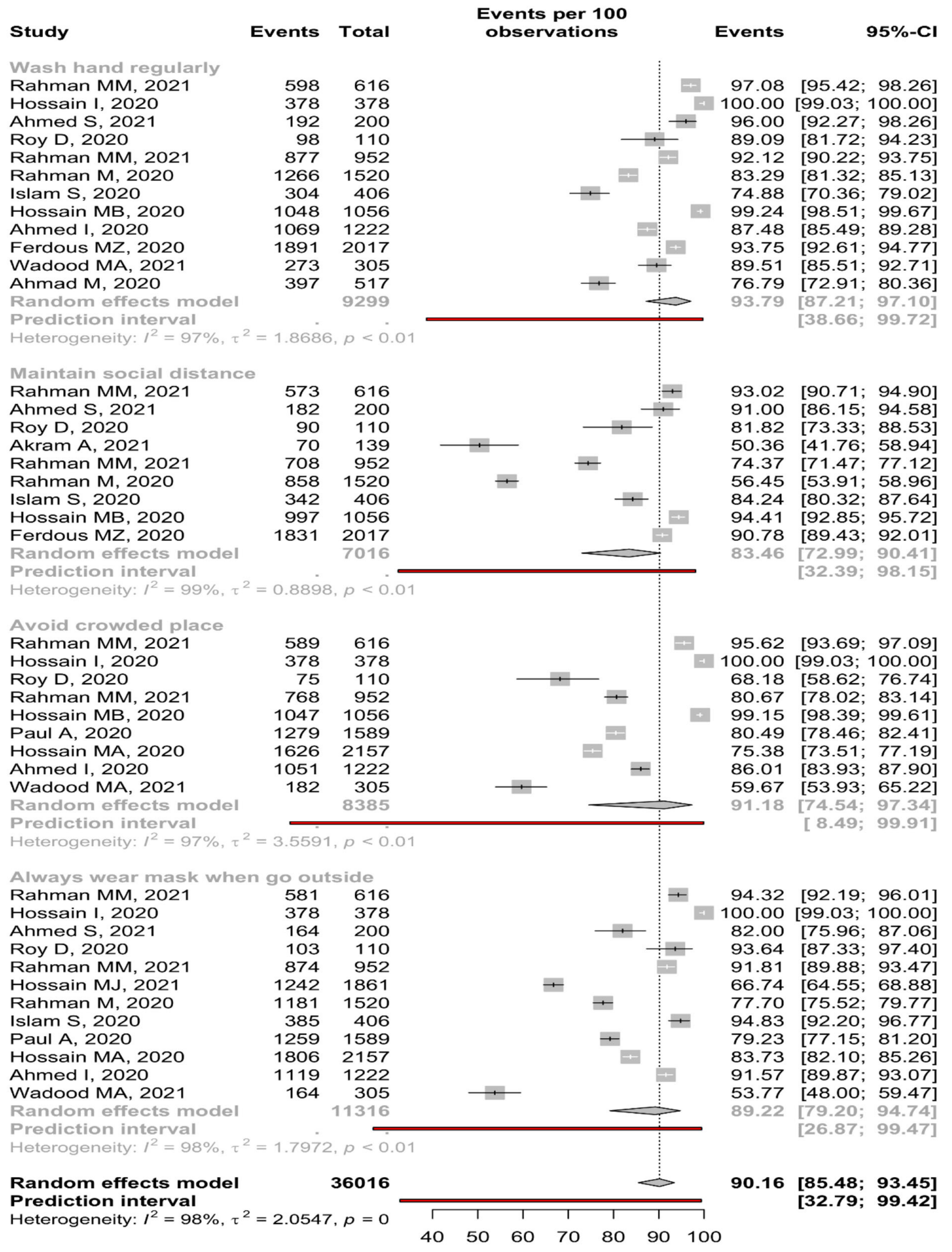

FIGURE 6 | Practice about COVID-19 among Bangladeshi residents.

respiratory signs were found to be known to the participants. But, less than half of the participants were not aware of diarrhea (39.24%) and weakness (49.28%) as the COVID-19 symptoms, and only 56.23% of people had positive knowledge about the headache; this may be due to those symptoms being less common among the COVID-19 infected individuals. In addition, a high percentage of participants were reported to know about COVID-19 transmission through respiratory droplets (92.09%) and the unavailability of its specific treatment (79.51%). In subgroup analysis, male gender had better knowledge than females, only in knowledge related to the symptom of dry cough, weakness, and diarrhea, while participants of the community-based studies were more informed about a sore throat, headache, diarrhea, dry cough, and fever as a symptom of COVID-19 than participants of the institutional-based studies. Those findings might denote that residents of Bangladesh have shallow and insufficient knowledge about some domains of the COVID-19 knowledge, where inappropriate and poor knowledge could potentially lead to a hover in the attempt to find medical support and, consequently, a hover in the early diagnosis and treatment (13, 14). Therefore, smattering knowledge about the disease impedes control and elimination due to negligence in disease prevention practices (33, 35). Therefore, it is suggested that the country's public health authority focuses on those knowledge aspects that are poorly reported while implementing health education programs.

Based on this review, it is found that only 44.16% of Bangladeshi residents thought that the country would win the battle against the COVID-19 pandemic. On the contrary, a higher level of positive attitude, that is, 72.39% of general people of Ethiopia, was enumerated in a meta-analysis of COVID-19 KAP studies (36), reflecting dissatisfaction about pandemic management in Bangladesh. Several challenges and probable poor management of the pandemic in the country can be the forces for driving such a poor attitude among the Bangladeshi residents (37). However, as the pandemic is new to the management authority of the country, such dissatisfaction can be resolved over time by growing up the competency of the respective authorities.

Regarding practice related to COVID-19, this study reveals that a significant portion of the participants maintained washing hands (93.79%), wearing a mask (89.22%), and avoiding crowded places (91.18%), but maintaining social distancing was not always possible for a large portion, especially for the participants of institution-based studies (77.17%). Furthermore, males more frequently wore masks than females, but females had other better prevention practices such as maintaining social distance and avoiding crowded places. This may be because males are more likely to visit outside the home, which leads them to wear a mask and wash hands more frequently than females. In addition, the higher mortality of COVID-19 rate among the Bangladeshi males (37, 38) could make them more concerned about following more precautious measures despite going outside (8).

Before concluding the importance and potential implications of this meta-analysis findings, several limitations are supposed to be noted. First of all, journal articles published in English were only taken into consideration, limiting other sources such as preprint articles. All of the included studies that were conducted in online data collection approaches, limiting the findings' generalizability to the entire country's population. Besides, some of the studies were excluded because of not meeting the inclusion criteria [e.g., ten-thousand nationwide data were collected in the study of Hosen et al. (16), which could help generate evidence based on such a wider-spaced population's findings]. Factors associated with the COVID-19 KAP were not considered in the present study. Despite those limitations, the potency of this meta-analysis lies in the compilation of the results of 18 papers, which accentuated the results of the individual studies and permitted to acquire a merged prevalence that generated a shred of stronger evidence about COVID-19 KAP among the general Bangladeshi population. The findings of this study are likely to aid Bangladeshi governments and policymakers in putting evidence into action by identifying gaps and emphasizing the importance of educating the less informed public about COVID-19 transmission.

CONCLUSION

A number of KAP studies were undertaken in Bangladesh with populations from various categories, with notable variation in terms of gender, geography, occupation, and education. As a result, the study gives an overall KAP scenario for COVID-19 prophylaxis. This research should be taken into account by policymakers to underline the necessity of educating the less informed people about COVID-19 to restrict the spread of infection.

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/s.

AUTHOR CONTRIBUTIONS

AR and MM conceptualized the study. AR and RR did data extraction, where AR and Fa-M performed formal analysis. AR and SJ wrote the first draft, which has been extensively reviewed and edited by MM. Later on, further review and subsequent edits were performed by AR, AH, Fa-M, and MM. AR, Fa-M, and MM contributed to the study's methodology. AR managed resources and software with the help of Fa-M. AR, AH, and MM supervised the project. All authors read and finally approved the submission for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.856156/full#supplementary-material

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Perception of Global Participants of ITEC Nations on Country's Preparedness and Response to COVID-19 Pandemic

Kritika Upadhyay[1†], *Sonu Goel*[1,2,3*†] and *Kathirvel Soundappan*[1†]

[1] Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [2] Faculty of Education and Health Sciences, School of Medicine, University of Limerick, Limerick, Ireland, [3] Faculty of Human and Health Sciences, Swansea University, Swansea, United Kingdom

Background: The Coronavirus disease 2019 (COVID-19) pandemic has exposed the public health preparedness and response system across the world. The current study was conducted to gauge the perception of public health professionals of Indian Technical and Economic Cooperation (ITEC) countries regarding the preparedness and responses of their countries in mitigating the COVID-19 pandemic.

Methodology: Three capacity-building programs, namely "Managing COVID-19 Pandemic–Experience and Best practices of India" were conducted by PGIMER, Chandigarh, for public health professionals from ITEC countries from April to May 2021 in which 97 participants from 13 countries have participated. The tools used in the study were adapted from WHO's COVID-19 Strategic Preparedness and Response (SPRP), Monitoring and Evaluation Framework, interim guidelines for Critical preparedness, readiness and response actions for COVID-19, and a strategic framework for emergency preparedness, and finalized using Delphi technique. The overall preparedness of managing COVID-19 was rated using five-point Likert scale, whereas the overall score for the country in combating the COVID-19 pandemic was assessed using 10 point scale.

Results: We found that the perception of public health professionals to government response regarding COVID-19 for fostering improvement on COVID-19 situation was "moderate" with respect to transmission and surveillance mechanism, uniform reporting mechanism, and availability of adequate personal protective equipment (PPE) for health workers. However, the participants rated government response as "poor" in the availability of multisectoral national operational plan, human resource capacity, availability of trained rapid response team (RRT), preparedness in prevention and clinical management, training of healthcare workers, communication and community engagement strategies, facilities to test samples of patients, and transparent governance and administration.

Conclusion: A poor level of preparedness of countries in diverse domains of managing the COVID-19 pandemic was observed. As the global threat of COVID-19 is still looming, great efforts on building a robust preparedness and response system for COVID-19 and similar pandemics are urgently required.

Keywords: COVID-19, preparedness, response, senior administrators, ITEC

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Roger Nlandu Ngatu,
Kagawa University, Japan

Reviewed by:
Suneela Garg,
University of Delhi, India
Rano Mal Piryani,
Liaquat University of Medical and Health Sciences, Pakistan

Correspondence:
Sonu Goel
sonugoel007@yahoo.co.in

† These authors have contributed equally to this work and share first authorship

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INTRODUCTION

The occurrence of an unknown cause of viral pneumonia in Wuhan, China, in late 2019 has led to the worldwide spread of the disease resulting in a pandemic named Coronavirus disease 2019 (COVID-19). Globally, there have been 239,007,759 confirmed COVID-19 cases, including 4,871,841 deaths as of 14th October 2021 (1). High-income countries reported the maximum number of cases and deaths as compared to the developing and underdeveloped countries (2). The World Bank reported a 5.2% contraction in the global gross domestic product (GDP), the most significant global recession in the last several decades (3).

This unprecedented crisis due to the COVID-19 pandemic has warranted various governments to take extraordinary efforts to combat the transmission and hence reduce the morbidity and mortality associated with the disease (4–6). The developed and developing nations adopted almost similar policies such as restriction of movement across the borders, closure of non-essential businesses, a complete shutdown of offices and institutions and home quarantine, social distancing, and closure of schools and colleges, etc. While the developed countries like the USA (7), UK (8), and Russia (9) had expertise in the management of rising cases, the low and middle-income countries (LMICs) like India (10), Vietnam (11), and Bangladesh (12) faced limitations in resources and expertise to manage the crisis (13). As the cases started rising, the developed countries adopted a pharmaceutical approach, whereas most LMICs used non-pharmaceutical interventions (NPIs) (2).

Even after meticulous measures were taken by the countries, various gaps were identified in the delivery of healthcare services like human resource shortage, increased demand for specialized care, inappropriate personal protective equipment (PPE), overtaxing hospitals and non-healthcare-related issues like loss of employment and financial vulnerability. It has led to inequity between the higher and low socioeconomic households, resulting in the overburdening of the system (14, 15). The COVID-19 pandemic has not just impacted the population's health rather the whole economy. It affected all the sectors of the economy, such as hospitality, tourism and aviation, education, goods manufacturing, supply chain, currency exchange, food and agriculture, healthcare and the pharmaceutical industry, and petroleum and oil industry (16, 17). Hence, it is important for the stakeholders (viz. public health professionals, health authorities, research and medical institute, decision-makers, and healthcare providers) involved in the mitigation of COVID-19 to understand the dynamics of the viral outbreak, which is critical for policy development and practice. Gombos et al. (18) from Hungary found that the formation of research groups helped in translating the scientific findings into relevant information, which is highly significant for the government and policymakers in deciding on various aspects of the mitigation due to the COVID-19 pandemic. Further, Zeliha et al. (19) have stated the role of various stakeholders like local authorities, ministry of health, disease control centers, and research institutions and centers at the national and international level in managing the COVID-19 pandemic along with information dissemination for its preparedness and response. Similarly, centers for diseases control and health protection agencies of various countries are involved in decision making related to redeployment, retention of the staff, testing facility, and PPE, etc., based upon the evidence and expert opinions (20). It has also been found that the COVID-19 challenges policymakers to balance political judgment with the responsible use of expert advice (21). However, the decisions or responses differed across countries. We conducted the current study to assess the perception of public health professionals regarding the preparedness and response of the governments of various Indian Technical and Economic Cooperation (ITEC) countries.

MATERIALS AND METHODS

Study Settings and Duration

A total of three capacity building programs, namely "Managing COVID-19 Pandemic–Experience and Best practices of India" were conducted by the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, an institute of National Importance in India, with technical support from the Ministry of External Affairs, Government of India. These programs were conducted under the flagship International Public Health Management Development Programs (IPHMDP), being conducted since 2016 by the institute. The programs aim at building the capacity of public health professionals of 161 ITEC countries on COVID-19 by illustrating the best practices and experience of the Indian government in managing the COVID-19 pandemic.

Study Participants

We included all public health professionals, such as academic faculty, mid and senior-level program managers, researchers, and clinicians who were directly or indirectly managing the COVID-19.

Data Collection Tool and Procedure

We adapted the data collection tool from WHO's COVID-19 Strategic Preparedness and Response (SPRP), Monitoring and Evaluation Framework (22), interim guidelines for Critical preparedness, readiness and response actions for COVID-19 (23), and a strategic framework for emergency preparedness (24), which was later finalized using modified Delphi technique (25). It was administered using an online Google form. The first section of the questionnaire was about the background characteristics of participants, whereas the second part comprised four questions that were intended to evaluate the status of COVID-19 infection in the participant's respective countries. The third section comprised of 15 questions to assess the overall preparedness in terms of managing COVID-19, while the last section had four questions on the overall score for the country in combating the COVID-19 pandemic, challenges by the country in controlling the disease, innovative measures, and suggestions undertaken by countries to control the pandemic. We have developed this questionnaire as a Google form and collected the responses anonymously.

Data Management and Analysis

The overall preparedness of managing COVID-19 was rated using a five-point Likert scale (completely disagree-1, disagree-2, neither disagree nor agree-3, agree-4, and completely agree-5), whereas the overall score for the country in combating COVID-19 pandemic was assessed using a 10-point scale (1 being the poorest to 10 extraordinary). Further, the overall score is classified as low/mild (<4), moderate (4–7), and excellent (≥7) preparation. In order to evaluate the challenges faced by the country in controlling the pandemic, participants selected the challenges faced in controlling the pandemic.

Ethics

The Institute Ethics Committee of the PGIMER, Chandigarh, exempted this study from ethical review (IEC-08/2020/1743).

RESULTS

Table 1 shows the demographic characteristics of participants who opined on their country's response to COVID-19. A total of 97 individuals from 13 countries responded to the survey. The maximum participants who responded to the survey were from Bangladesh, ($n = 41$, 42.3%) followed by Nepal ($n = 19$, 19.6%), and Kenya ($n = 12$, 12.4%). The participants were between the age of 29–44.5 years. Majority were men ($n = 67$, 69.1%), postgraduates ($n = 55$, 56.7%), and specialized in medical sciences ($n = 77$, 79.4%). Majority of the participant's reported their primary role as academic faculty ($n = 33$, 34%) while rests were program managers ($n = 23$, 23.7%), researchers ($n = 13$, 13.4%), patient management ($n = 12$, 12.4%), and students ($n = 8$, 8.2%).

Table 2 shows the perception of participants on the status of COVID-19 transmission and surveillance mechanisms in their respective countries. In terms of transmission, ($n = 67$, 69.1%) believed it as community transmission and majority ($n = 68$, 70.1%) reported active contact-based surveillance system used in their country during the COVID-19. The majority ($n = 80$, 82.5%) of participants had responded that there is a dedicated website for COVID-19 in their countries.

Table 3 summarizes the perception of participants regarding the COVID-19 response undertaken by their respective countries. Around 37 (38.1%) participants agreed on non-availability or poorly prepared multisectoral national operational plans to mitigate the COVID-19 pandemic in their countries. Most ($n = 44$, 45.3%) reported that resource (equipment and other inventories) and human resource capacity assessment had been poorly assessed to address the COVID-19 pandemic. The adequacy of trained rapid response team (RRT) and their placement at all levels of healthcare were opined by merely 40 (41.2%) participants. Although a structured and uniform format for reporting COVID-19 cases was agreed upon by 60 (61.9%) participants, half ($n = 50$, 51.5%) of the participants responded to the use of epidemiological data on COVID-19 for reviewing the public health interventions and resource allocation at regular intervals. Less than half of the participants ($n = 45$, 46.4%) mentioned the presence of appropriate infection prevention and control strategies and standard operating procedures/guidelines at all entry points in their country. The country's preparedness to reorganize the health systems in prevention and clinical management was mostly inadequate ($n = 49$, 50.5%) as per the participants. With regard to the training of health workers and provision of PPE, the vast majority of participants responded that it was insufficient ($n = 39$, 40.2%) or inadequate ($n = 59$, 60.8 %). Most participants disagreed upon the parameters of risk communication and community engagement strategies

TABLE 1 | Demographic characteristics of participants from Indian Technical and Economic Cooperation countries in the study.

		Number (*N* = 97)	Percentage (%)
Region/Country	**Asian**		
	Bangladesh	41	(42.3)
	Nepal	19	(19.6)
	Bhutan	3	(3.1)
	Afghanistan	1	(1.0)
	Maldives	1	(1.0)
	African		
	Kenya	12	(12.4)
	Nigeria	2	(2.1)
	Eastern Mediterranean		
	Oman	3	(3.1)
	South American		
	Colombia	5	(5.2)
	Mexico	5	(5.2)
	Peru	2	(2.1)
	Western Pacific		
	Mongolia	2	(2.1)
	Fiji	1	(1.0)
Median (IQR) age in years		35.0 (29.0, 44.5)	
Gender	Male	67	(69.1)
	Female	30	(30.9)
Highest education	Post graduation	55	(56.7)
	Graduation	42	(43.3)
Median (IQR) years of experience		8.0 (3.0, 15.0)	
Area of specialization	Medical Sciences	77	(79.4)
	Others	22	(20.7)
Primary role in their organization	Academic faculty	33	(34.0)
	Programme manager	23	(23.7)
	Researcher	13	(13.4)
	Patient management	12	(12.4)
	Student	8	(8.2)
	Others	2	(2.1)

IQR, Interquartile range.

TABLE 2 | Perception of participants about COVID-19 transmission and surveillance mechanism in their country.

Parameter		*n* (n-97)	(%)
Transmission	Community transmission	67	(69.1)
	Sporadic	19	(19.6)
	Cluster of cases	9	(9.3)
	Don't know	2	(2.1)
COVID-19 surveillance system[a]	Active contact-based	68	(70.1)
	SARI based	37	(38.1)
	Hospital based	35	(36.1)
	Community-based	26	(26.8)
	ILI based	16	(16.5)
	None	5	(5.2)
Presence of dedicated website for COVID-19	Yes	80	(82.5)
	No	12	(12.4)
	Don't know	5	(5.1)

SARI, Severe acute respiratory illness; ILI, Influenza like illness; [a]More than one response.

adopted, response, and cooperation of the general public to control the COVID-19, adequate testing facility for COVID-19 and delivery of essential healthcare need other than COVID-19. No statistically significant difference was observed in the responses from participants with medical vs. non-medical background except for the implementation of appropriate infection prevention and control strategies (Agree or more: 52 vs. 25%, $p = 0.04$) and excellent response and cooperation from the general public (Disagree or more: 33.8 vs. 75%, $p = 0.005$). Similarly, no significantly different responses were observed based on the primary role of the participant (academic faculty, program manager, researcher, and patient management provider except for the availability of a multisectoral national operational plan ($p = 0.014$) (data not tabulated). The overall median (interquartile) score for measures taken for the control of COVID-19 by the country ranged between 4.5 and 7 (average 6) which did not significantly vary between the above sub-group of participants.

Table 4 listed the challenges faced by the countries in control of the COVID-19 pandemic. The majority of the participants mentioned the under testing of susceptible population ($n = 79$, 81.4%), lack of appropriate PPEs ($n = 69$, 71.1%), lack of awareness ($n = 65$, 67%) as the biggest challenges faced in controlling the deadly situation. These were followed by other challenges such as safety and security concerns of healthcare workers, underreporting of cases, the low or poor human resource capacity, poor implementation of public health interventions, poor governance/administration, low inventories other than PPE, and panic due to misinformation.

DISCUSSION

The COVID-19 pandemic response speckled widely across countries. We set out to measure the perceptions of public health professionals from ITEC countries toward their countries' response and preparedness to mitigate the COVID-19 pandemic. This study is not meant to compare countries with one another. Rather, to help the governments to understand the current status, track and measure the countries' response for developing a policy document for disease prevention and mitigation, which will ultimately strengthen the social, health, and economic sectors affected by COVID-19 and other pandemics. We found that the perception of public health professionals to government response regarding fostering improvement on COVID-19 situation was "moderate," with respect to transmission and surveillance mechanism, uniform reporting mechanism, and availability of adequate PPE for health workers. However, the participants were rated the government response as "poor" in the availability of multisectoral national operational plan, human resource capacity, availability of trained RRTs, preparedness in prevention and clinical management, communication and community engagement strategies, facilities to test samples of the patient, and transparent governance and administration. Jeffrey et al. (26) also developed a 10-item instrument to help policymakers in designing and implementing COVID-19 prevention and treatment strategies; however, it was limited by the number of variables studied and opinions from a limited number of stakeholders from one country. Oleribe et al. (27) reported that interventions adopted by the government regarding the use of PPEs and management of isolation rooms were poor, which is in sharp contradiction to the current study. Further, we captured the information on community transmission of highly virulent viral strains as the dominant mode of spread in their countries, as reported in other studies (28–30).

In the current study, over one-third of participants responded that the governance and administration in their country were transparent and appropriate to control the COVID-19 pandemic. It is in contrast to the study by Jeffrey et al. (26) and Azlan et al. (31) where respondents trusted their government for the measures taken to control the COVID-19 pandemic and the health systems in optimum utilization of medical resources. Globally, the public perception of government decisions in the form of reports and statistics, or other approaches has scored the above average, which also contradicts the findings of the current study (26).

The multisectoral national operational plan to mitigate the COVID-19 pandemic was successfully implemented by various countries (32–34). In contrast, less than one fourth of participants reported a well-developed operational plan in their respective countries in our study. The rapidly growing imbalance between demand and supply during the COVID-19 pandemic led to scarcities of critical goods, thereby posting challenges in maintaining and restocking supplies (35). Similar to our findings, the workforce exacerbated the shortage of N-95 masks, availability of intensive care unit beds and ventilators to patients was reported in the countries like the USA, Italy, and South Korea (36–39). Further, the implementation of non-pharmacological measures like physical distancing, compliance

TABLE 3 | Perception of participants (*n* = 97) on COVID-19 response undertaken by their countries.

SN	Response	Agree or more		Neutral		Disagree or more	
		n	(%)	*n*	(%)	*n*	(%)
National/sub-national level coordination, planning and monitoring							
1.	Availability of multisectoral-national operational plan	23	(23.7)	37	(38.1)	37	(38.1)
2.	Human resource capacity and risk analysis assessment	27	(27.8)	26	(26.8)	44	(45.3)
3.	Transparent governance and administration	40	(41.2)	28	(28.9)	29	(29.9)
Health systems preparedness							
4.	Adequate preparedness in reorganization of health systems in prevention and clinical management	28	(28.9)	20	(20.6)	49	(50.5)
5.	Training of healthcare providers	32	(32.9)	26	(26.8)	39	(40.2)
6.	Structured and uniform format for reporting	60	(61.9)	23	(23.7)	14	(14.5)
7.	Adequate facility to test the samples of patients	25	(25.7)	31	(32.0)	41	(42.2)
Surveillance, rapid response team and case investigation							
8.	Availability of trained Rapid Response Team at all levels of healthcare	40	(41.2)	27	(27.8)	30	(30.9)
9.	Regular analysis of epidemiological data for reviewing public health interventions	50	(51.5)	30	(30.9)	17	(17.5)
10.	Availability of Standard Operating Procedures at all points of entry for screening and risk communication.	49	(50.5)	30	(30.9)	18	(18.5)
Infection prevention and control							
11.	Implementation of appropriate infection prevention and control strategies (like adequate triage system and isolation rooms, trained staffs, and other sufficient materials)	45	(46.4)	25	(25.8)	27	(27.8)
12.	Availability of adequate and appropriate Personal Protective Equipment for healthcare providers	59	(60.8)	18	(18.6)	20	(20.6)
Risk communication and community engagement							
13.	Well-developed communication and community engagement strategies.	26	(26.8)	37	(38.1)	34	(35.1)
14.	Excellent response and cooperation of the general public	27	(27.8)	29	(29.9)	41	(42.2)
Maintaining essential health services							
15.	Adequate addressal of all essential healthcare needs of the population	29	(30.1)	28	(28.9)	40	(41.1)
	Overall median (interquartile) score for control measures			6.0 (4.5, 7.0)			

TABLE 4 | Challenges faced during the countries in control of COVID-19 pandemic.

Parameter	*n*	(%)
Under testing of the susceptible population	79	(81.4)
Lack of appropriate PPEs	69	(71.1)
Lack of awareness in the public	65	(67.0)
Safety and security concerns of healthcare workers	58	(59.8)
Underreporting of cases	52	(53.6)
Poor implementation of public health interventions	51	(52.6)
Poor capacity of human resources	51	(52.6)
Poor multi-sectoral action	48	(49.5)
Poor governance/administration	47	(48.5)
Low inventories other than PPE	44	(45.4)
Panic due to misinformation	31	(32.0)
Others	4	(4.1)
No challenges	2	(2.1)

with facemasks, lockdowns, hand washing, self-isolation, and adoption of other behavioral changes was also difficult (26). The published literature for the pandemics also states that the compliance to public health measures differs across countries based on their socio-cultural norms and belief along with the presence of resources (40). For example, Asians fared better by utilizing massive testing campaigns, aggressive lockdown policies and, contact tracing, as equated to countries in Europe and the America (41). Some countries in Latin and North America and Europe delayed imposing any restrictions and faced severe consequences (42). We did not attempt to undertake an analysis of stakeholder perception between countries. Other studies on healthcare workers perspectives to the government response to COVID-19 stated that appropriate infection prevention measures were adopted during the pandemic, like systematic or streamlined supply and use of PPE, and adoption of prevention guidelines (43, 44). We observed that in one-third of cases, trained RRTs consisting of health professionals was present in their country while two-third opined the presence of structured use of reporting system, similar to other studies (45–47). The preparedness for the reorganization of the health system in preventing the magnitude of COVID-19 has helped in containing the outbreak through a rapid increase in bed capacity, adequate equipment and staffing, triaging mechanism, and safe delivery of primary care services which is contrary to the current study which scored below average (48–50). The most significant challenges faced by countries in the current study reported were poor human resource capacity, lack of multisectoral approach and poor governance similar to the other studies (35, 51). The results highlight the importance of adequate preparedness in context to the mitigation of pandemic. The effective preparedness of countries to tackle such a pandemic is important to prevent paralysis of the existing health systems in delivering effective health services.

Our Study Had the Following Strengths

First, it collated the experiences and perceptions of public health professionals of different countries toward their country's response during the COVID-19 pandemic, which will be useful for framing appropriate policies for pandemic preparedness and response. Second, the study included all the essential aspects of the prevention and control of COVID-19 in the comprehensive tool used for collecting the responses. Our study is not without limitations. The perception of stakeholders might not truly reflect the country's preparedness toward the COVID-19 pandemic as it was self-reported and dependent upon participants' honesty and recall ability. Further, only public health professionals of 13 countries were included in the survey, of which 61.9% were from two countries namely, Bangladesh and Nepal. Hence, the results might not reflect the opinion of all ITEC nations and might limit generalization. There was a lag period between the actual response and seeking the opinion from the participants. Despite these limitations, the present study provides valuable information about the perception of senior stakeholders about their country's response during the COVID-19 pandemic.

CONCLUSION

We identified a low to moderate preparedness of various countries in diverse domains of managing the COVID-19 pandemic. As the global threat of COVID-19 is still to end, great efforts on building a robust preparedness and response system for COVID-19 and similar pandemics are urgently required.

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

SG contributed to the concept. SG and KU did a literature search and wrote the manuscript. KS contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Mass Media Use to Learn About COVID-19 and the Non-intention to Be Vaccinated Against COVID-19 in Latin America and Caribbean Countries

Guido Bendezu-Quispe[1,2], Jerry K. Benites-Meza[3,4], Diego Urrunaga-Pastor[5]*, Percy Herrera-Añazco[2,6,7], Angela Uyen-Cateriano[8], Alfonso J. Rodriguez-Morales[9,10], Carlos J. Toro-Huamanchumo[11,12], Adrian V. Hernandez[13,14] and Vicente A. Benites-Zapata[2,11]*

[1] Escuela de Medicina, Universidad César Vallejo, Trujillo, Peru, [2] Red Internacional en Salud Colectiva y Salud Intercultural, Mexico, Mexico, [3] Sociedad Científica de Estudiantes de Medicina de la Universidad Nacional de Trujillo, Trujillo, Peru, [4] Grupo Peruano de Investigación Epidemiológica, Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, Lima, Peru, [5] Universidad Científica del Sur, Lima, Peru, [6] Escuela de enfermería, Universidad Privada San Juan Bautista, Lima, Peru, [7] Instituto de Evaluación de Tecnologías Sanitarias en Salud e Investigación–IETSI, EsSalud, Lima, Peru, [8] Medecins Sans Frontieres, Health Politics Team, Brussels, Belgium, [9] Latin American Network of COVID-19 Research (LANCOVID), Pereira, Colombia, [10] Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Americas, Pereira, Colombia, [11] Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru, [12] Unidad de Investigación Multidisciplinaria, Clínica Avendaño, Lima, Peru, [13] Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, United States, [14] Unidad de Revisiones Sistemáticas y Metaanálisis, Guías de Práctica Clínica y Evaluaciones Tecnológicas Sanitarias, Universidad San Ignacio de Loyola, Lima, Peru

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***Correspondence:**
Diego Urrunaga-Pastor
diego.urrunaga.pastor1@gmail.com
Vicente A. Benites-Zapata
vbeniteszapata@gmail.com

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Background: The Latin American and Caribbean (LAC) region has been one of the regions most affected by the COVID-19 pandemic, with countries presenting some of the highest numbers of cases and deaths from this disease in the world. Despite this, vaccination intention is not homogeneous in the region, and no study has evaluated the influence of the mass media on vaccination intention. The objective of this study was to evaluate the association between the use of mass media to learn about COVID-19 and the non-intention of vaccination against COVID-19 in LAC countries.

Methods: An analysis of secondary data from a Massachusetts Institute of Technology (MIT) survey was conducted in collaboration with Facebook on people's beliefs, behaviors, and norms regarding COVID-19. Crude and adjusted prevalence ratios (aPR) with their respective 95% confidence intervals (95%CI) were calculated to evaluate the association between the use of mass media and non-vaccination intention using generalized linear models of the Poisson family with logarithmic link.

Results: A total of 350,322 Facebook users over the age of 18 from LAC countries were included. 50.0% were men, 28.4% were between 18 and 30 years old, 41.4% had a high school education level, 86.1% lived in the city and 34.4% reported good health condition. The prevalence of using the mass media to learn about COVID-19 was mostly through mixed media (65.8%). The non-intention of vaccination was 10.8%.

A higher prevalence of not intending to be vaccinated against COVID-19 was found in those who used traditional media (aPR = 1.36; 95%CI: 1.29–1.44; $p < 0.001$) and digital media (aPR = 1.70; 95%CI: 1.24–2.33; $p = 0.003$) compared to those using mixed media.

Conclusion: We found an association between the type of mass media used to learn about COVID-19 and the non-intention of vaccination. The use of only traditional or digital information sources were associated with a higher probability of non-intention to vaccinate compared to the use of both sources.

Keywords: mass media, SARS-CoV-2, COVID-19, Latin America, vaccines

INTRODUCTION

Since the WHO declared the COVID-19 pandemic in March 2020 (1), it is estimated that as of December 20, 2021, there were more than 274,000 cases globally and more than five million deaths from this disease (2). The vaccine against COVID-19 is the most cost-effective strategy to combat this pandemic, and it is estimated that as of December 20, 2021, more than eight billion doses of the vaccine have been administered worldwide.

To date, several highly effective vaccines have been licensed to reduce the incidence of hospitalization and death. However, vaccine coverage remains insufficient (3, 4) due to aspects such as low acceptance of vaccination (5) as in the Middle East/North Africa, Europe and Central Asia, and West/Central Africa, which reported higher proportions of COVID-19 vaccine hesitancy (6). This implies a public health problem since the control of an infectious disease through the use of vaccines involves having high vaccination coverage, which in the case of COVID-19 has been suggested should be of 70 to 80% of the population (7).

The Strategic Advisory Group of Experts on Immunization (SAGE) of the World Health Organization (WHO) defines vaccine reluctance as a "delay in accepting the vaccine or refusing the vaccine despite its availability" (8). This phenomenon is influenced by complacency, trust and convenience (5) and is considered by the WHO as one of the 10 greatest challenges of global health (9).

Different factors influence vaccine reluctance, including the information disseminated by the mass media (10). Although these media played an important role in disseminating community mitigation strategies and other favorable measures during the pandemic (11), their impact is not always positive. Various studies have shown that media coverage of coronavirus news during geo-blockades, prolonged quarantines, and financial and social hardships induced fear and provoked psychological stress (11). Likewise, they fueled rumors, hoaxes, and misinformation about the etiology, the results, the prevention, and the cure of the disease (12). In this sense, the mass media plays a key role in the perception of vaccines (13–15). Indeed, before the pandemic, critical digital media against vaccines influenced vaccination intentions (16), suggesting the importance of designing public policies to counteract this influence.

Latin America and the Caribbean (LAC) is one of the regions most affected by the pandemic (17), and the need to prioritize access to vaccines against COVID-19 (18) has been called for in low- and middle-income countries. Countries such as Mexico, Brazil, and Peru are among those with the highest number of cases and deaths from this disease in the world (2). Although previous studies have described a high vaccination intention in the region, this is not homogeneous (10, 19), and some access barriers have hindered the early and extensive vaccination campaign against COVID-19 in the region (20). Likewise, it has been described that in LAC there is greater mistrust of science so that whoever provides information on vaccines, beyond medical or scientific authorities, maybe more persuasive (21). This is relevant because the population with low acceptance of the vaccine could respond positively to available and accessible information from promoters related to the general population (22–24). Although some studies in Latin American countries have evaluated some aspects of the impact of the mass media and social networks on the search for information during the pandemic (25, 26), to the best of our knowledge, no study has evaluated the influence of the mass media related to the intention of vaccination. Therefore, the objective of our research was to evaluate the association between the use of mass media news and information to learn about COVID-19 and the non-intention of vaccination against COVID-19 in LAC countries.

METHODS

Study Design

A secondary analysis was performed using a database compiled by the Massachusetts Institute of Technology (MIT) in collaboration with Facebook. This survey aimed to assess beliefs, behaviors, and norms due to COVID-19. Data collection began on July 7, 2020, and ended on March 28, 2021. It was conducted in more than 60 countries and translated into 51 languages. Two versions of the survey were available. First, in countries with a sufficient pool of users to sample, a multi-wave survey was conducted continuously over several 2-week waves with the goal of collecting 3,000 respondents per wave. Second, in countries with a limited survey pool, we fielded a snapshot survey in which Facebook aimed to deliver 3,000 respondents over a 2-week period.

Population, Sampling, and Sample

The survey included participants aged 18 or older who were Facebook users. Participants who resided in LAC and who participated in the survey between July 7, 2020, and March 28, 2021, were included. Participants were asked the question: In the past week, did you see more or less news than you wanted to see about coronavirus (COVID-19)? to which the answers could be: (1) Much less, (2) Less, (3) About the right amount, (4) More, or (5) Much more. However, only those who answered (i) About the right amount, (ii) More, and (iii) Much more were considered. Finally, participants who did not present data for the variables of interest and did not have the weighting factor to perform the corresponding analyses were excluded.

Variables

The outcome variable was the non-intention to be vaccinated, which was operationalized from the answer to the question: If a vaccine for COVID-19 becomes available, would you choose to get vaccinated? The possible answers to this question were: yes, no, I don't know, I have already been vaccinated. The construction of the variable was carried out considering only those who answered yes or no.

The exposure variable was defined using the question: In the past week, from which of the following, if any, have you received news and information about COVID-19? with the following response alternatives: (1) Online sources (websites, apps, social media), (2) Messaging apps/SMS/text messaging, (3) Newspapers, (4) Television and (5) Radio. For the analysis, three categories of exposure to information media were constructed: digital media (online sources or messaging apps), traditional media (newspapers or television or radio) and mixed media (digital media and traditional media).

Other variables included were gender (male, female, non-binary), age (18–30, 31–40, 41–50, 51–60, 61–70, 71–80, over 80), educational level (less than primary school, primary school, secondary school, college/university, graduate school), area of residence (city, town, village or rural area) and state of health (poor, fair, good, very good, excellent).

Statistical Analysis

The databases were compiled and downloaded in ".txt" text format, then imported into the statistical package STATA v15.0 (StataCorp, TX, USA). All analyses were performed considering the complex sampling of the survey using the svy command.

A descriptive analysis was performed using absolute frequencies and weighted proportions with their respective 95% confidence intervals (95% CI) according to the complex sampling of the survey. In the bivariate analysis, we used the Pearson Chi-square test with Rao-Scott correction. To evaluate the association between the mass media use to learn about COVID-19 and the non-intention to be vaccinated, generalized linear models of the Poisson family with log link function were constructed. The crude prevalence ratio (cPR) and adjusted prevalence ratio (aPR) were calculated with their respective 95% CI for the associations studied. Adjustment for confounders was performed considering an epidemiological approach. Collinearity was evaluated using variance inflation factors (VIF), considering a cut-off point <10. A $p < 0.05$ was considered statistically significant for all analyses performed.

Ethical Aspects

Before starting the survey, all participants provided informed consent. An analysis of a secondary database that did not have personal identifiers and that respected the integrity of the participants was performed. Access to the data was granted by the Massachusetts Institute of Technology, Boston, United States of America.

RESULTS

Selection of the Sample Included in the Study

The population surveyed was 2,040,594 Facebook users over the age of 18 worldwide. For this study, participants residing in LAC countries (350,322), and those who in the past week saw about the right amount or more or much more news than they wanted to see about COVID-19 were included. All those who did not have information on the variables of interest were excluded. The final study population was 82,092 participants (**Figure 1**).

Characteristics of the Study Samples

There was a higher proportion of men (50.0%), participants aged between 18 and 30 years (28.4%), with a secondary school education level (41.4%) and who lived in the city (86.1%). Likewise, the health condition reported in a greater proportion was good (34.4%). The prevalence of the use of the media to learn about COVID-19 was mostly through mixed media (65.8%). The non-intention of vaccination was 10.8% (**Table 1**).

Proportion of Non-vaccination Intention According to the Mass Media Used to Learn About COVID-19 in Each LAC Country

The proportion of non-vaccination intention according to the means of communication used to learn about COVID-19 varied by country in LAC. In relation to participants using traditional media, the proportion not intending to be vaccinated was highest in Jamaica (46.1%), Trinidad and Tobago (32.1%), and Uruguay (17.9%), while the lowest proportions were in Venezuela (8.0%), Ecuador (8.8%) and Peru (9.2%) (**Figure 2A**). In those using mixed media, the proportion not intending to be vaccinated was highest in Jamaica (48.2%), Trinidad and Tobago (26.5%), and Uruguay (19.6%), while the proportion was lowest in Brazil (7.1%), Ecuador (7.7%) and Peru (8.2%) (**Figure 2B**). In participants who used digital media, the proportion not intending to be vaccinated was highest in Jamaica (50.2%), Uruguay (37.5%), and Trinidad and Tobago (29.5%), and the lowest proportion was in

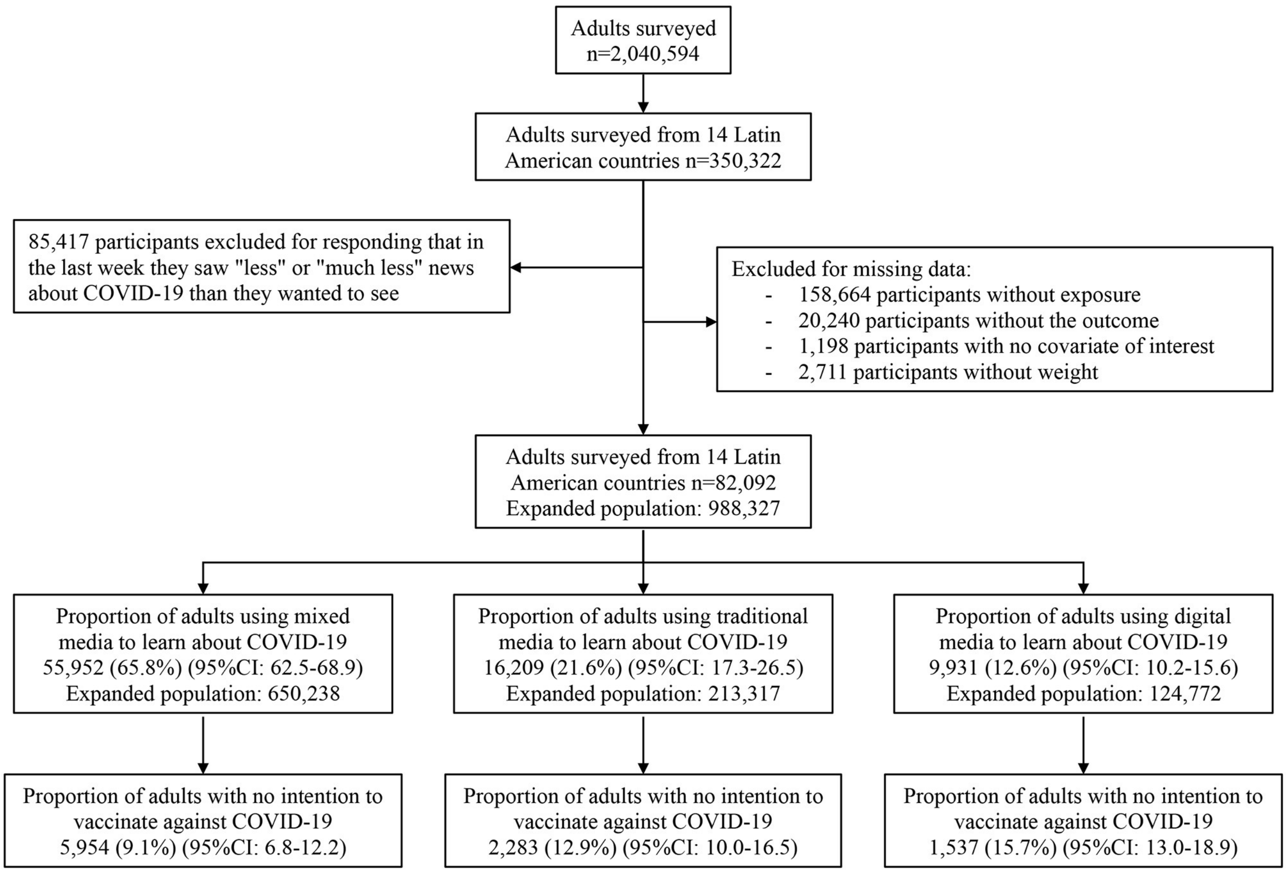

FIGURE 1 | Flowchart of the selection of the study sample.

Guatemala (7.8 %), Ecuador (13.3%) and Honduras (13.3%) (**Figure 2C**).

Bivariate Analysis According to the Media Used to Learn About COVID-19

We found a higher proportion of non-vaccination intention among participants who used only traditional (12.9%) and digital (15.7%) media compared to those who used mixed media (9.1%) ($p = 0.003$). Likewise, we observed statistically significant differences according to sex, age, level of education, area of residence, and health status (**Table 2**).

Bivariate Analysis According to the Non-intention of Vaccination Against COVID-19

The bivariate analysis according to the non-vaccination intention showed statistically significant differences for the means of communication used and for the health condition of the participants (**Table 3**).

Association Between the Mass Media Used to Learn About COVID-19 and the Non-intention of Vaccination Against COVID-19

In the crude analysis, a higher prevalence of not intending to be vaccinated against COVID-19 was found in those who used traditional media (cPR = 1.42; 95%CI: 1.35–1.49; $p < 0.001$) and digital media (cPR = 1.72; 95%CI: 1.21–2.46; $p = 0.006$) compared to those using mixed media. This association remained statistically significant in the analysis adjusted for sex, age, education level, living area and health condition [traditional media (aPR = 1.36; 95%CI: 1.29–1.44; $p < 0.001$); digital media (aPR = 1.70; 95%CI: 1.24–2.33; $p = 0.003$)] (**Table 4**).

DISCUSSION

The objective of this study was to evaluate the association between the use of mass media news and information to learn about COVID-19 and the non-intention of vaccination against COVID-19. As a result, it was found that people who use only traditional or digital media had a higher non-vaccination

TABLE 1 | General characteristics of the study sample (*n* = 82,092; *N* = 988,327).

Characteristics	Absolute frequency	Weighted proportion*	
	n	%	95%CI
Gender			
Female	44,699	49.6	48.5-50.6
Male	37,211	50.0	48.8-51.2
Not binary	182	0.4	0.3-0.5
Age (years)			
18–30	24,489	28.4	24.0–33.2
31–40	19,879	20.5	19.2–22.0
41–50	15,872	18.4	17.7–19.1
51–60	13,002	16.5	15.6–17.4
61–70	6,839	11.9	10.5–13.4
71–80	1,774	3.7	2.8–4.7
80 or more	237	0.6	0.4–0.9
Education level			
Less than primary school	844	3.2	1.1–9.0
Primary school	4,553	9.0	5.2–15.3
Secondary school	30,494	41.4	35.7–47.4
College / University	35,851	35.4	22.8–50.5
Graduate school	10,350	10.9	8.9–13.3
Area of residence			
City	67,341	86.1	75.0–92.8
Town	9,776	8.9	3.3–21.6
Village or rural area	4,975	5.0	4.3–5.8
Health condition			
Poor	1,942	3.1	2.4–4.1
Fair	12,331	17.7	15.7–19.8
Good	27,575	34.4	31.5–37.4
Very good	25,680	28.0	26.5–29.6
Excellent	14,564	16.8	13.5–20.8
Mass media used to learn about COVID-19			
Mixed	55,952	65.8	62.5–68.9
Traditional	16,209	21.6	17.3–26.5
Digital	9,931	12.6	10.2–15.6
Vaccination intention			
Yes	72,318	89.2	86.4–91.5
No	9,774	10.8	8.5–13.6

95%CI: 95% Confidence interval.
**Weights and the design effect of the complex survey sampling were included.*

intention compared to those who use both types of information about COVID-19.

The COVID-19 pandemic is a scenario of health challenges due to the so-called infodemic (27), and therefore, it is important that accessible information on health issues is reliable (28). Some studies indicate that mass media news and information could be an important source of both information and disinformation about COVID-19. In Italy, a study showed that during the first wave of COVID-19, the Italian press preferred to resort to infodemic and moderately infodemic terms, while scientific sources favored the correct names (29). In Brazil, a study found that a social network such as Twitter had coverage of topics related to COVID-19 similar to that of the media (25). In addition, some media reports presented a negative feeling toward political issues in the media and that a high incidence of mentions of a specific drug denoted a high political polarization during the pandemic (25). Another investigation showed that between May and June 2020, the top six terms related to COVID-19 searched on Google were "coronavirus," "corona," "COVID," "virus," "corona virus" and "COVID-19" (30). The countries with a higher number of COVID-19 cases had a higher number of COVID-19 queries on Google. Searches for "tips and cures" for COVID-19 increased in connection with the then-president of the United States speculating about a "miracle cure" and suggesting an injection of disinfectant to treat the virus (30). This same study noted that around two-thirds of Instagram users used the hashtags "COVID-19" and "coronavirus" to spread information related to the virus (30).

In relation to the intention to vaccinate against COVID-19, it has been described that exposure to misinformation leads to less intention to vaccinate, including people who, before being exposed to misinformation, indicated that they would definitely get vaccinated (31). It has also be described that exposure to misinformation about COVID-19 decreases the intention to vaccinate in those people who are motivated to get vaccinated to provide protection against the disease to family members, friends or other people at risk (31).

Several studies have described the influence of the mass media news and information on the intention of vaccination against COVID-19, with results that disagree with what we found. One study showed that newspapers could be a source of information that increases vaccination intention (32). Other research showed that in the United States population, traditional media such as both local and national television and national newspapers are used more to obtain information about the COVID-19 vaccine and that these means increase the probability of vaccination (33). On the other hand, another study also carried out in the United States found that compared with people who use digital media, those who use traditional media to know about COVID-19 had a greater intention to vaccinate (33). It is likely that these discrepancies are due to the quality of the information of the traditional media in LAC and the distrust that people who seek more reliable information have about them (34–36). This can lead to the consumption of these media by people who are more likely to accept information that encourages their own misconceptions about the vaccine, as in Italy, where the press gave false news (29). Given the spread of false and erroneous information about post-immunization deaths at the beginning of the vaccination campaign in Italy, it was reported that between 10 and 20% of Italian candidates for the AstraZeneca vaccine rejected it, causing a delay in vaccination and the non-administration of ∼200,000 doses (37).

The effect of digital media on non-vaccination intention has been previously described. In England, a study associated vaccine reluctance with belief in conspiracy theories and attitudes in general toward vaccines, as well as an informative dependency

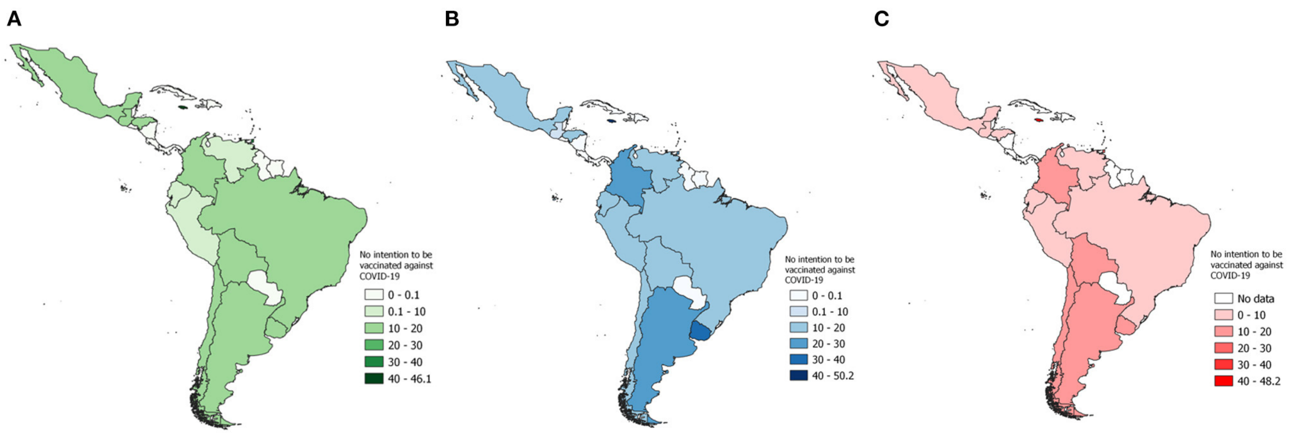

FIGURE 2 | Proportion of non-vaccination intention according to the mass media used to learn about COVID-19 for each LAC country: **(A)** Traditional media; **(B)** Mixed media; **(C)** Digital media.

on social networks (38). In the United States, it was found that persons who are less likely to receive the COVID-19 vaccine, use social networks as their only source of information, or at least as one of their sources of information (33, 39). This preponderance of digital media among people who do not have the intention of vaccination may be due to the influence of the anti-vaccine movement in these media. Indeed, previous research has identified social networks such as Facebook and Twitter as popular platforms for members of the anti-vaccine movement (40). In recent years, this movement has expanded to all major digital platforms, including YouTube, Instagram, and personal messaging services such as WhatsApp, and during the pandemic, the growth of this movement accelerated (41).

Although our study did not evaluate the possible reasons, it is likely that the greater intention to vaccinate against COVID-19 in people who seek information in both traditional and digital media is due to the fact that they are people who contrast information. In other words, before accepting information from a single medium, they decide to compare its veracity with other media. This form of information would make them less susceptible to misinformation and, therefore, more likely to accept vaccination.

The media are essential for the public to acquire scientific information from reliable, authoritative, and responsible sources, and people can even use these sources when they want to convince others (41). This poses some challenges that governments must face to improve their strategies of communication, such as the monitoring of social networks for timely changes in strategies or even the design of specific communication strategies to modify the intention of vaccination. One study identified top themes related to COVID-19 vaccines in tweets globally. The tweets were related to negative sentiments and largely framed the themes of emotional reactions and public concerns related to COVID-19 vaccines (42). Tweets related to facilitators of vaccination showed temporal variations over time, while barrier-related tweets remained largely constant throughout the study period (42). A study in Pakistan explored the potential effects of various communication strategies and identified fear appraisal as the most viable communication strategy for combating vaccine hesitancy (43). In addition, public skepticism negatively moderated the effects of media types and attributes of public service messages on willingness to get vaccinated (43). These strategies should consider the credibility of each of the media to employ. For example, in Germany, a study examined the relationship between exposure and credibility of different sources of health information and vaccination intention against COVID-19. The results revealed that in addition to reliable information from experts and health authorities, local newspapers also have a positive impact on vaccination intention (32). However, this effect decreases to a certain extent when age is considered. Furthermore, alternative information sources pose a notable threat to vaccination intent against COVID-19 (32). In the context of vaccination against COVID-19, a study evaluated that mechanisms such as the perception of information and persuasion of the individual affect attitudes toward vaccination (44). This is based on the influence of the completeness of the information, the veracity of the information, as well as the exchange of experiences and social pressure on the individual attitude of people, representing important aspects in the dissemination of information (44).

Our study has some limitations. The cross-sectional design does not allow causal relationships to be established between the variables of interest. Likewise, the universe studied corresponds to the population that has a social network, that is, the population with Internet access, reducing the generalization of results to the population that does not have this access. Additionally, some variables that would have made it possible to better characterize the phenomenon under study were not included in the analysis since the inclusion of variables was dependent on their availability in the database. It should also be mentioned that the survey data were obtained by self-reporting, and thus,

TABLE 2 | General characteristics according to each mass media group used in LAC ($n = 82,092$; $N = 988,327$).

Characteristics	Mixed		Traditional		Digital		*p*-Value*
	n	%	*n*	%	*n*	%	
Vaccination intention							0.003**
Yes	49,998	90.9	13,926	87.1	8,394	84.3	
No	5,954	9.1	2,283	12.9	1,537	15.7	
Gender							0.021**
Female	30,680	50.4	8,831	49.2	5,188	45.9	
Male	25,165	49.4	7,334	49.7	4,712	53.8	
Non-binary	107	0.2	44	1.1	31	0.3	
Age (years)							0.002**
18–30	17,284	30.2	3,420	18.9	3,785	35.2	
31–40	13,896	21.4	3,414	17.8	2,569	20.8	
41–50	10,826	18.3	3,404	20.2	1,642	16.3	
51–60	8,518	15.8	3,281	20.4	1,203	13.6	
61–70	4,289	10.8	1,970	15.6	580	10.8	
71–80	1,012	3.2	622	5.5	140	3.1	
80 or more	127	0.3	98	1.6	12	0.2	
Education level							<0.001**
Less than primary school	444	2.6	306	5.0	94	2.9	
Primary school	2,333	7.3	1,845	14.9	375	8.2	
Secondary school	19,578	39.9	7,784	48.7	3,132	37.3	
College / University	25,731	38.0	5,114	24.6	5,006	40.3	
Graduate school	7,866	12.2	1,160	6.8	1,324	11.3	
Living area							0.030**
City	46,311	87.1	12,950	83.4	8,080	85.3	
Town	6,433	8.2	2,080	10.3	1,263	10.0	
Village or rural area	3,208	4.6	1,179	6.3	588	4.7	
Health condition							<0.001**
Poor	1,190	2.8	511	4.2	241	3.3	
Fair	8,022	16.8	2,831	20.7	1,478	16.7	
Good	19,024	35.1	5,404	33.2	3,147	32.6	
Very good	18,242	29.2	4,305	23.9	3,133	29.0	
Excellent	9,474	16.1	3,158	18.0	1,932	18.4	

95%CI: 95% Confidence interval.
Weights and the design effect of the complex survey sampling were included.
**Refers to the statistical significance obtained from the comparison of the proportions between the categories of the variables considering the complex sampling of the survey.*
*** Pearson Chi-square test with Rao-Scott correction.*

memory or social desirability bias could occur. Although these limitations affect the generalization of the results obtained for the general population of LAC, the use of the social network Facebook in this region of the world is high, with four out of five inhabitants of this region using Facebook, thereby making these data useful for an initial approach to study the relationship between the sources of news and information on COVID-19 and the intention to vaccinate against this disease.

In conclusion, it was found that in the LAC population, two out of 10 people who only used digital media to learn about COVID-19 had no intention of vaccination, while only one in 10 people who used traditional or traditional and digital media had no intention of vaccination. We found an association between the type of information source used to learn about COVID-19 and the non-intention of vaccination. The use of only traditional or digital information sources was associated with a higher probability of non-intention of vaccination compared to the use of both information sources. Given this scenario, the communication of information supported by scientific evidence should be promoted as well as the development of strategies aimed at promoting vaccination in populations with less intention of receiving the COVID-19 vaccine. Reporting by traditional media and social media companies should be aimed at addressing vaccine hesitancy and the dissemination of correct and easy-to-digest information to the public.

TABLE 3 | General characteristics according to vaccination intention in LAC ($n = 82,092$; $N = 988,327$).

Characteristics	Vaccination intention						*p*-Value*
	No			Yes			
	n	%	95%CI	*n*	%	95%CI	
Mass media used to learn about COVID-19							0.003**
Mixed	5,954	9.1	6.8–12.2	49,998	90.9	87.8–93.2	
Traditional	2,283	12.9	10.0–16.5	13,926	87.1	83.5–89.9	
Digital	1,537	15.7	13.0–18.9	8,394	84.3	81.1–87.0	
Gender							0.860**
Female	5,851	10.9	7.6–15.4	38,848	89.1	84.6–92.4	
Male	3,881	10.6	9.3–12.1	33,330	89.4	87.9–90.7	
Non-binary	42	10.8	2.8–33.6	140	89.2	66.4–97.2	
Age (years)							0.144**
18–30	2,670	10.2	7.5–13.8	21,819	89.8	86.2–92.5	
31–40	2,380	11.3	8.6–14.7	17,499	88.7	85.3–91.4	
41–50	1,905	10.5	8.3–13.2	13,967	89.5	86.8–91.7	
51–60	1,652	10.5	7.9–14.0	11,350	89.5	86.0–92.1	
61–70	920	12.4	11.2–13.8	5,919	87.6	86.2–88.8	
71–80	223	10.5	8.5–12.8	1,551	89.5	87.2–91.5	
80 or more	24	5.1	2.0–12.4	213	94.9	87.6–98.0	
Education level							0.270**
Less than primary school	115	12.1	7.3–19.3	729	87.9	80.7–92.7	
Primary school	608	11.1	8.9–13.7	3,945	88.9	86.3–91.0	
Secondary school	3,894	11.2	8.6–14.4	26,600	88.8	85.6–91.4	
College / University	4,117	10.5	8.3–13.0	31,734	89.5	87.0–91.6	
Graduate school	1,040	9.8	7.2–13.1	9,310	90.2	86.8–92.8	
Area of residence							0.016**
City	7,298	10.4	8.3–13.1	60,043	89.6	86.9–91.7	
Town	1,484	12.7	9.6–16.6	8,292	87.3	83.4–90.4	
Village or rural area	992	14.0	12.2–16.1	3,983	86.0	83.9–87.8	
Health condition							<0.001**
Poor	227	11.6	9.8–14.7	1,715	88.4	85.3–90.2	
Fair	1,206	9.0	7.7–10.6	11,125	91.0	89.4–92.3	
Good	2,701	8.4	6.3–11.1	24,874	91.6	88.9–93.7	
Very good	3,073	10.6	8.1–13.8	22,607	89.4	86.2–91.9	
Excellent	2,567	17.7	15.2–20.5	11,997	82.3	79.5–84.8	

95%CI: 95% Confidence interval.
Weights and the design effect of the complex survey sampling were included.
Refers to the statistical significance obtained from the comparison of the proportions between the categories of the variables considering the complex sampling of the survey.
** *Pearson Chi-square test with Rao-Scott correction.*

TABLE 4 | Crude and adjusted prevalence ratio for non-intention to vaccinate according to each mass media group used to learn about COVID-19.

No vaccination intention	Crude Model[a]		Adjusted Model[a,b]	
	cPR (95%CI)	*p*-Value	aPR (95%CI)	*p*-Value
Mass media used				
Mixed	Ref.	—	Ref.	—
Traditional	1.42 (1.35–1.49)	<0.001	1.36 (1.29–1.44)	<0.001
Digital	1.72 (1.21–2.46)	0.006	1.70 (1.24–2.33)	0.003

cPR: crude prevalence ratio; aPR: adjusted prevalence ratio; 95%CI: 95% Confidence interval.
[a] *A generalized linear model of the Poisson family was carried out with link log considering the effect of the design and the weights of the complex sampling of the survey.*
[b] *Adjusted for sex, age, education level, living area and health condition.*

DATA AVAILABILITY STATEMENT

The datasets analyzed in this research article are not publicly available. This datasets were shared by the Massachusetts Institute of Technology due to signed agreement. Any request of them should be directed to vbeniteszapata@gmail.com.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GB-Q, JB-M, DU-P, and VB-Z participated in concept design and supervising the study. PH-A, AU-C, AR-M, CT-H, and AH participated in concept design. JB-M, DU-P, and VB-Z conducted the statistical analysis. All authors participated in manuscript writing, editing, final revision, and have read and agreed on the submitted manuscript.

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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.2022.877764/full#supplementary-material

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Factors Associated With the Decay of Anti-SARS-CoV-2 S1 IgG Antibodies Among Recipients of an Adenoviral Vector-Based AZD1222 and a Whole-Virion Inactivated BBV152 Vaccine

Sivaprakasam T. Selvavinayagam[1†], Yean Kong Yong[2†], Hong Yien Tan[3], Ying Zhang[4], Gurunathan Subramanian[1], Manivannan Rajeshkumar[1], Kalaivani Vasudevan[1], Priyanka Jayapal[1], Krishnasamy Narayanasamy[5], Dinesh Ramesh[1], Sampath Palani[1], Marie Larsson[6], Esaki M. Shankar[7] and Sivadoss Raju[1*]*

[1] State Public Health Laboratory, Directorate of Public Health and Preventive Medicine, Chennai, India, [2] Laboratory Center, Xiamen University Malaysia, Sepang, Malaysia, [3] School of Traditional Chinese Medicine, Xiamen University Malaysia, Sepang, Malaysia, [4] Chemical Engineering, Xiamen University Malaysia, Sepang, Malaysia, [5] Government Corona Hospital, Chennai, India, [6] Department of Biomedicine and Clinical Sciences, Linkoping University, Linköping, Sweden, [7] Infection Biology, Department of Life Sciences, Central University of Tamil Nadu, Thiruvarur, India

Background: The magnitude of protection conferred following recovery from COVID-19 or by vaccine administration, and the duration of protective immunity developed, remains ambiguous.

Methods: We investigated the factors associated with anti-SARS-CoV-2 S1 IgG decay in 519 individuals who recovered from COVID-19 illness or received COVID-19 vaccination with two commercial vaccines, viz., an adenoviral vector-based (AZD1222) and a whole-virion-based inactivated (BBV152) vaccine in Chennai, India from March to December 2021. Blood samples collected during regular follow-up post-infection/-vaccination were examined for anti-SARS-CoV-2 S1 IgG by a commercial automated chemiluminescent immunoassay (CLIA).

Results: Age and underlying comorbidities were the two variables that were independently associated with the development of a breakthrough infection. Individuals who were >60 years of age with underlying comorbid conditions (viz., hypertension, diabetes mellitus and cardiovascular disease) had a ∼15 times and ∼10 times greater odds for developing a breakthrough infection and hospitalization, respectively. The time elapsed since the first booster dose was associated with attrition in anti-SARS-CoV-2 IgG, where each month passed was associated with an ebb in the anti-SARS-CoV-2 IgG antibody levels by a coefficient of −6 units.

Conclusions: Our findings advocate that the elderly with underlying comorbidities be administered with appropriate number of booster doses with AZD1222 and BBV152 against COVID-19.

Keywords: AZD1222, BBV152, COVID-19, IgG decay, SARS-CoV-2, vaccination

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Zisis Kozlakidis, International Agency For Research on Cancer (IARC), France

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Renata Maria Grifantini, National Institute of Molecular Genetics (INGM), Italy
Marc Emmenegger, University Hospital Zürich, Switzerland
Ashok Iyaswamy, Hong Kong Baptist University, Hong Kong SAR, China

***Correspondence:**
Sivadoss Raju
dphpmlab@gmail.com
Esaki M. Shankar
shankarem@cutn.ac.in

†*These authors have contributed equally to this work and share first authorship*

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BACKGROUND

The COVID-19 pandemic has caused an unprecedented global crisis, and having lasted for more than 2 years, has resulted in over 524 million COVID-19 cases, claiming >6.27 million deaths by Mid-May 2022, causing huge levels of economic damage (1, 2). Although antiviral agents against SARS-CoV-2, the virus causing COVID-19, are becoming available, vaccines and public health interventions remain the most promising approach against this global peril. Notwithstanding anti-SARS-CoV-2 vaccines are successful in reducing the mortality and morbidity rates, and the level of neutralizing antibodies has correlated with protection against SARS-CoV-2 reinfection (3) as well as severe COVID-19 (4–6), breakthrough infections do continue to recur. Importantly, it still remains a conundrum, how long this vaccine-induced acquired immunity would last in an individual.

Several studies have investigated the dynamics and the duration of protection of neutralizing antibodies developed following the onset of natural SARS-CoV-2 infection or vaccination (7–11). The results thus far remain inconsistent, with some reporting rapid waning of antibodies months after virus exposure or following vaccine administration (7–13), whereas others report the prolonged presence of neutralizing antibodies (14–16). This discrepancy partly stems from numerous factors including differences in patient demography, vaccine type, and number of infections/vaccinations one has become exposed to, SARS-CoV-2 strains, intrinsic properties of immunity, underlying disease and many other miscellaneous factors. Given the complex interaction between intrinsic and extrinsic factors, the duration of protective immunity developed post-vaccination against COVID-19 still remains uncertain. Here, by using an appropriate statistical model, we investigated the factors such as age, gender, vaccine status, type of vaccine viz., a viral vector-based AZD1222 and an inactivated BBV152 vaccine as well as comorbidities and their association with antibody decay.

MATERIALS AND METHODS

Study Population

We conducted a population-based study among Chennai's adult who received treatment for COVID-19-related illness or received COVID-19 vaccination at the State Public Health laboratory, Directorate of Public Health and Preventive Medicine, Chennai, India, and the Government Corona Hospital, Chennai, India from March until December 2021. The inclusion criteria were that the participants needed to be >18 years, and there were no exclusion criteria. The medical records of the participants were reviewed and data such as patient demography, comorbidities, history of SARS-CoV-2 infection, date and type of vaccine received were recorded. Blood samples were collected during regular follow-up post-infection and/or post-vaccination, and tested for their levels of anti-SARS-CoV-2 IgG. The study was approved by the Human Ethics Committee of the Madras Medical College (EC No. 03092021).

Diagnosis of COVID-19 and Breakthrough SARS-CoV-2 Infection

Diagnosis of COVID-19 was made based on clinical and laboratory diagnoses; the former based universal Clinical Criteria 2021 defined by the Centers for Disease Control and Prevention, Atlanta, USA (https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019--2021/), and the later confirmed by a commercial TaqPath^{TM} COVID-19 RT-PCR test (Applied Biosystems, Thermo Fisher Scientific, Pleasanton, CA) for the *in vitro* qualitative detection of nucleic acid from the SARS-CoV-2. Breakthrough cases were detected after tele-consultation with the vaccinated individuals following the development of COVID-19 symptoms and a laboratory diagnosis with the aforesaid RT-PCR test.

Anti-SARS-CoV-2 S1 IgG Chemiluminescent Assay

Blood collected were tested for their levels of anti-SARS-CoV-2 S1 IgG by VITROS anti-SARS-CoV-2 S1 IgG assay, a commercial automated chemiluminescent immunoassay (CLIA), according to manufacturer's instructions using a VITROS Anti-SARS-CoV-2 IgG Calibrator on the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems. The assay targeted to the spike protein S1 antigen and the cut-off (minimum detection limit) was ≥1.00.

Statistical Analyses

The primary analysis was to compare individuals with natural infection with those who received the AZD1222 and the BBV152 vaccines. Comparison of categorical variables was tested using the Chi-Square test, whereas continuous variables (e.g., age) were compared using the unpaired *t*-test. Potential risk factors for breakthrough infection and hospitalization such as demographics between those who had natural infection, or received AZD1222 and BBV152 vaccination were evaluated by simple and adjusted binary logistic regression. The odds ratio (OR) and 95% confidence interval (CI) were estimated. The predictive power of age in predicting a breakthrough infection and hospitalization were examined using the receiver operating characteristic (ROC) analysis. The decay of anti-SARS-CoV-2 S1 antigen IgG levels was assessed using an adjusted linear regression. Statistical analyses were performed using PRISM, version 5.02 (GraphPad Software, San Diego, CA). Binary regression was performed using SPSS, version 20 (IBM, Armonk, NY), Two-tailed $P < 0.05$ was considered as statistical significance for all the tests performed, and *P*-values <0.05, <0.01, <0.001, <0.0001 were marked as *, **, *** and ****, respectively.

RESULTS

Demographics and Cohort Characteristics

In India, two vaccines were initially approved for administration to the public, one the adenoviral vector vaccine AZD1222 (ChAdOx1) manufactured by the Serum Institute of India, Pune, and the other, a whole-virion inactivated BBV152 vaccine developed by Bharat Biotech International Limited, Hyderabad, in collaboration with the Indian Council of Medical

Research (ICMR) (17). Five-hundred and fifty four individuals recruited into the study were separated into two groups, i.e., "unvaccinated" (n = 52) vs "vaccinated" (n = 502). The "unvaccinated" group was further bifurcated into two sub-groups with those who did not have a history of natural infection of SARS-CoV-2 (n = 25) and those who had a natural COVID-19 infection (n = 27). Those who received only one dose of vaccine were excluded from analysis (n = 35). The vaccinated group was also divided into two groups i.e., participants who received the AZD1222 (n = 259) and those who received the BBV152 (n = 208) vaccines. Of note, a small fraction of vaccinees had developed a natural infection prior to completion of two doses of vaccination (n = 85); whilst another portion of the participants had developed a breakthrough infection after completion of two doses of vaccination (n = 149). The colored boxes in **Figure 1** represent the three main study groups in our investigation. The median age of the cohort was 34 years with an interquartile range (IQR) of 26–52, with 47.8% male participants. Of note, 14.3% (n = 74) of the participants had some form of underlying comorbid conditions such as hypertension (n = 37), diabetes mellitus (n = 24), and heart disease (n = 4). Of all the participants, 176 (33.9%) were infected by SARS-CoV-2 (**Table 1**). There was a significantly higher number of individuals with COVID-19 among the non-vaccinees (51.9%) as compared to the vaccine recipients (AZD1222 = 31.7% and BBV152 = 32%) (P = 0.016). There was no significant difference between the percentage of individuals developing breakthrough infection with both the vaccines, indicating that the protective efficacy of both the vaccines are similar and the onset of a breakthrough infection appears to have been attributed to inadequate cross-neutralizing potential conferred by the vaccine to the circulating virus.

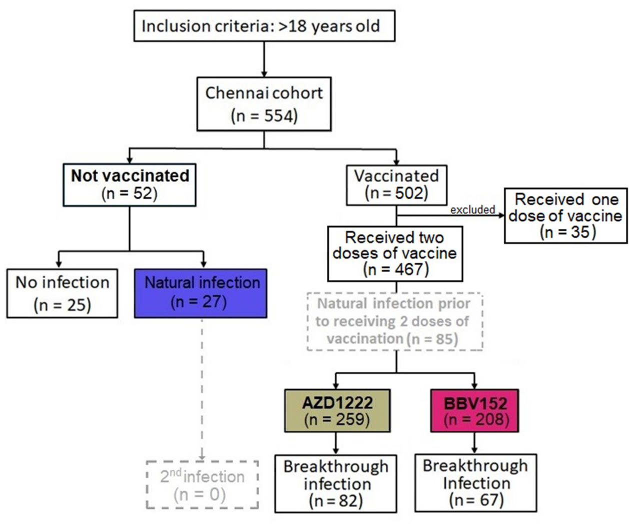

FIGURE 1 | Flow diagram of 519 participants recruited into the Chennai (India) Cohort from March to December 2021. Based on the sequence of natural infection and type of vaccine administered, the cohort is divided into four groups viz., **(i)** No vaccination, no natural infection, **(ii)** no vaccination, with natural infection, **(iii)** vaccination with AZD1222 and **(iv)** with BBV152. Of note, a small fraction of vaccine recipients had a documented history of natural infection prior to receipt of the corresponding vaccine (n = 85); whilst another group of participants developed a breakthrough infection 14 days post-vaccination (n = 149). The colored boxes, present three main patient groups in the investigation.

Factors Predisposing the Development of a Breakthrough Infection

Since a substantial proportion of individuals develop breakthrough infections despite administration with two doses of the vaccine, we sought to investigate the factors that predispose to breakthrough infection. The association between development of a breakthrough infection and other demographic parameters such as age, gender, occupation as healthcare workers, type of vaccine received and comorbidities were first assessed univariately using a binary regression model. Variables with P-value <0.05 will then be included in the multivariate analysis. Variables with P-value <0.05 were

TABLE 1 | Clinico-demographic characteristics of the Chennai, India study cohort.

Characteristics	**Total**	**Unvaccinated**	**Vaccinated (n = 467)**		***P*-value**	
			AZD1222	**BBV152**	**a.**	**b.**
Number of participants, no. (%)	519 (100)	52 (10)	259 (55.5)	208 (44.5)	…	…
Age, year; median (IQR)	34 (26-52)	32 (25.5–42.7)	35 (27-53)	34 (25-52)	0.419	
Gender, (male) no, (%)	248 (47.8)	27 (51.9)	115 (44.4)	106 (51)	0.855	
Healthcare workers, no. (%)	237 (45.7)	18 (34.6)	117 (45.2)	102 (49)	0.097	
Comorbidities, no. (%)	74 (14.3)	7 (13.5)	36 (13.9)	31 (14.9)	0.775	
Hypertension, no. (%)	37 (7.1)	4	19	14	…	
Diabetes, no. (%)	24 (4.6)	2	10	12	…	
Heart disease, no. (%)	4 (0.8)	0	3	1	…	
Others†, no. (%)	9 (1.7)	1	4	4	…	
SARS-CoV-2 infection; no. (%)	176 (33.9)	27 (51.9)	82 (31.7)	67 (32)	0.016[a*]	0.25

Others† *consist of asthma = 4, arthritis = 2, cancer/cured cancer = 2, chronic lung disease = 1. (a) Comparison between three groups, i.e., Unvaccinated, AZD1222 and BBV152; (b) Comparison between, AZD1222 and BBV152. *P < 0.05.*

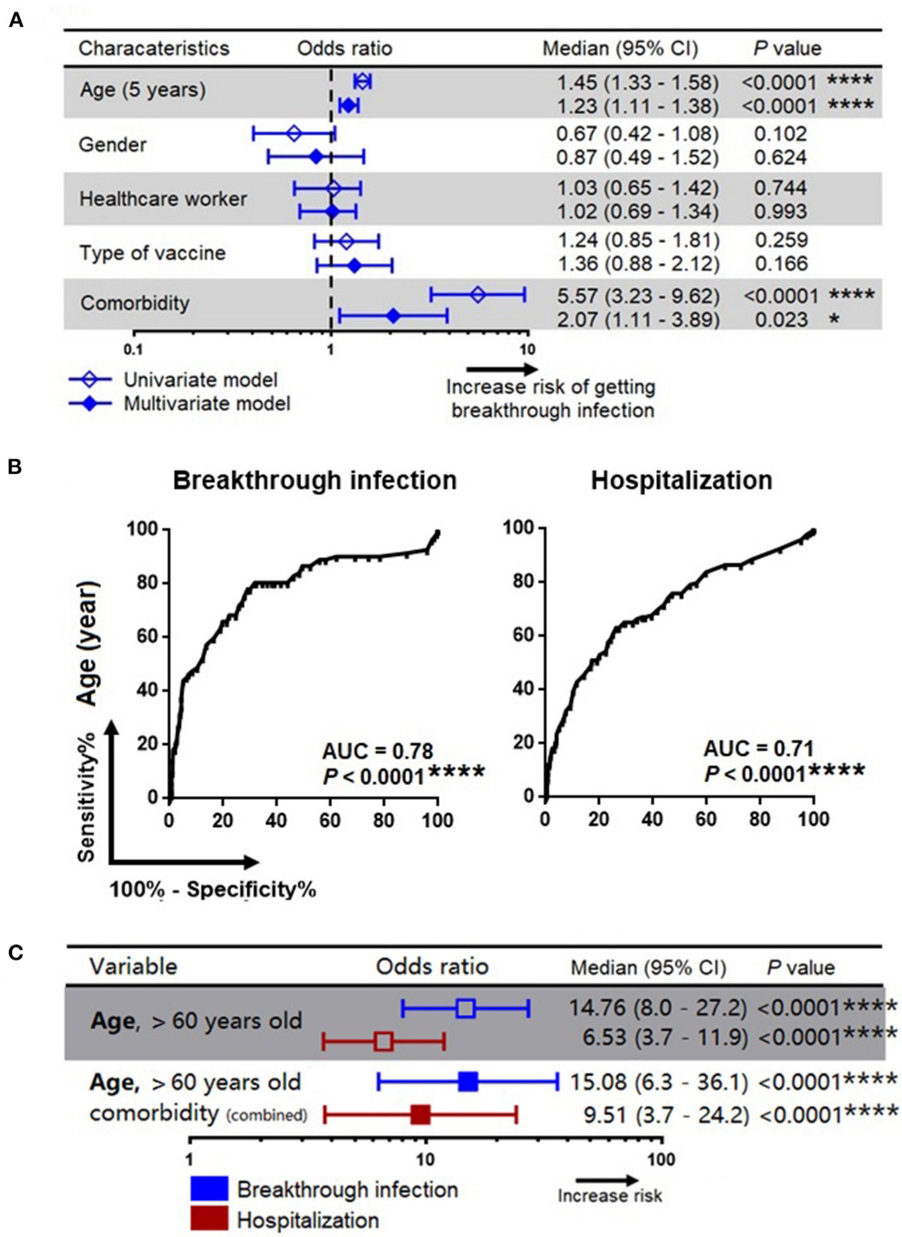

FIGURE 2 | Association of patients' characteristics with risk for development of breakthrough infection and hospitalization. **(A)** A simple and adjusted binary regression models assessing the factors that associated with breakthrough infection. Odds ratios for values below or above threshold levels were displayed in a forest plot; median and 95% CI were calculated. **(B)** Receiver operating characteristics analysis for prediction of breakthrough infection and hospitalization. **(C)** Association of age and comorbidity with the risk of breakthrough infection and hospitalization. CI, confidence interval; Comorbidity refers to diabetes mellitus, cardiovascular disease, hypertension and other underlying medical conditions as detailed in **Table 1**; *, **, ***, *** represent $P < 0.05$, <0.01, <0.001, <0.0001, respectively.

considered as independent predictors. Our multivariate analysis showed that age and underlying comorbidities were the two variables that were independently associated with development of a breakthrough infection. We also found that every increase in age by 5 years was associated with an increased risk of developing a breakthrough infection by 1.23 unit (95% CI=1.11–1.38; $P < 0.0001$). Further, an existing comorbid condition was associated with an increased risk of contracting a breakthrough infection by 2.07 units (95% CI=1.11–3.89; $P < 0.023$) (**Figure 2A**). We also found that age and comorbidity were independently associated with hospitalization (**Table 2**).

The ROC analysis revealed that age was a strong predictor for the development of a breakthrough infection (area under curve, AUC=0.78; $P < 0.0001$) as well as hospitalization (AUC=0.71; $P < 0.0001$) (**Figure 2B**), and the cut-off age was determined as 60 years. Our binary regression analysis showed that participants

TABLE 2 | Clinical and demographic characteristics associated with hospitalization.

Characteristics	Univariate model			Multivariate model		
	Coeff.	(95% CI)	*P*-value	Coeff.	(95% CI)	*P*-value
Age (5 years)	1.312	(1.224–1.401)	<0.0001 ****	1.267	(1.179–1.362)	<0.0001 ****
Gender	1.451	(0.988–2.128)	0.058	0.771	(0.509–1.168)	0.219
Vaccine status	0.653	(0.326–1.31)	0.229	…	…	…
Vaccine type						
AZD1222	0.687	(0.331–1.425)	0.313	…	…	…
BBV152	1.095	(0.732–1.637)	0.659	…	…	…
Comorbidity	3.973	(2.392–6.601)	<0.0001 ****	1.930	(1.098–3.394)	0.022 *

*Coeff, coefficient; CI, confident interval. *, **, ***, ****, represent P < 0.05, <0.01, <0.001, <0.0001, respectively.*

who were >60 years of age and with underlying comorbid conditions had a ∼15 times and ∼10 times greater odds for developing a breakthrough infection and hospitalization, respectively (**Figure 2C**).

Factors Associated With the Decay of Anti-SARS-CoV-2 S1 IgG

Given that the titer of antibodies will decay gradually with time, next we investigated the decay of anti-SARS-CoV-2 S1 IgG levels in individuals who experienced a natural infection, and having vaccinated with AZD1222 and BBV152. In this analysis, we only included those who had a natural infection (without vaccination, $n = 27$), and those who had received two doses of vaccination ($n = 233$). We excluded those who had natural infection prior completion of two doses of vaccination ($n = 85$) and those who had a breakthrough infection ($n = 82$ with AZD1222 and $n = 67$ from BBV152, total $n = 149$). The total number of participants in this analysis was ($n = 260$). Using a linear regression model, we first studied the decay of anti-SARS-CoV-2 S1 IgG levels across the two vaccine groups in comparison with natural infection, controlling for the time elapsed since recovering from a natural infection or after administration with the second dose of the respective vaccines (**Figure 3A**).

The univariate analysis showed that the anti-SARS-CoV-2 S1 IgG levels were waning progressively over time with varying rates, where the IgG levels in those who received AZD1222 were decayed slightly faster compared to that from a natural infection. Time lapse analysis showed that each month passed was associated with an antibody attrition levels by a coefficient of −6 unit (95% CI = −9.88 to −2.1; $P = 0.003$) and by a coefficient −5.22 unit (95% CI = −9.6 to −0.85; $P = 0.019$) in those who received AZD1222 and those who recovered from a natural infection, respectively (**Table 3**). In the adjusted model, we found that participants who were >60 years of age had an accelerated decay rate, where each month of lapse was associated with a decrease of IgG by a coefficient of 23 units (95% CI = −46.69 to −0.05; $P = 0.047$). However, such decay of IgG was only observed among participants who received AZD1222, but not among those who had a history of recovery from a natural SARS-CoV-2 infection (partly owing to a small sample size) and those received BBV152 (**Figure 3B**). Using binary regression, we assessed the time elapsed since vaccination and their association with development of a breakthrough infection and hospitalization, controlling for age (>60 years). Here, we showed that time elapsed since vaccination was an independent predictor of development of a breakthrough infection and hospitalization in those who had received the AZD1222 vaccine. As the level of anti-SARS-CoV-2 S1 IgG gradually decays with time, our regression model showed that each month of lapse was associated with increased risk of contracting a breakthrough infection and hospitalization by 0.85 (95% CI = 0.72–1.01; $P = 0.048$) and 0.85 (95% CI = 0.73–0.98; $P = 0.041$), respectively (**Figure 3C**).

DISCUSSION

In this large population-based real-life investigation conducted in Chennai, Tamil Nadu, India, we studied 519 individuals examined for anti-SARS-CoV-2 S1 IgG antibody titers following either vaccination or recovery from documented COVID-19 infection. We investigated the factors associated with development of a breakthrough infection, as well as hospitalization, and correlated them with the dynamics of anti-SARS-CoV-2 S1 IgG titers, as well as factors that might be associated with the decay. We found that age and comorbid conditions were the two factors independently associated with development of a breakthrough infection and hospitalization in the study population. A combination of both age (>60 years) and underlying comorbid conditions were associated with increased risk for contracting a breakthrough infection and hospitalization by ∼15 and ∼10 times, respectively. Anti-SARS-CoV-2 S1 IgG decay was only observed among recipients of AZD1222, but not BBV152 and those who recovered from a natural SARS-CoV-2 infection. Due to the decay of anti-SARS-CoV-2 S1 IgG, we also reported that the risk of developing a breakthrough infection and hospitalization gradually increased by 0.85 times with each month.

It is pivotal to understand when and how a breakthrough infection with SARS-CoV-2 occurred in fully vaccinated individuals as it is paramount to determine how long the public health measures needs to be in place and whether or not a

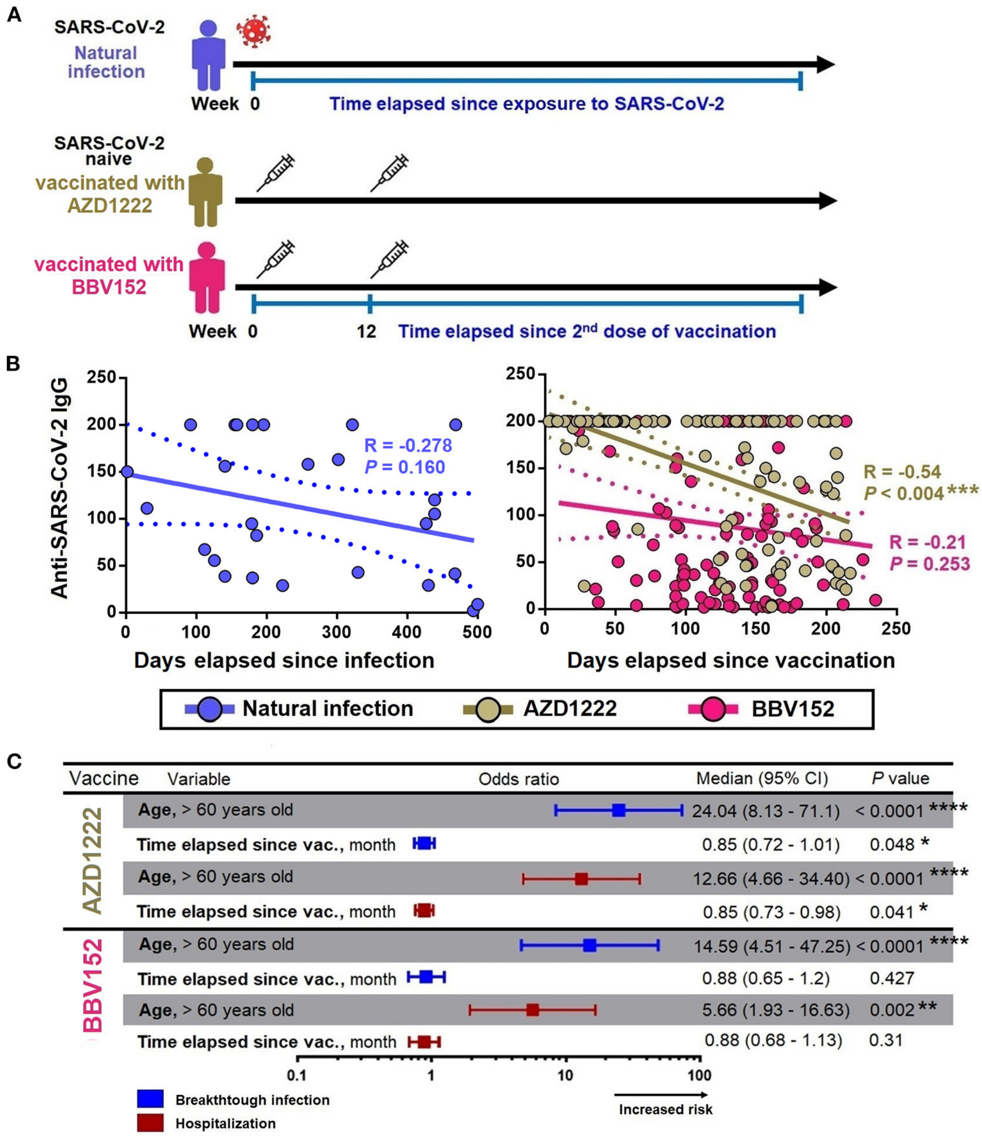

FIGURE 3 | Factors associated with decay of anti-SARS-CoV-2 S1 IgG. **(A)** Anti-SARS-CoV-2 S1 IgG decay cohort design. **(B)** Spearman correlation between the levels of anti-SARS-CoV-2 S1 IgG with the time elapsed since exposure to infection/vaccine administration. **(C)** Binary regression models assessing the association between age (>60 years) and time elapsed since vaccination with breakthrough infection and hospitalization. Odds ratios were displayed in a forest plot; median and 95% CI were calculated. CI, confidence interval; month define as 30 days. *, **, ***, *** represent $P < 0.05$, <0.01, <0.001, <0.0001, respectively.

community required a booster dose (18). Immunity against viruses works primarily by inhibiting the infection phenomenon either by humoral (e.g., neutralizing antibodies) or by killing the infected cells *via* cell-mediated immune responses. While a vaccine works by generating immune memory in the form of memory B-cells and T-cells that permits a more rapid and intensified immune response against secondary infection; most vaccines are not completely designed to prevent exposure or transmission of an airborne pathogen such as SARS-CoV-2. Hence, acquisition of a breakthrough infection is determined by whether the vaccinated individual at the time of exposure has adequate levels of protective immunity to prevent the establishment of an infection (18). Many factors are known to influence immune surveillance including the age of the host, the dynamics of antibody responses (19), type/nature of vaccine used (4), interval between the vaccine doses (20, 21), underlying comorbid conditions and other health issues (viz., neoplasms and immunocompromised state) (22).

Several studies on the dynamics of anti-SARS-CoV-2 IgG levels post-vaccination and after recovering from a natural SARS-CoV-2 infection have revealed that the antibody levels induced by vaccines generally undergo rapid decay (over the months). One study reported that individuals who received a AZD1222 vaccine had a substantial decline in antibody levels after 6 months and

TABLE 3 | Factors associated with decay of anti-SARS-CoV-2 S1 IgG levels.

Characteristics	Level of IgG, Coeff. (95% CI); *P* value		
	Natural infection	AZD1222[†]	BBV152[‡]
Age, years	0.4 (−0.05 −0.85) $P = 0.097$	0.105 (−0.3 −0.61) $P = 0.679$	0.422 (−0.32–1.16) $P = 0.264$
Age (60), ≥60 years	14.5 (−7.22 −36.15) $P = 0.391$	14.44 (−8.14–37.02) $P = 0.209$	−8.18 (−45.9–29.55) $P = 0.670$
Gender, male	−5.3 (−18.8–8.65) $P = 0.0470$	0.52 (−15.06–16.1) $P = 0.948$	−4.51 (−27.25–18.23) $P = 0.696$
Comorbidities	6.98 (−12.57 − 26.53) $P = 0.483$	20.47 (−1.77 − 42.7) $P = 0.71$	−3.59 (−35.52–28.24) $P = 0.825$
Time elapsed since vaccination, month	…	− 5.31 (−9.17 to −1.44) ***P* = 0.007****	−4.1 (−12.74 − 5.54) $P = 0.351$
Time since natural infection, month	−4.7 (−9.3 to −0.35) ***P* = 0.034***	…	…
Adjusted model			
Time elapsed since vaccination, month	…	−6 (−9.88 to −2.1) ***P* = 0.003****	−3.86 (−12.8–5.1) $P = 0.576$
Age (60), ≥ 60 years old		−23.32 (−46.69 to −0.05) ***P* = 0.047***	4.68 (−38.2 −47.62) $P = 0.83$
Time elapsed since natural infection, month	−5.22 (−9.6 to −0.85) ***P* = 0.019***	…	…
Age (60), ≥ 60 years old	20.7 (3.64–44.89) $P = 0.195$		

*Factors associated with decay of anti-SARS-CoV-2 S1 IgG levels over time among study participants who experienced a natural infection vs. vaccination with the commercial AZD1222[†] and BBV152[‡]. Since circulating IgG levels will decay gradually over time following a natural infection and/or vaccination, the levels of the antibodies were analyzed by using a linear regression model controlling for the days since participants become exposed to a natural infection or has completed the second dose of vaccination. Coeff., coefficient; CI, confident interval; month, define as 30 days. *, **, ***, ****, represent P-value <0.05, <0.01, <0.001, <0.0001, respectively. The Hosmer–Lemeshow value for this model was P = 0.534.*

Included only age (60 years) in the adjusted model but not comorbidity. This is because old age and comorbidity are highly associated. [†]AZD1222 contains a replication-deficient chimpanzee adenovirus, which has a genetic material similar to that of SARS-CoV-2. [‡]BBV152 is a whole-virion inactivated vaccine.
Bold indicates significance.

that the decline was significantly associated with development of a breakthrough infection (23). Similarly, although individuals who received the BNT162b2 mRNA vaccine had high antibody titers compared to those who had survived a natural infection, the antibody titers experienced a rapid decay by up to 40% for every subsequent month; whereas the decrease of antibody levels was only <5% per month among convalescing individuals (24). This is consistent with our observation that individuals administered with AZD1222 experienced a more rapid attrition in IgG antibody levels.

B-cells that encounter their cognate antigens during an infection upon activation migrate to the center of the B-cell follicle, where they form germinal centers (GCs) (25, 26). Within the GCs, B-cells compete for a limited amount of T-cell-derived signals, such as cytokines and CD40 ligand that promote further maturation and differentiation into memory B-cells or plasmablasts (27, 28). Some of these plasmablasts will mature in the secondary lymphoid tissue itself into antibody-secreting plasma cells with short life spans; the other plasmablasts may enter into the circulation together with memory B-cells, home to bone marrow and other mucosal tissues, where they mature into long-lived plasma cells or memory B-cell that reside in these tissues to secrete antibodies for prolonged periods (25, 29, 30). Although both infection and vaccination can induce memory B-cells and plasmablasts that participate in humoral immune response, due to subtle differences in the nature of antigen stimulation, the memory B-cells generated in each case may be different. One study compared the memory B-cells induced following inoculation of a BNT162b2 mRNA vaccine and recovery from a natural infection and found that the mRNA vaccine induced robust plasmablast responses as compared to a natural infection that more prone to memory B-cells, thereby generating more plasma cells as well as better antigen-binding maturation (31). Another study compared the immune responses generated by both mRNA-based vaccine and the inactivated whole-virion vaccine and reported that the mRNA-based vaccine induced stronger humoral immune responses than the inactivated whole-virion vaccine (32). Further, the inactivated whole-virion vaccine induced significantly higher levels of IFN-γ response in $CD4^+$ and $CD8^+$ T cells as compared to that by the mRNA-based vaccine (32). Because T cell-derived signals (e.g., cytokines, ligands) are pivotal in promoting B cell maturation in germinal centers (27, 28), the inactivated whole-virion vaccine likely induced long-lived plasma cells and memory B cells.

Of note, there appears to be a fundamental difference between the adenovirus-based vaccine (AZD1222) and the mRNA-based subunit vaccine. Since adenovirus-based vaccine presents as a whole virus, it likely induces B-cell maturation much similar to inactivated SARS-CoV-2, and hence be able to generate long-lasting antibody responses. However, because this is an adenovirus-based vaccine and given that adenovirus is common in the population, the presence of anti-adenovirus neutralizing antibodies and anti-adenovirus specific T-cell response can prevent the vector from transducing the target cells, thereby limiting the efficacy of the vaccine (33). In fact, this likely could be a universal concern with all vaccines because of the presence of T and B cross-reactive memory responses to seasonal coronaviruses. Hence, it is difficult for a subunit vaccine that uses spike protein alone without adjuvants to induce long-lived plasma cells (34). These warrants improved vaccine formulations with suitable adjuvants to enhance antigenic stimulation.

Our study has also highlighted that the elderly age group (>60 years) and those with underlying comorbid conditions are at risk for acquisition of a breakthrough infection and hospitalization. Further, we have also reported that individuals administered with the AZD1222 also appear to undergo an accelerated decline in the levels of anti-SARS-CoV-2 S1 IgG. This likely could stem from an ongoing aging phenomenon involving the immune system known as immunosenescence (immune aging), where the generation of new T-cells appears to undergo progressive decline owing to thymic atrophy. The attrition is compensated for by the homeostatic proliferation of mature T-cells in the periphery. Eventually, the continually replicating mature T-cells undergo exhaustion due to telomere shortening (35) resulting in the expansion of senescent T-cell phenotypes indicated by the loss of co-stimulatory receptors (e.g. CD28, CD69) (36, 37), and de novo expression of co-inhibitory molecules such as killer-like immunoglobulin receptors (KIR) and PD-1 (35, 37). Our findings also reflect that the elderly with underlying comorbid conditions represent a high-risk population that requires additional medical attention, and specific measures to boost anti-SARS-CoV-2 immune responses (such as administering a second booster dose of the vaccines) in these groups are urgently warranted.

The limitation of this study is that we have not taken into account, the genetic variants of SARS-CoV-2 (38–41), especially the Delta and Omicron variants that have led to increased viral loads and high transmissibility. Notwithstanding, our study has provided a detailed information *via* a relatively large cohort involving both vaccinated and convalescent individuals recovering from SARS-CoV-2 infection. Our results indicate that the declining slope of anti-SARS-CoV-2 S1 IgG levels in AZD1222-vaccinated individuals is much steeper than in convalescent individuals and those who had received the BBV152 vaccine in Chennai, India. We have also provided an estimation of the rate of IgG decline as well as corresponding development of breakthrough infection and hospitalization risks by taking age, underlying comorbid conditions and time-scales into account. Given the expanding quantum of therapeutics against COVID-19, incapacitating the pandemic successfully is equally reliant on active public cooperation (42), which is of paramount importance to development of herd immunity against SARS-CoV-2.

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 human participants were reviewed and approved by Human Ethics Committee of the Madras Medical College (EC No. 03092021). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The study was designed by SS, YY, GS, KN, SR, and ES. SS, GS, and KN provided regulatory oversight. SS and KN provided project management. SS, GS, KN, MR, and SR collected study data and oversaw participant visits. Participant data analysis and interpretation were done by YY, HT, YZ, ES, SR, and ML. Patient data collected and analyzed by SS, KN, GS, KV, PJ, DR, SP, SR, YY, HT, YZ, ES, SR, and ML and was interpreted by SS, KN, SR, YY, ML, and ES. SS, YY, HT, KN, GS, and ES wrote the manuscript. Data were accessed and verified by SS, GS, and SR. All authors contributed to the article and approved the submitted version.

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Association Between Vaccination Coverage Disparity and the Dynamics of the COVID-19 Delta and Omicron Waves in the US

Diego F. Cuadros[1], Claudia M. Moreno[2], Godfrey Musuka[3], F. DeWolfe Miller[4], Phillip Coule[5] and Neil J. MacKinnon[6]*

[1] Digital Epidemiology Laboratory, Digital Futures, University of Cincinnati, Cincinnati, OH, United States, [2] Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, WA, United States, [3] ICAP at Columbia University, Harare, Zimbabwe, [4] Department of Tropical Medicine and Medical Microbiology and Pharmacology, University of Hawaii, Honolulu, HI, United States, [5] Department of Emergency Medicine, Medical College of Georgia, Augusta University, Augusta, GA, United States, [6] Department of Population Health Sciences, Medical College of Georgia, Augusta University, Augusta, GA, United States

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Roger Nlandu Ngatu, Kagawa University, Japan

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***Correspondence:**
Diego F. Cuadros
diego.cuadros@uc.edu

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Objective: The US recently suffered the fourth and most severe wave of the COVID-19 pandemic. This wave was driven by the SARS-CoV-2 Omicron, a highly transmissible variant that infected even vaccinated people. Vaccination coverage disparities have played an important role in shaping the epidemic dynamics. Analyzing the epidemiological impact of this uneven vaccination coverage is essential to understand local differences in the spread and outcomes of the Omicron wave. Therefore, the objective of this study was to quantify the impact of vaccination coverage disparity in the US in the dynamics of the COVID-19 pandemic during the third and fourth waves of the pandemic driven by the Delta and Omicron variants.

Methods: This cross-sectional study used COVID-19 cases, deaths, and vaccination coverage from 2,417 counties. The main outcomes of the study were new COVID-19 cases (incidence rate per 100,000 people) and new COVID-19 related deaths (mortality rate per 100,000 people) at county level and the main exposure variable was COVID-19 vaccination rate at county level. Geospatial and data visualization analyses were used to estimate the association between vaccination rate and COVID-19 incidence and mortality rates for the Delta and Omicron waves.

Results: During the Omicron wave, areas with high vaccination rates (>60%) experienced 1.4 (95% confidence interval [CI] 1.3–1.7) times higher COVID-19 incidence rate compared to areas with low vaccination rates (<40%). However, mortality rate was 1.6 (95% CI 1.5–1.7) higher in these low-vaccinated areas compared to areas with vaccination rates higher than 60%. As a result, areas with low vaccination rate had a 2.2 (95% CI 2.1–2.2) times higher case-fatality ratio. Geospatial clustering analysis showed a more defined spatial structure during the Delta wave with clusters with low vaccination rates and high incidence and mortality located in southern states.

Conclusions: Despite the emergence of new virus variants with differential transmission potential, the protective effect of vaccines keeps generating marked differences in the distribution of critical health outcomes, with low vaccinated areas having the largest COVID-19 related mortality during the Delta and Omicron waves in the US. Vulnerable communities residing in low vaccinated areas, which are mostly rural, are suffering the highest burden of the COVID-19 pandemic during the vaccination era.

Keywords: COVID-19, vaccination, omicron variant, healthcare disparities, geospatial mapping

INTRODUCTION

After almost 2 years into the COVID-19 pandemic, the B.1.1.529, Omicron SARS-CoV-2 variant was identified in South Africa on November 24, 2021, and 2 days after it was declared as a Variant of Concern (VOC) by the World Health Organization (1). Despite several efforts to contain the spread of this variant, Omicron was quickly reported in several European countries and in the US, becoming the dominant global variant driving the latest wave of the pandemic (2). The Omicron variant harbors 37 mutations in the spike protein that mediates the entry of the virus to the host cell (3). These mutations have conferred Omicron the unique ability to evade antibody neutralization while exhibiting unprecedented transmissibility (4). This genetic evolution allowed Omicron to spread around the world faster than any previous variant, outcompeting other circulating SARS-CoV-2. Omicron was first reported in the US on December 1, 2021, in California (1), and it became the variant responsible for the fourth and most severe wave in the country. New daily confirmed cases per million people under the Omicron wave tripled the highest number ever recorded during the pandemic, with 2,410 cases per million reported on January 15, 2022, compared to 756 reported on January 11, 2021 (5).

Each of the four pandemic waves has shown a characteristic epidemiological landscape determined by external forces. The first wave was mainly shaped by enforcing strict health policy measures, including lockdowns and mask mandates. In contrast, the third and fourth waves have been highly influenced by the severity and transmissibility of the emergent Delta and Omicron variants. Moreover, one of the most significant factors was implementing the vaccination campaign that started in early 2021 (6). However, the potential of massive vaccination to tackle the pandemic has been hampered by substantial heterogeneity in vaccination coverage and uptake. Some areas of the US have achieved full vaccination (people who have received two doses of the mRNA Pfizer-BioNTech or Moderna vaccines, or a single dose of the Janssen/Johnson & Johnson vaccine) in more than 80% of their population whereas other areas have less than 40% (7, 8). Vaccination coverage influences the spatial dispersion of the epidemic. In a recent publication, we showed that during the Delta wave, areas with low vaccination in the US experienced the highest rates of infection and became the pandemic's epicenter (9). We established a negative ecological association between the percentage of the vaccinated population and the number of new COVID-19 cases at the county level. Most COVID-19 cases were concentrated in the rural areas of the Western and Southern part of the country, while cases remained relatively low in the Northern region. Tracking how these external forces continue to shape the epidemic dynamics within distinct populations and communities is essential to understand the local differences in the transmission of the virus and the severity of health outcomes.

Higher transmissibility of the Delta variant compared to the previous Alpha variant along with its higher hospitalization and mortality rate shaped the dynamics of the third wave, whereas the high transmissibility of the Omicron variant, along with its ability to evade neutralizing antibodies, even those induced by vaccination, are forces that have strongly influenced the epidemic dynamic of the fourth wave. Thus, we conducted a geospatial and data visualization analysis to measure the effect of vaccination coverage disparity in the US during the fourth Omicron wave. Moreover, by comparing the epidemiological dynamics of the Delta and Omicron waves, we show how uneven vaccination coverage is influencing the local landscape of the pandemic. Refining the impact of vaccination coverage disparities under the epidemic conditions of past and present transmission waves will help to identify the most vulnerable communities with the highest health needs in the country that might suffer the highest impact during the emergence of new variants and potential upcoming waves.

MATERIALS AND METHODS

Data Sources

We implemented a similar methodology used in a previous study aimed to assess the association of the heterogeneous distribution of vaccination coverage with the dynamics of COVID-19 during the third wave of the pandemic in the US (9). Briefly, we focused our study in the growing phase of both the Delta and Omicron waves in the US, as a result, we used data for COVID-19 cases and related mortality at the county level from July 1, 2021 to August 31, 2021, and from December 1, 2021, to January 31, 2022, obtained from Johns Hopkins University (5). Data for cumulative full vaccination rates in the total population at a county level were obtained from the CDC COVID data tracker for the contiguous US (10). We excluded the states of Colorado, Georgia, Texas, Virginia, and West Virginia due to incomplete or unreliable vaccination data. Counties were classified as rural or urban based on the 2013 National Center for Health Statistics (11, 12). As a result, data from 2,417 counties were included in the analysis. Temporal changes in COVID-19 incidence rate (i.e., new cases per 100,000 people in each time interval) and COVID-19 related mortality rate (i.e., new deaths per 100,000 people in each time interval) was estimated by generating 4-time intervals of equal length for each wave, July 1–15, July 16–31, August 1–15, and August 16–31, for the Delta wave; and December 1–15, December 16–31, January 1–15, and January 16–31, for the Omicron wave. Data were also grouped in two time periods for waves comparisons, with aggregated data from July 1 to August 31 corresponding to the Delta wave, and aggregated data from December 1 to January 31 corresponding to the Omicron wave. Cumulative vaccination rates for each time interval were estimated for the last day of each interval. Vaccination rates were aggregated in 4 groups: <40%, 40% to <50%, 50 to 50%, and >60% for visual data analysis. Institutional review board approval and informed consent were not necessary for this cross-sectional study because all data were deidentified and publicly available (Common Rule 45 CFR §46). This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Ecological Data Visualization Analysis

We conducted several visualization data and comparison analyses among the different periods. First, we created bivariate scatterplots illustrating associations between COVID-19 incidence and vaccination rates and COVID-19 related mortality and vaccination per county for each period in each wave. Second, we calculated the incidence and mortality rate during each wave's entire period of study and aggregated the data using the vaccination rate groups previously described. Bar charts illustrating these estimations were created, and rate ratios for incidence and mortality between high (>60%) and low (<40%) vaccination rates and 95% confidence intervals (CI) were estimated using the *rateratio.test* function in the statistical software environment R (13). Case-fatality ratios were also calculated for each vaccination group in each wave and plotted as multiple variable plots using the GraphPad software.

Geospatial Data Analysis

The geospatial structure of the pandemic during both waves in the US was assessed using spatial bivariate and multivariate analysis using the geospatial GeoDa environment (14). First, spatial correlations between vaccination rate and incidence or mortality rate were identified using bivariate local indicators of spatial association (LISA). The bivariate LISA statistics identified significant spatial clustering based on the degree of linear association between the vaccination rate at a given location and the incidence (or mortality) rate at neighboring locations (15). Maps were generated illustrating the locations with statistically significant associations and the type of spatial association between vaccination and incidence (or mortality) rate estimations (i.e. high–high, low–low, low–high, and high-low). Second, multivariable spatial associations between all three variables, vaccination, incidence, and mortality rate, were estimated using K-means clustering analysis. K-means is a partitioning clustering method in which the data are partitioned into k groups (i.e., fourth groups). In this clustering method, the n observations are grouped into k clusters such that the intra-cluster similarity is maximized (or dissimilarity minimized), and the between-cluster similarity minimized (or dissimilarity maximized). A further detailed description of these geospatial methods can be found elsewhere (16, 17). Rates for each variable vaccination, incidence, and mortality in each cluster identified were reported, and maps of the results were generated using ArcGIS Pro (18).

RESULTS

The incidence rate (new COVID-19 cases per 100,000 people) during the Omicron wave increased from 538.9 (95% CI 538.0–539.8) on T1, to 2,827.9 (95% CI 2,825.9–2,829.9) on T4, whereas the mortality rate (COVID-19 related deaths per 100,000 people) increased from 6.1 (95% CI 6.0–6.2) to 11.2 (95% CI 11.1–11.4) during the same period. Scatterplots in **Figure 1** illustrate the changes in incidence and mortality rates during the Delta and Omicron waves during the four-time periods of the study (T1–T4). Contrary to the pattern observed during the Delta wave (first row in **Figure 1**), areas with higher vaccination rates (>60%) experienced the higher and more intense spread of the disease during the Omicron wave (third row in **Figure 1**). During this wave, the incidence rate was similar in all vaccination rate areas during T1 (December 1 to 15). The infection started spreading faster and more intensively in high vaccination areas during T2 (December 16 to 31) and T3 (January 1 to 15). The incidence rate increased in all vaccination rate areas by T4 (January 16 to 31). It was 1.4 (95% CI 1.3–1.5) times higher in high vaccination rate areas than the lower vaccination areas during the entire period of the study. Conversely, the mortality rate had similar patterns during both the Delta (second row in **Figure 1**) and the Omicron wave (fourth row in **Figure 1**), with areas with lower vaccination rate (<40%) having 1.6 (95% CI 1.5–1.7) higher mortality rate compared to areas with higher vaccination rate (>60%), 42.0 (95% CI 40.1–43.2) per 100,000 people in lower vaccination areas, compared to 26.2 (95% CI 25.9–26.5) in higher vaccination areas during the entire period of the study of the Omicron wave. The compiled data for both waves show a clear uncoupling of the vaccination rate and the incidence rate for Omicron while preserving an association with the mortality rate (**Figure 2**) bottom bar chart. This contrasts with the association between vaccination rate and the number of cases and deaths observed during the Delta wave (**Figure 2**) top bar chart.

Comparing incidence and mortality rates values between the two waves needs to take into account that the large number of cases observed during the Omicron wave relative to Delta. For this, we calculated and compared the case-fatality ratio for each vaccination group. Case-fatality ratio estimations illustrated similar patterns during the Delta and Omicron waves (**Figure 3**), with a consistent reduction of the case-fatality ratio with an increasing vaccination rate. Areas with low vaccination rate had a 2.2 (95% CI 2.1–2.2) higher case-fatality ratio compared to areas with higher vaccination rate during the Omicron wave (0.7% case fatality rate in areas with vaccination rate < 40%, and 0.3% in areas with vaccination rate > 60%).

Spatial analyses identified a distinct spatial structure of the pandemic during each wave. The southern part of the country was the epicenter of the Delta wave, whereas the Northeast and Midwest regions experiencing the highest burden of the Omicron wave. Consistent with the results of the incidence rate by vaccination rate group, bivariate LISA analysis identified clusters of low vaccination/high infection rate during the Delta wave in Southern states like Alabama, Arkansas, Louisiana, Mississippi, and Missouri, areas that also suffered high mortality

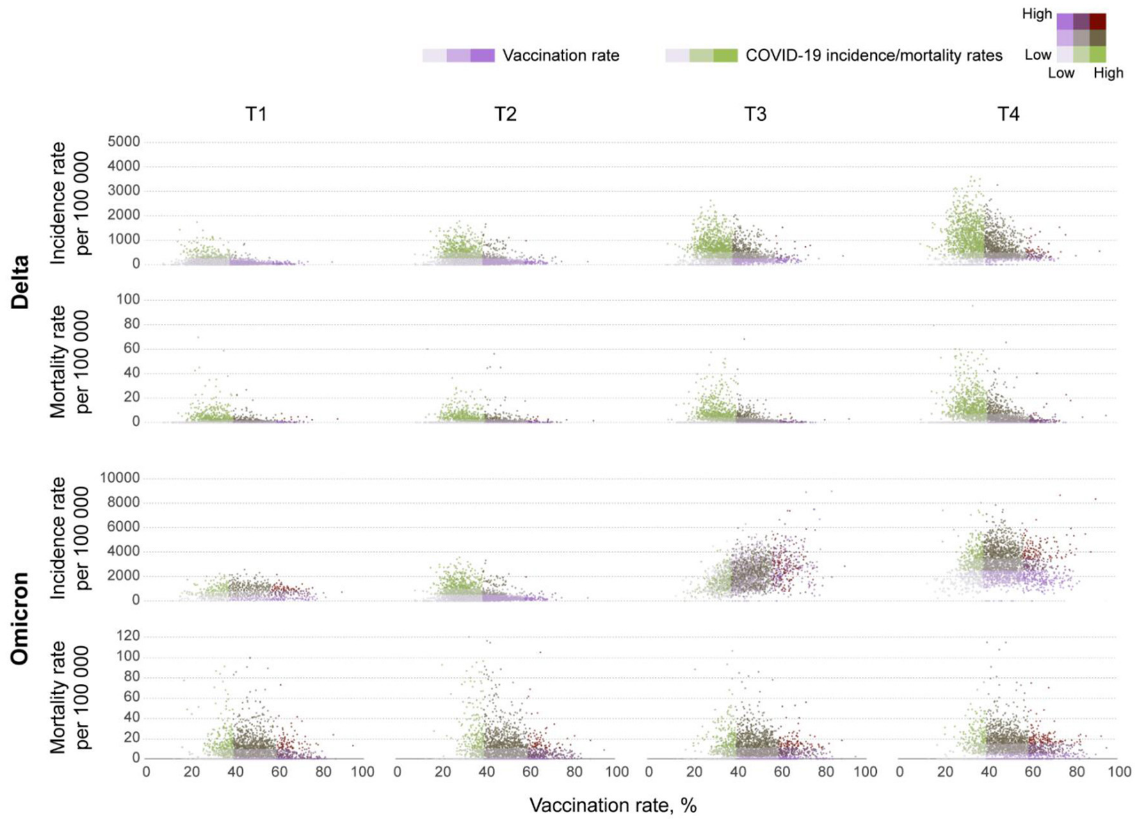

FIGURE 1 | Bivariate scatterplots of the association between vaccination rates and new COVID-19 cases and deaths at the county level in the contiguous U.S. Bivariate scatterplots illustrating the changes of the association between vaccination rates and new COVID-19 cases (incidence rate) and deaths (mortality rate) per 100,000 people at the county level during T1 (July 1–15), T2 (July 16–31), T3 (August 1–15), and T4 (August 16–31) in 2021 for the Delta wave, and T1 (December 1–15), T2 (December 16–31) 2021, T3 (January 1–15), and T4 (January 16–31) in 2022 for the Omicron wave.

rate during this wave (dark blue areas in the first two maps on top, **Figure 4**). During the Omicron wave, clusters of high infection rates were concentrated in areas with high vaccination rates in Northeast and Midwest states like Connecticut, New Jersey, Rhode Island, parts of Ohio and Indiana, Illinois, and Wisconsin. Clusters of mortality were not identified in Connecticut, Rhode Island, and New Jersey (areas with high vaccination rates). These clusters moved more to the Midwest and mostly affected states like Pennsylvania, Ohio, Kentucky, Tennessee, and Indiana (dark purple areas in the first two maps on the bottom, **Figure 4**). Another cluster of high mortality rates was identified in the Western part of the country, including Arizona and New Mexico.

Multivariable K-means clustering analysis illustrated the disease's more defined spatial structure during the Delta compared to the Omicron wave. Clusters 3 and 4 (light and dark blue in the upper right map, **Figure 4**), both with the lowest vaccination rate (<36%), had the highest incidence and mortality rate (**Table 1**) and were located in the southern states previously identified by the LISA analysis. Conversely, multivariable K-means clustering analysis showed a more dispersed and less structured distribution of the clusters of these three variables, with Cluster 4 (Dark purple areas in lower right map, **Figure 4**) primarily located in the states of Tennessee, Pennsylvania, Ohio, Indiana, and Michigan having the highest mortality rates (91.5 deaths per 100,000 people) and the lowest vaccination rates (44.9%). Most of the areas within these clusters with low vaccination and high mortality rates for Delta and Omicron waves were rural. Rural areas corresponded to 73.4% (186 of 252 counties) in Cluster 4 during the Delta wave and 75.4% (355 of 471 counties) in Cluster 4 during the Omicron wave. The percentage of areas with vaccination rate lower than 40% that were rural increased from 75.2% (956 of 1,271 counties) during the Delta wave to 81.6% (421 of 516 counties) during the Omicron wave, and the percentage of areas with vaccination rate lower than 50% that were rural increased from 69.9% (1,377 of 1,970 counties) during the Delta wave to 75.8% (1,029 of 1,358 counties) during the Omicron wave.

DISCUSSION

The dynamics of the COVID-19 pandemic have been modulated by control interventions (i.e., non-pharmaceutical interventions and vaccine rollout) and new variants with different transmission dynamics. This has defined the trajectory of the disease, which has been characterized by waves of outbreak peaks, followed

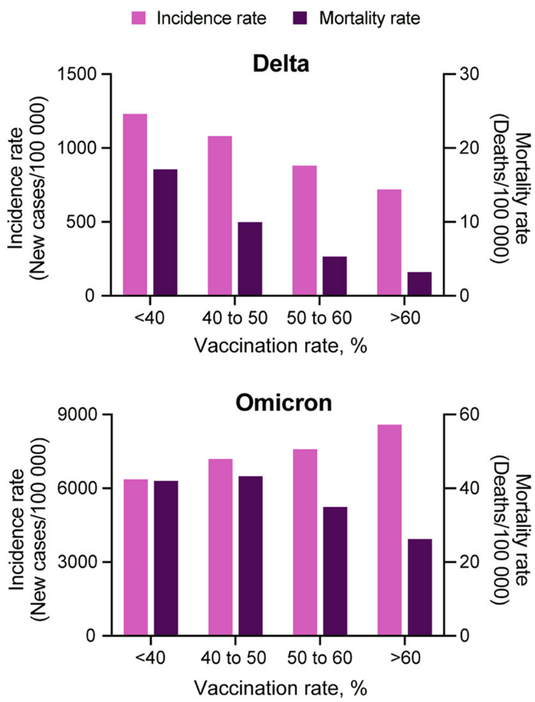

FIGURE 2 | Comparison among COVID-19 incidence and mortality rate and vaccination coverage. COVID-19 incidence (light purple bars) and mortality (dark purple bars) rate estimations for each of the four vaccination rate groups, <40, 40 to 50, 50 to 60% and more than 60%, during the Delta (July 1, 2021 to August 31, 2021) and Omicron (December 1, 2021 to January 31, 2022) waves in the US.

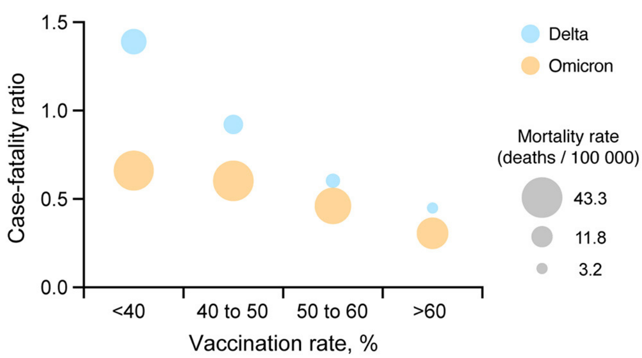

FIGURE 3 | Comparison between COVID-19 case-fatality ratio and vaccination coverage. A multiple variable plot illustrating the COVID-19 case-fatality ratio during the Delta (July 1, 2021 to August 31, 2021; blue circles) and Omicron (December 1, 2021 to January 31, 2022; orange circles) waves for each of the four vaccination rate groups <40, 40 to 50, 50 to 60% and more than 60% in the US.

by valleys after infection declines. The COVID-19 vaccines developed so far have proven to be the most effective intervention to reduce disease outcomes (hospitalizations and deaths). In an earlier study, we showed that vaccination rollout in the US could influence the epidemiological landscape of the third wave driven by the Delta variant. We also showed that areas with lower vaccination coverage experienced the highest burden of the disease and had 2.4 times higher cases than those with higher vaccination coverage (9). The emergence of the new Omicron variant identified in late 2021 posed a new public health challenge. Omicron is characterized by higher transmissibility conferred by its ability to evade the immune response generated by vaccination or by the previous infection compared to the Delta variant (19, 20), and its ability to evade immune response made this variant responsible for the highest number of breakthrough cases ever reported and changed the virus' scenario compared to the Delta variant.

This study found that contrary to the patterns observed during the Delta wave, highly vaccinated areas in the US experienced the highest burden of new infections during the Omicron wave. Areas with a higher than 60% vaccination rate had 1.4 times more new infections than areas with lower vaccination rates (<40%). This could be explained by the combination of high transmissibility and high population density since most of the areas with high vaccination coverage are urban areas (65%), facilitating transmission (21, 22). However, despite incidence being more prominent in highly vaccinated areas, a completely different result was observed for Omicron related mortality. COVID-19 related mortality rate was 60% higher in areas with low vaccination rate (<40%) compared to areas with high vaccination coverage (>60%). Hence, the case-fatality ratio was more than 2 times higher in low vaccination coverage areas compared with areas with more than 60% vaccination rate, following a similar pattern to that observed for Delta. These results are aligned with other studies conducted in several countries in Europe and the rest of the world, in which the rapid growth of the number of COVID-19 cases has occurred even in countries with high levels of vaccinations. A lower case-fatality ratio in these highly vaccinated countries highlights the fact that although available vaccines cannot prevent new infections or virus spread, they have a high impact on the number of COVID-19 related deaths per capita (23–25).

By comparing the dynamics of the Delta and Omicron's waves, it becomes evident how the different strategies to escape immune response evolved by these two variants have an apparent effect on the epidemiological landscape (26). This new feature in the fusion machinery of Omicron might result in a more efficient infection which can account for the high transmissibility observed in highly populated urban areas despite the high vaccination rate in these areas. The epicenter of the Omicron wave might have started in densely populated and highly connected regions of the Northeast and Midwest in Connecticut, New Jersey, Rhode Island, and Illinois, with large international airports that facilitated the entrance and propagation of this highly infectious variant, a similar pattern observed during the early stages of the pandemic, when vaccines were not available, and large metropolitan areas of the country suffered the highest burden of both COVID-19 infections and deaths (27). However, the introduction of vaccines changed this scenario during the Omicron wave, and although areas with a high percentage of the population fully vaccinated experienced the highest burden of infections product of the high transmissibility and Omicron's

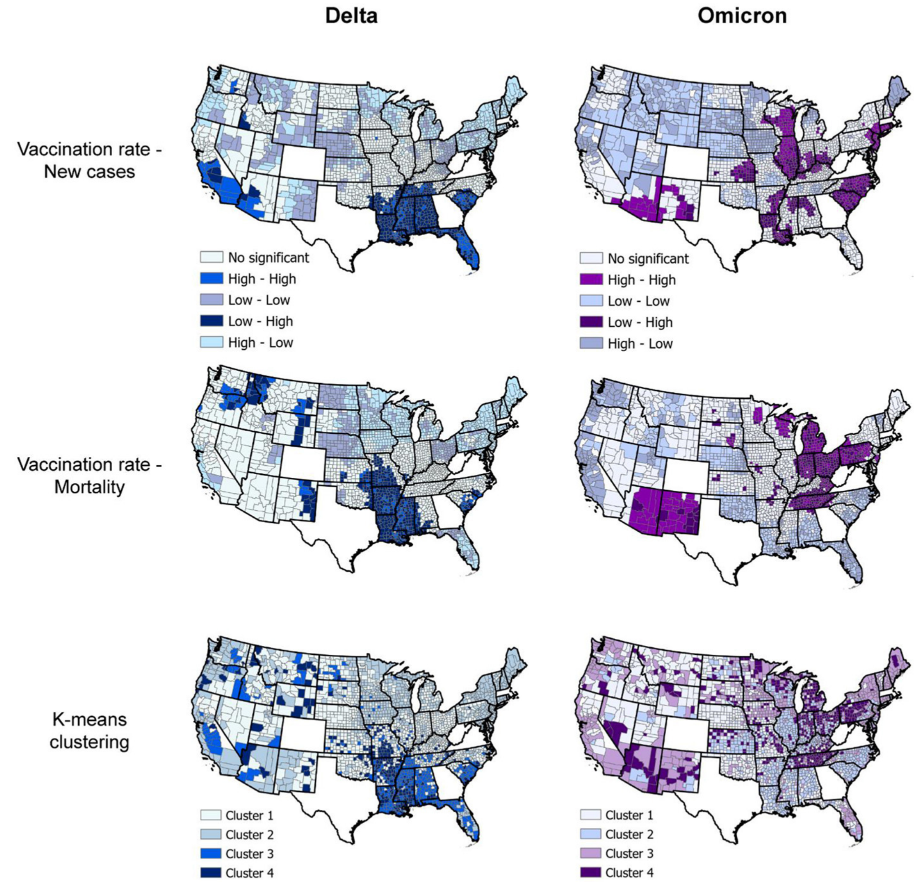

FIGURE 4 | Geospatial clustering of COVID-19 incidence and mortality rates. Bivariate local indicators of spatial autocorrelation and K-means clustering analysis maps for the association between vaccination rate and new COVID-19 cases and deaths per 100,000 people during the Delta (July 1, 2021, to August 31, 2021; blue maps) and Omicron (December 1, 2021 to January 31, 2022; purple maps) in the US. K-means cluster information is summarized in **Table 1**.

ability to evade the immune response, the high vaccination rate prevented a high COVID-19 related mortality in these areas. Conversely, while low vaccination areas had lower transmission intensity, these areas suffered the most increased mortality and case-fatality rate during the Omicron wave in the US, primarily in rural areas (81%).

Despite the lower transmission intensity experienced in lower vaccinated and rural areas, these areas suffered the highest COVID-19 related mortality during the Omicron wave. Low vaccinated areas also experienced the highest burden of cases and deaths during the Delta wave and comparing the percentage change of rural areas with low vaccination rate (<40%) during both waves, vaccination rollout appears to be slower in these rural areas, with the percentage of areas with vaccination coverage lower than 50% that are rural increasing from about 70% during the Delta wave to more than 75% during the Omicron wave. Collectively, these results underscore the persistent vulnerability of the communities residing in these rural areas and highlight the importance of the intensification of vaccination campaigns in these low vaccinated areas. Rural communities often face many challenges that exacerbate health disparities in the country. These areas usually run short on resources, including limited cold chain vaccine storage facilities and healthcare workers to administer vaccines. The geography can also compound disparities in access that affect rural clinics, which face unique challenges to provide vaccinations to residents who live many miles away (28). Moreover, it has been shown that rural residents are less likely to receive flu shots than residents of urban areas (29). This tendency, combined with the hesitancy in rural areas to adopt other COVID-19 mitigation measures, can hamper vaccination efforts in these communities. Furthermore, many of the risk factors for COVID-19 infection complications and deaths are exacerbated in rural areas, particularly in older adults (30, 31). Rural populations are older and have lower general health conditions than urban populations. Therefore, they are vulnerable populations at higher risk of COVID-19 related hospitalization and deaths, with an estimated 10% higher hospitalization rate for COVID-19 per capita than urban residents given equal infection rates (32). Additionally, significant vulnerabilities in rural areas include fewer physicians and lack of access to intensive care and ventilators, which are critical aspects of care needed for at least 5% of critical COVID-19 infection-related complications

TABLE 1 | K-means clustering estimations for the Delta (July 1, 2021 to August 31, 2021) and Omicron (December 1, 2021 to January 31, 2022) waves in the US.

	Cluster	Vaccination rate, %	Incidence rate	Mortality rate
Delta	1	34.6	623.5	8.7
	2	52.1	614.1	5.7
	3	35.4	2,404.6	16.9
	4	34.2	1,038.6	51.8
Omicron	1	41.0	4,760.3	19.8
	2	47.6	8,932.0	35.8
	3	62.8	6,883.4	29.8
	4	44.9	6,188.4	91.5

*Cluster locations are illustrated in maps in **Figure 4**.*

(33). These combined factors can worsen disease outcomes and influence the higher mortality observed in rural communities during the past two pandemic waves.

Our study had limitations worth noting. An ecological study like the one presented here is an approach for examining the association between factors and diseases by analyzing at the population level in specific areas. Therefore, due to the lack of individual data in ecological studies, it is difficult to adjust for all potential confounding factors. Moreover, there are other factors that might impact the regional incidence and mortality rates including local disparities in healthcare capacity, effectiveness of non-pharmaceutical interventions, COVID-19 testing coverage, and even in data collection and reporting. Lastly, vaccination coverage was estimated using the definition of fully vaccinated individuals, and we did not include data for boosted vaccination. However, by February 2022, boosted vaccination coverage is still lower in the country (∼25%) and follows the same spatial pattern of full vaccination coverage.

In conclusion, in this study we found that communities residing in low vaccinated areas are suffering the highest burden of the COVID-19 pandemic during the vaccination era. Despite the emergence of new virus variants with differential transmission potential, the protective effect of vaccines has generated marked differences in the distribution of critical health outcomes, with low vaccinated areas having the largest COVID-19 related mortality during the Delta and Omicron waves. These areas are the most vulnerable even when communities residing in these low vaccinated areas experience lower infection intensity than other areas, which was the epidemiological scenario observed during the Omicron wave. Healthcare disparities and differential vaccination coverage might continue influencing the pandemic trajectory and holding back efforts for epidemic control. Therefore, public information campaigns and vaccine promotions along with the setup of new sites for vaccinations in rural underserved areas should be intensified to target vulnerable populations in rural communities. A successful containment of the epidemic can only be achieved if vaccination intensity is substantially increased to protect the vulnerable population in these underserved areas to diminish the spatial heterogeneity of vaccination in the country. Pandemic control might become a reality only if no one is left behind, not only at local but also at global scale.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: Johns Hopkins Coronavirus Resource Center repository (https://coronavirus.jhu.edu/map.html), and the Centers for Disease Control and Prevention COVID data tracker repository (https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-County/8xkx-amqh).

AUTHOR CONTRIBUTIONS

DC and CM: drafting of the manuscript and statistical analysis. All authors: concept and design, acquisition, analysis, interpretation of data, and critical revision of the manuscript for important intellectual content.

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COVID-19 Preventive Measures in Northern California Jails: Perceived Deficiencies, Barriers, and Unintended Harms

Yiran E. Liu[1,2*†], *Christopher LeBoa*[1†], *Marcela Rodriguez*[3], *Beruk Sherif*[3], *Chrisele Trinidad*[3], *Michael del Rosario*[4], *Sophie Allen*[5,6], *Christine Clifford*[7], *Jennifer Redding*[8], *Wei-ting Chen*[9], *Lisa G. Rosas*[9], *Carlos Morales*[4], *Alexander Chyorny*[10] *and Jason R. Andrews*[1]

[1] Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford, CA, United States, [2] Cancer Biology Graduate Program, Stanford University School of Medicine, Stanford, CA, United States, [3] Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, CA, United States, [4] Division of Correctional Health Services, San Mateo County Health, Redwood City, CA, United States, [5] Stanford Law School, Stanford, CA, United States, [6] Department of Sociology, Stanford School of Humanities and Sciences, Stanford, CA, United States, [7] Silicon Valley De-Bug, San Jose, CA, United States, [8] Santa Clara County Office of the Public Defender, San Jose, CA, United States, [9] Office of Community Engagement, Stanford University School of Medicine, Stanford, CA, United States, [10] Division of Custody Health, Department of Medicine, Santa Clara Valley Health and Hospital System, San Jose, CA, United States

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Marc Jean Struelens,
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Brandy F. Henry,
The Pennsylvania State University
(PSU), United States

****Correspondence:***
Yiran E. Liu
yiranliu@stanford.edu

† These authors have contributed equally to this work

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Background: Carceral facilities are high-risk settings for COVID-19 transmission. Little is known about the hidden burden of infection or practical barriers to infection control in these settings, especially in jails. There is also limited research on the mental health impacts of the pandemic among people living and working in carceral facilities.

Methods: Between July 8, 2020 and April 30, 2021, we performed SARS-CoV-2 rapid antibody testing and administered a questionnaire among residents and staff of four Northern California jails. We utilized multivariable logistic regression, adjusting for demographic and carceral characteristics, to analyze factors associated with prior infection, including perceived likelihood of prior infection and access to new masks. We additionally assessed the implementation of, perceptions toward, and impacts of COVID-19 policies in practice. We engaged stakeholder representatives, including incarcerated individuals, to guide study design, procedures, and results interpretation.

Results: We enrolled 788 jail residents and 380 jail staff. Nearly half of residents and two-thirds of staff who were antibody-positive had not previously tested positive for COVID-19. Among residents without a prior COVID-19 diagnosis, antibody positivity was significantly associated with perceived likelihood of prior infection (adjusted OR = 8.9; 95% CI, 3.6–22.0). Residents who had flu-like illness in jail cited inadequate responses to reported illness and deterrents to symptom reporting, including fears of medical isolation and perceptions of medical neglect. Residents also disclosed deficient access to face masks, which was associated with antibody positivity (adjusted OR = 13.8, 95% CI, 1.8–107.0). Worsened mental health was pervasive among residents, attributed not only to fear of COVID-19 and unsanitary jail conditions but also to intensified isolation and deprivation due to pandemic restrictions on in-person visitation, programs, and recreation time.

Conclusion: Carceral settings present significant challenges to maintaining infection control and human rights. Custody officials should work diligently to transform the conditions of medical isolation, which could mitigate deterrents to symptom reporting. Furthermore, they should minimize use of restrictive measures like lockdowns and suspension of visitation that exacerbate the mental health harms of incarceration. Instead, custody officials should ensure comprehensive implementation of other preventive strategies like masking, testing, and vaccination, in conjunction with multisector efforts to advance decarceration.

Keywords: COVID-19, incarceration, jails, infection control, stakeholder engagement, community-based research, seroprevalence, mental health

INTRODUCTION

Prisons, jails, and detention centers present numerous challenges to public health, especially during the COVID-19 pandemic (1–3). Physical distancing is difficult in congregate settings, and people residing in carceral facilities may experience inadequate access to personal protective equipment (PPE), sanitation, and medical care (4–8). Furthermore, restrictive strategies for infection control in carceral settings such as facility lockdowns and suspension of visitation and programming may be especially harmful to well-being in an already isolated population with high rates of pre-existing mental illnesses and medical conditions (4, 9–14).

Recognizing these challenges, many public health practitioners and researchers have called for large-scale decarceration (7, 15–19); however, most policies enabling decarceration have been short-lived (20). For the millions of incarcerated individuals and staff who continue to be exposed daily to high-risk carceral settings, major knowledge gaps persist that preclude evidence-based improvements to infection prevention and control in carceral facilities (21–23). First, the hidden burden of COVID-19 in carceral settings remains unclear. While confirmed case counts in carceral facilities are already alarmingly high, they are likely underestimated due to inadequate testing, asymptomatic transmission, and population turnover (24–28). Antibody testing, which can identify prior infection by detecting antibodies to SARS-CoV-2 in the blood, is one strategy to assess the extent of undetected infection in a population and to determine factors associated with risk of prior infection (29, 30). However, to our knowledge few studies–none in the U.S.–have employed antibody testing in a carceral setting (31–35).

We also have a poor understanding of how COVID-19 preventive measures in prisons and jails fared in practice (23). Although vaccination has become an effective strategy (36), its utility is limited by insufficient vaccine uptake among incarcerated individuals and staff (37–39) and new viral variants that may evade existing immunity (40–42). Therefore, it is vital to maintain other preventive strategies such as masking and testing. However, little is known about the de facto implementation of such measures in carceral settings. While media outlets, advocacy groups, and human rights organizations have documented deficiencies in practice (3, 8, 28, 43, 44), the extent and direct consequences of these deficiencies remain unclear. Relatedly, there has been little research on the perceptions of incarcerated individuals or staff toward COVID-19 policies, or on the unintended impacts of such policies, both of which can influence acceptability and effectiveness (45, 46). For instance, medical isolation and quarantine may be damaging for mental health in a carceral setting and may stoke fears that disincentivize testing uptake (11, 43, 46, 47).

These knowledge gaps are especially dire for jails, which generally have worse data transparency than prisons despite their potentially outsized role in COVID-19 transmission (27, 48–50). Whereas in prisons, all residents are serving sentences of years or more, in jails most residents are legally innocent and being held pre-trial, with the remainder serving shorter sentences (51). As a result, jails have higher rates of population turnover than prisons, with an estimated 4.9 million people passing through jails each year (52). This phenomenon of "jail churn," on top of the daily commutes of hundreds of thousands of jail staff (53), may compound the risk of outbreaks and infection spillover into outside communities (17, 18).

Against this backdrop, we conducted a cross-sectional study across four county jails in Northern California to shed light on three understudied but important topics: (1) the extent of, and potential contributors to, undetected COVID-19 infection in carceral settings; (2) the implementation of preventive measures in practice, and perceptions toward them among incarcerated individuals and staff; and (3) the effects of restrictive COVID-19 policies on the health and well-being of incarcerated individuals and staff. To do this, we performed SARS-CoV-2 antibody testing and administered self-report questionnaires to people living and working in these four jails. In order to ensure the study's relevance and sensitivity for stakeholder populations, we engaged a community advisory board (CAB) consisting of incarcerated individuals, local and national advocates for criminal justice reform, a public defender, and custody health representatives to inform study design, procedures, and results interpretation. With guidance from the CAB, we hypothesized that flaws in the operationalization of preventive measures such as the response to reported illness or the provision of masks contributed to a hidden burden of COVID-19 infection. Furthermore, we hypothesized that restrictive pandemic policies had substantial deleterious impacts on the mental health of people living in the jails.

METHODS

Overview and Study Design

Between July 8, 2020 and April 30, 2021, we enrolled individuals living and working in four jails in San Mateo County and Santa Clara County, California to participate in a cross-sectional study consisting of SARS-CoV-2 antibody testing and a self-report questionnaire. This study was approved by the Stanford University and Valley Medical Center Institutional Review Boards (protocol #56169 and #20-022, respectively).

Participant Population and Recruitment

In response to the pandemic, both San Mateo County and Santa Clara County implemented an emergency bail schedule and arrest reductions in order to de-densify their jails, resulting in jail populations of ∼520 and 2,000 incarcerated individuals, respectively. The staff population–including custody staff, health care workers, and program staff–remained relatively stable, with approximately 480 and 1,050 staff members in San Mateo County and Santa Clara County, respectively. Incarcerated individuals were recruited through flyers and announcements in their housing units; in single-cell units, recruitment was done door-to-door. Research assistants (RAs) recruited from each housing unit in each jail at least once during the study period, with the exception of isolation units for COVID-19-positive individuals, units deemed by custody staff to be of high security risk, and units housing people with severe mental illnesses. Staff were recruited through flyers posted at work, emails sent by custody health officials, and radio announcements by custody leadership. RAs obtained written informed consent from all participants and emphasized that participation in any part of the study was voluntary with no compensation for participating nor penalty for refusal to participate or for withdrawing from the study. Due to timelines for administrative approvals, enrollment periods in each county were relatively distinct, with enrollment in Santa Clara County beginning only in January 2021 (**Supplementary Figure S1**). Details on sampling and representativeness are provided in **Supplementary Methods** and **Supplementary Table S1**.

Antibody Testing

To determine the prevalence of prior SARS-CoV-2 infection among residents and staff, we performed antibody testing on finger-prick blood samples using the RightSign COVID-19 IgG/IgM Rapid Test Cassette manufactured by Hangzhou Biotest Biotech, granted emergency use authorization by the FDA (54). All jails had an up-to-date Clinical Laboratory Improvement Amendments (CLIA) certificate of waiver. In an internal validation of test performance using serum samples from a separate study of COVID-19-positive patients (true positives), the RightSign Rapid Antibody Test had 81.5% and 92.1% sensitivity on patient samples from the day of and 28th day following COVID-19 diagnosis, respectively (55). Conversely, it had 100% specificity on 50 serum samples collected prior to 2019 (true negatives). Incarcerated participants received a hard copy of their antibody results on the day of sample collection; staff received results over secure email within 1–2 days. All participants were provided with an informational flier in English

TABLE 1 | Characteristics of study participants.

	Incarcerated (N = 788)	Staff (N = 380)
County (%)		
San Mateo County	424 (53.8)	213 (56.1)
Santa Clara County	364 (46.2)	167 (43.9)
Gender (%)		
Men	703 (89.2)	199 (52.4)
Transgender/gender non-conforming	6 (0.8)	1 (0.3)
Women	79 (10.0)	180 (47.4)
Age (%)		
18–29	252 (32.0)	49 (14.8)
30–49	419 (53.2)	179 (47.1)
50+	114 (14.5)	102 (26.8)
Unknown	3 (0.4)	50 (13.2)
Race/ethnicity (%)		
Asian	53 (6.7)	68 (17.9)
Black	147 (18.7)	16 (4.2)
Hispanic/Latinx	376 (47.7)	121 (31.8)
White	83 (10.5)	62 (16.3)
Other/Unknown	129 (16.4)	113 (29.7)
Comorbidities (%)		
One or more of:	335 (42.5)	110 (28.9)
Asthma	113 (14.3)	40 (10.5)
Diabetes	51 (6.5)	24 (6.3)
Heart disease or hypertension	61 (7.7)	34 (8.9)
Obesity	40 (5.1)	27 (7.1)
Substance misuse	191 (24.2)	0
Other	44 (5.6)	17 (4.5)
None of the above	383 (48.6)	183 (28.9)
Prefer not to answer	70 (8.9)	87 (22.9)
Already COVID-19 vaccinated (%)	82 (10.4)	77 (20.3)
Stable housing (%)		
Yes	521 (66.1)	351 (92.4)
No	235 (29.8)	1 (0.3)
Prefer not to answer	32 (4.1)	28 (7.4)
Median days incarcerated (IQR)	80 (15–285)	
Median number of cellmates (IQR)	1 (0–7)	
Health care worker (%)		
Yes		134 (35.3)
No		216 (56.8)
Prefer not to answer		30 (7.9)
Contact with incarcerated individuals (%)		
No		48 (12.6)
Yes		299 (78.7)
Prefer not to answer		33 (8.7)

Percentages may not sum to 100 due to rounding. Other comorbidities not listed included cancer, immunosuppression, kidney or liver disease, chronic lung disease or COPD. IQR, interquartile range.

TABLE 2 | Prevalence of antibodies to SARS-CoV-2 among incarcerated participants and association with demographic characteristics, perceived likelihood of prior infection, and access to masks.

	% Antibody positive (N/Total)	Adjusted OR (95% CI)
County		
San Mateo County	5.6 (22/394)	Ref
Santa Clara County	22.3 (66/296)	3.3 (1.8–6.2)***
Gender		
Men	12.4 (77/620)	Ref
Transgender/gender non-conforming	0 (0/6)	0 (NA)
Women	17.2 (11/64)	1.4 (0.6–3.0)
Age		
18–29	13.6 (31/228)	Ref
30–49	12.8 (47/368)	1.0 (0.6–1.7)
50+	10.9 (10/92)	1.0 (0.4–2.2)
Unknown	0 (0/2)	
Race/ethnicity		
Other/Unknown	5.6 (4/72)	Ref
Asian	23.8 (10/42)	5.7 (1.5–21.0)**
Black	7.5 (10/134)	1.6 (0.4–5.5)
Hispanic/Latinx	15.9 (52/328)	3.0 (1.0–9.4)
White	10.5 (12/114)	2.2 (0.7–7.8)
Secure housing		
Yes	13.5 (61/451)	Ref
No	9.4 (20/213)	0.7 (0.4–1.2)
Prefer not to answer	26.9 (7/26)	3.0 (1.0–8.7)*
Length of time incarcerated		
<30 days	11.6 (26/225)	Ref
30–183 days	12.5 (26/208)	0.7 (0.4–1.4)
184 + days	15.3 (31/203)	0.9 (0.5–1.7)
Unknown	9.3 (5/54)	
Number of cell mates		
0–1	9.8 (40/410)	Ref
2–07	7.2 (9/125)	0.9 (0.4–2.0)
8+	25.3 (38/150)	1.8 (1.0–3.3)*
Unknown	20.0 (1/5)	
Perceived likelihood of prior infection		
Very unlikely/unlikely	3.9 (14/355)	Ref
Possible	5.1 (8/158)	1.3 (0.5–3.2)
Likely/very likely	24.5 (13/53)	8.9 (3.6–22.0)***
Prefer not to answer	14.8 (4/27)	1.6 (0.4–6.7)
I tested positive for COVID-19	50.5 (49/97)	
Access to new masks		
Once a week	1.9 (1/54)	Ref
Less than once a week	18.4 (77/419)	13.8 (1.8–107.0)*
Prefer not to answer	17.9 (5/28)	9.2 (1.0–89.4)
Flu-like illness since Feb 2020		
Sick in jail, reported symptoms	42.4 (28/66)	
Sick in jail, did not report symptoms	16.7 (7/42)	
Sick outside of jail	20.3 (16/79)	
None	6.6 (32/483)	
Prefer not to answer	25.0 (5/20)	
Total	12.8 (88/690)	

Participants already vaccinated at the time of enrollment were excluded. Adjusted odds ratios (ORs) from Model 1 are shown for demographic and carceral characteristics (county, gender, age, race/ethnicity, secure housing, length of time incarcerated, number of cell mates). Adjusted ORs from Model 2 and Model 3 are shown for perceived likelihood of past infection and access to new masks, respectively. CI, confidence interval.
$^{*}p < 0.05$.
$^{**}p < 0.01$.
$^{***}p < 0.001$.

or Spanish on how to interpret their antibody test results and the option of consultation with study staff regarding their results.

Self-Report Questionnaire

We developed separate self-report questionnaires for incarcerated participants and staff participants. The questionnaire for incarcerated participants included the following sections and variables:

1. Demographic and carceral characteristics: age, gender, race/ethnicity, housing, comorbidities including substance misuse, time incarcerated, number of cell mates, COVID-19 vaccination history
2. Infection control policies in practice: reporting of recent flu-like illness, actions taken in response to reporting of illness, COVID-19 test history, frequency of access to new masks (cloth or surgical)
3. Perceptions surrounding COVID-19 and access to care: perceived likelihood of prior infection, fear of getting COVID-19, perceived ability to protect oneself from COVID-19, perceptions toward jail's pandemic response, perceptions of whether health concerns and needs would be recognized and fulfilled in and out of jail
4. Impacts of the COVID-19 pandemic on mental health, routine health care, and court dates

The staff questionnaire included the following sections and variables:

1. Demographic and employment characteristics: age, gender, race/ethnicity, housing, comorbidities, contact with incarcerated individuals at work, health care worker status, COVID-19 vaccination history
2. Perceptions surrounding COVID-19: perceived likelihood of prior infection, fear of getting COVID-19, perceived ability to protect oneself from COVID-19, perceptions toward jail's pandemic response
3. Impacts of the COVID-19 pandemic on mental health

Detailed information on questionnaire variables is provided in **Supplementary Methods**. For participants whose age, length of time incarcerated, or number of cell mates was unknown,

TABLE 3 | Prevalence of antibodies to SARS-CoV-2 among staff participants and association with demographic and employment characteristics.

	% Antibody positive (N/Total)	Adjusted OR (95% CI)
County		
San Mateo County	3.4 (7/207)	Ref
Santa Clara County	20.0 (17/85)	5.5 (2.0–15.0)***
Gender		
Men	10.9 (18/165)	Ref
Transgender/gender non-conforming	0 (0/1)	0 (NA)
Women	4.8 (6/126)	0.3 (0.1–0.8)*
Age		
18–29	10.0 (4/40)	Ref
30–49	10.0 (14/140)	0.6 (0.2–2.2)
50+	1.4 (1/70)	0.1 (0–1.2)
Unknown	11.9 (5/42)	
Race/ethnicity		
Other/unknown	14.8 (8/54)	Ref
Asian	2.6 (1/38)	0.3 (0–2.8)
Black	18.2 (2/11)	1.7 (0.2–14.1)
Hispanic/Latinx	8.5 (8/94)	0.8 (0.2, 3.6)
White	5.3 (5/95)	0.5 (0.1–2.5)
Health care worker		
Yes	4.8 (4/83)	Ref
No	8.2 (15/183)	0.9 (0.2, 3.4)
Prefer not to answer	19.2 (5/26)	5.3 (0–1167.1)
Contact with incarcerated individuals		
No	4.9 (2/41)	Ref
Yes	7.7 (17/222)	0.9 (0.2–4.6)
Prefer not to answer	17.2 (5/29)	0.1 (0–40.6)
Flu-like illness since Feb 2020		
Yes	8.8 (5/57)	
No	6.8 (14/205)	
Prefer not to answer	16.7 (5/30)	
Perceived likelihood of past infection		
Very unlikely/unlikely	2.0 (2/102)	
Possible	4.6 (5/108)	
Likely/very likely	10.0 (4/40)	
Prefer not to answer	17.2 (5/29)	
I tested positive for COVID-19	61.5 (8/13)	
Total	8.2 (24/292)	

Participants already vaccinated at the time of enrollment were excluded. OR, odds ratio; CI, confidence interval.
*$p < 0.05$.
***$p < 0.001$.

we imputed these variables using all other variables from the questionnaire as detailed in **Supplementary Methods**.

For incarcerated participants, RAs administered the questionnaire using an electronic tablet. Incarcerated participants could choose to read and respond to questions themselves or to respond orally to questions read aloud. Spanish-speaking RAs and Spanish, Chinese, and Vietnamese text translations were available. To increase privacy, study procedures were conducted in a separate multi-purpose room within each housing unit. Staff participants completed the questionnaire online. Questionnaire data were recorded in a HIPAA-secure REDCap database (56).

Community Advisory Board and Stakeholder Engagement

Two community advisory boards (CABs), one in each county, guided the overall design and implementation of this study. The goal of the CABs was to ensure that all parts of the study were relevant and sensitive to incarcerated individuals and community stakeholders. In each county, the CAB consisted of people who were currently incarcerated in the jails, representatives from custody health, community organizers from a local advocacy organization, a national advocate for criminal justice reform, and in Santa Clara County, a public defender. Participation in the CAB was voluntary and non-binding. The Stanford study team met with each CAB periodically throughout the study via video conferencing, during which researchers provided an overview of the study aims, design, and procedures and solicited feedback and suggestions from the CAB. Meeting notes were circulated to CAB members following each meeting. In addition to CAB meetings, research staff conducted focus group discussions in various housing units within the jails prior to the enrollment start date as well as halfway through the study.

Of note, CAB and focus group discussions were not transcribed nor analyzed as qualitative data. Rather, they were intended to provide greater transparency into the research process, address questions or concerns regarding the study, and solicit important feedback from stakeholders on five major components of the study: recruitment, enrollment, questionnaire design, results interpretation, and results dissemination. For each of these components, we describe examples of CAB insights and how they were incorporated in the study in **Supplementary Table S2**. Key insights surrounding results interpretation are also presented as context throughout the Discussion.

Statistical Analysis

For all seroprevalence analyses, we excluded 82 incarcerated participants and 77 staff participants who were vaccinated prior to enrollment, based on self-reported vaccination status and/or Correctional Health data on vaccine uptake in custody, accessed as previously described (39). We calculated 95% confidence intervals for seroprevalence using the Wilson method for binomial data (57).

For incarcerated participants, we fit multivariate logistic regression models to examine the association between seroprevalence and predictors of interest. Model 1 included only demographic and carceral variables (county, gender, age, race/ethnicity, secure housing before incarceration, length of time incarcerated, and number of cell mates). Model 2 adjusted for demographic and carceral variables and examined perceived likelihood of prior infection as the main predictor of interest. Model 3 adjusted for demographic and carceral variables and examined frequency of access to new masks as the main predictor of interest. Ninety-seven participants who reported previously testing positive for COVID-19 and 189 participants who did not answer the mask access question were excluded from Model 2 and Model 3, respectively. Finally, we fit additional multivariate logistic regression models, adjusted for demographic and carceral variables, to test associations between seroprevalence and perceptions surrounding COVID-19 or barriers to care.

For staff participants, we fit a multivariate logistic regression model for seroprevalence with the following explanatory variables: county, gender, age, race/ethnicity, health care worker status, and contact with incarcerated individuals at work. All analyses were performed in R 4.1.3.

RESULTS

Study Population

We enrolled 788 incarcerated individuals and 380 staff members across four jails in adjacent Northern California counties. This sample represented 31% and 25% of the average daily resident and staff population, respectively, across both counties combined. The incarcerated participant population was mostly male (89%), between the ages of 18 and 49 (85%), and Hispanic/Latinx or non-Hispanic Black (66%). Approximately three in ten reported unstable housing prior to incarceration, and 43% reported at least one medical condition considered a potential COVID-19 comorbidity (**Table 1**). The median and interquartile range (IQR) for length of time incarcerated was 80 days (IQR 15–285). The median number of cell mates was one (IQR 0–7).

The staff participant population was approximately half women (47%) and mostly 30 years of age and older (74%), with a plurality identifying as Hispanic/Latinx (32%). Approximately three in ten staff participants reported at least one potential COVID-19 comorbidity. Most staff participants (79%) indicated contact with incarcerated individuals at work, and 35% identified as health care workers.

Prevalence of SARS-CoV-2 Antibodies by Demographic Characteristics

First, we examined the prevalence of antibodies to SARS-CoV-2 (IgG and/or IgM) and its association with demographic or carceral characteristics among people living and working in the jails. In our sample, 13% (88/690; 95% CI, 10–15%) of incarcerated participants (**Table 2**) and 8% (24/292; 95% CI, 6–12%) of staff participants tested positive for SARS-CoV-2 antibodies (**Table 3**). After adjusting for other demographic characteristics, antibody positivity was significantly higher in Santa Clara County than San Mateo County, with an adjusted odds ratio (AOR) of 3.3 (95% CI 1.8–6.2) for incarcerated participants and 5.5 (95% CI 2.0–15.0) for staff participants (**Tables 2**, **3**). However, this difference may have been confounded by the later enrollment start in Santa Clara County (**Supplementary Figure S1**). Among incarcerated participants, other factors associated with higher antibody positivity were Asian race (AOR = 5.7, 95% CI 1.5–21.0) and having eight or more cell mates (AOR = 1.8, 95% CI 1.0–3.3) (**Table 2**). Among staff, women had significantly lower odds of antibody positivity than men (AOR = 0.3, 95% CI 0.1–0.8) (**Table 3**).

Contributors to Undetected COVID-19 Infection

To assess the extent of undetected COVID-19 infection in the jails, we compared participants' antibody test results with self-reported history of a positive COVID-19 test. Nearly half (39/88; 44%) of incarcerated participants who were antibody-positive did *not* report a prior COVID-19 diagnosis (**Table 2**). Among these antibody-positive incarcerated participants without a prior COVID-19 diagnosis, 46% reported having flu-like illness since February 2020 (31% outside jail, 15% in jail). To test our hypothesis that the hidden burden of infection was attributable in part to inadequate responses to reported illness or symptom underreporting, we analyzed responses from 123 (16%) incarcerated participants who reported having flu-like illness in jail since February 2020 (**Table 2**). Among participants who reported their symptoms to jail staff, only 62% indicated getting tested for COVID-19 and over one in five (22%) indicated that no action was taken (**Table 4**). Moreover, 39% of participants who were sick in jail did not report their symptoms to jail staff. The leading reason for symptom underreporting was not thinking it was not serious enough to report (47%), followed by not thinking anything would be done about it (28%), concern about being put in isolation (26%), and worry about how jail staff would treat them (21%) (**Table 4**).

We next utilized multivariate logistic regression to examine the association between antibody positivity and perceived likelihood of prior infection among individuals without a prior COVID-19 diagnosis. We reasoned that a positive association would indicate that antibody-positive individuals who were aware of COVID-19 exposure or infection did not get tested, providing further evidence that limited access to testing and deterrents to symptom reporting or testing uptake contributed to undetected infection. After adjusting for demographic and carceral characteristics, the odds of prior infection were 8.9 (95% CI, 3.6–22.0) times higher among participants who thought it was likely or very likely that they had COVID-19, compared to participants who thought it unlikely or very unlikely (**Table 2**).

Of note, we also found undetected infection among staff, with only one-third of antibody-positive staff participants reporting a previous positive COVID-19 test (**Table 3**). Among the remaining two-thirds of antibody-positive staff who did not report a prior COVID-19 diagnosis, 13% reported having flu-like illness since February 2020. We were underpowered to test the association between antibody positivity and perceived likelihood of prior infection among staff participants.

Limited Access to Masks and Association With Infection Risk

Throughout the pandemic, face masks have been one of few ways in which incarcerated individuals have been able to protect themselves from COVID-19. Indeed, when incarcerated participants were asked to select three things that would protect them most from COVID-19, face masks were a leading protective

TABLE 4 | Reporting of illness and access to face masks among incarcerated participants.

	% Incarc respondents
Did you report your symptoms to jail staff? (Among participants who had flu-like illness in jail)	
Yes	60.7
No	39.3
What action was taken when you reported your symptoms? (Among participants who responded "Yes" to the first question) (Select all that apply)	
I was tested for COVID-19	62.1
I was put in isolation	51.7
I was taken to the medical clinic for evaluation	34.5
No action was taken	22.4
Why didn't you report your symptoms? (Among participants who responded "No" to the first question) (Select all that apply)	
I didn't think it was serious enough to report	46.8
I didn't think anything would be done about it	27.7
I was concerned about being put in isolation	25.5
I was worried about how staff in the jail would treat me	21.3
I was worried about how other incarcerated people would treat me	2.1
Other	12.8
How often do you get a new mask? (Among participants incarcerated for at least 30 days)	
Once a week	7.3
Once a month	17.5
Less frequent than once a month	40.2
I have only received **one** mask since the start of the pandemic	33.9
I do not have one	1.0

Percentages were calculated after excluding those with missing or "prefer not to answer" responses and may not sum up to 100 due to rounding.

measure cited by 56% of participants, second only to release from jail (75%) (**Supplementary Table S3**). However, we found that access to new masks for jail residents was extremely limited: among participants incarcerated for at least 30 days, only 7% received a new mask once a week and 17% once a month (**Table 4**). Alarmingly, nearly three-quarters of participants reported receiving a new mask less often than once a month.

To test our hypothesis that limited mask access was associated with increased risk of prior infection, we again used multivariate logistic regression to assess the association between antibody positivity and mask access, adjusting for demographic and carceral factors. Restricted access to masks—defined as receiving a new mask less often than once a week—was associated with significantly higher odds of prior infection (AOR 13.8, 95% CI 1.8–107.0) (**Table 2**).

Perceptions Surrounding COVID-19 and Barriers to Care

Among incarcerated participants, we identified prevalent experiences of frequent stress or fear around getting COVID-19 in jail (39% of participants), perceptions of being unable to protect oneself from COVID-19 in jail (54% of participants), and perceptions that not enough was being done to protect incarcerated individuals from COVID-19 (58% of participants) (**Supplementary Table S3**). We also identified pervasive perceptions of barriers to health care in jail, with only 23% and 35% of incarcerated participants who believed that their health concerns were taken seriously by correctional officers or jail health staff, respectively (**Supplementary Table S4**). This mistrust appeared setting-specific, as 60% of incarcerated participants believed that their health concerns were taken seriously by their doctor outside of jail. Similarly, 43% of incarcerated participants expressed concerns of being denied medical treatment or services while incarcerated, compared to 27% who expressed concerns of being denied treatment outside of jail (**Supplementary Table S4**). We tested whether any of these perceptions were associated with antibody prevalence. After adjusting for demographic and carceral characteristics, neutrality or disagreement regarding whether one's health concerns were taken seriously by jail health staff was associated with 2.1 (95% CI 1.0–4.5) increased odds of seropositivity, compared to those who agreed with this statement (**Supplementary Table S5**).

In contrast, an overwhelming majority of staff participants (95%) felt at least somewhat able to protect themselves from COVID-19 while at work (**Supplementary Table S3**). While only 20% reported experiencing frequent stress or fear around getting COVID-19 at work, 39% did report frequent stress or fear around bringing COVID-19 from work to others in their household or community. When asked whether enough was being done to protect incarcerated individuals from COVID-19, 67% of staff participants agreed or strongly agreed (**Supplementary Table S3**). When asked whether enough was being done to protect *staff* from COVID-19, 51% of staff participants agreed or strongly agreed.

TABLE 5 | Impacts of the COVID-19 pandemic on mental health and reasons for worsened mental health among incarcerated and staff participants.

	% Incarc respondents	% Staff respondents
How has your mental health been impacted by COVID19?		
It has been better	1.9	1.7
It has been better	4.0	5.7
My mental health has not been affected	45.0	60.1
It has been worse	23.5	22.8
It has been much worse	14.8	3.4
Prefer not to answer	10.9	6.3
What do you think has affected your mental health while in custody during COVID-19? (Among incarcerated participants with worsened mental health) (Select all that apply)		
Lack of connection to family and other loved ones	75.4	
Fear of getting COVID-19	66.5	
Lack of programs due to COVID-19 (i.e. classes, support groups)	56.4	
Changes in recreation time due to COVID-19	55.9	
Unsanitary/unsafe conditions	55.9	
Family or personal issues	55.1	
Financial insecurity due to COVID-19	45.8	
Lack of information about COVID-19	39.4	
Other	12.7	
Prefer not to answer	1.3	
What do you think has affected your mental health while in working in a correctional facility during COVID-19? (Among staff participants with worsened mental health) (Select all that apply)		
Fear of getting COVID-19		63.8
Unsanitary/unsafe conditions		44.7
Family or personal issues		42.6
Lack of information about COVID-19		25.5
Frequency of COVID-19 routine testing		23.4
Other		8.5
Nothing		6.4
Prefer not to answer		4.3

Percentages were calculated after excluding those with missing responses and may not sum up to 100 due to rounding.

Impacts of COVID-19 on Court Dates, Mental Health, and Routine Health Care

Among incarcerated participants, 61% indicated that their court dates were impacted by the COVID-19 pandemic. Delays (76%), limits on attendance (56%), and cancellations (39%) were the most common impacts cited (**Supplementary Table S6**). Notably, among participants whose court dates were delayed, 44% reported delays of over 2 months (**Supplementary Table S6**).

The COVID-19 pandemic also had impacts on mental health, with 38% of incarcerated participants citing worse mental health due to the pandemic (**Table 5**). Leading reasons for worsened mental health were lack of connection to family and other loved ones (75%) and fear of getting COVID-19 (67%) (**Table 5**). Other common reasons included limits on programming (ie., classes, support groups) (56%), changes in recreation time (56%), unsanitary/unsafe conditions (56%), family or personal issues (55%), financial insecurity due to COVID-19 (46%), and lack of information about COVID-19 (39%). Our findings also revealed impacts on routine mental or physical health care in jail. Of the 38% and 43% incarcerated participants who reported previously receiving regular mental or physical health care in jail, respectively, approximately 40% said their health care had decreased or stopped due to the pandemic (**Supplementary Table S6**).

Among staff participants, over one quarter reported worsened mental health due to the COVID-19 pandemic, with leading reasons including fear of getting COVID-19 (64%), unsanitary/unsafe conditions at work (45%), family or personal issues (43%), lack of information about COVID-19 (26%), and frequency of COVID-19 routine testing (23%) (**Table 5**).

DISCUSSION

In this study across four Northern California county jails, antibody testing revealed a hidden COVID-19 burden among people living and working in the jails. By pairing antibody data with questionnaire responses, we found that undetected infection was concentrated among jail residents who suspected prior infection but remained undiagnosed, which may have been due in part to symptom underreporting and/or inaction by staff in response to reported illness. Residents also indicated deficient access to face masks, which was strongly associated with increased risk of prior infection. Perceptions of medical neglect in jail were prevalent among residents, as well as experiences of worsened mental health due to restrictive COVID-19 policies. Together, these findings shed light on practical barriers to infection prevention and control in carceral settings and underscore the need for improved implementation of preventive measures as well as a pandemic response strategy that minimizes harm to mental health and well-being.

To our knowledge, this study was the first to employ antibody testing in a U.S. carceral setting. Among residents, dormitory-style housing was associated with increased risk of prior infection, corroborating prior work in prisons (58). In concordance with previous accounts of under-testing in prisons and jails (25–28), this study revealed substantial undetected COVID-19 infection among both residents and staff. These results are consistent with other studies employing antibody testing in carceral (31) and non-carceral settings (30, 59). We also found a significant association between antibody positivity and perceived likelihood of prior infection among residents without a prior COVID-19 diagnosis, suggesting that the hidden burden of infection was concentrated among individuals who were aware of exposure or infection but had not been tested. There could be several reasons for this, including limited access to testing and/or deterrents to testing uptake. While we were underpowered to directly assess whether and to what extent these two factors contributed to undetected infection, we did find evidence for the standalone existence of both phenomena.

First, regarding limited access to testing, we found that even among residents who reported their flu-like illness to jail staff, only 62% said they were then tested for COVID-19, and 22% said no action was taken. Relatedly, many residents believed that their health concerns were neglected by jail staff; this belief may reflect institutional or medical mistrust that could impede care-seeking or uptake of other preventive measures like vaccination, as has been shown in other studies (39, 46, 60). In particular, residents who were neutral or in disagreement about jail health staff taking their health concerns seriously had increased odds of antibody positivity; however, we were unable to infer causality or to determine the direction of causation. Regardless, these collective findings illustrate the need for more systematic, consistent, and transparent protocols for responding to residents' reported illness and other health concerns.

Second, regarding deterrents to testing uptake, we found that nearly four in ten individuals who had flu-like illness in jail did not report their symptoms to jail staff. Reasons cited for symptom underreporting included beliefs that nothing would be done about it and fears of being placed in isolation. Accordingly, incarcerated members of our CAB cited widespread fears that a positive COVID-19 test would effectively lead to solitary confinement. Considered in conjunction with evidence on the health harms of restrictive housing (11–13), these findings strongly caution against over-reliance on isolation and quarantine in place of comprehensive implementation of other preventive measures such as masking, testing, and vaccination for residents and staff. When medical isolation is necessary, jail administrators and staff should undertake exhaustive efforts to distinguish its conditions from solitary confinement, which could critically reduce barriers to reporting of illness. This could include providing individuals in isolation with free and enhanced access to entertainment, nutritious meals, outdoor time, phone and video calls with loved ones, and frequent oversight and status updates from healthcare staff (43, 47).

Incarcerated participants also indicated extremely limited access to new masks, which we found to be significantly associated with elevated infection risk as measured by antibody positivity. Of note, although the importance of proper mask wearing is well-understood, our incarcerated stakeholder representatives drew attention to the overlooked issue of mask maintenance and replacement. Namely, they reported peers having torn masks from overuse and spoke of being unable to wash their soiled cloth mask without another to wear while it dried. While the jails' official policy was to provide new masks for residents upon request, our findings highlight the need for an active rather than passive approach to periodic mask distribution and/or laundering, and generally for more systematic, consistent, and transparent protocols for responding to residents' reported illness and other health concerns.

This study also revealed detrimental impacts of the pandemic on residents' cases and mental health. Our finding of pervasive court delays and cancellations substantiates a recent investigation which uncovered severe case backlog in California that has only been exacerbated by the pandemic (61). Many residents also cited restrictions on court attendance; as our CAB pointed out, these restrictions hindered participatory defense, a community organizing model developed locally that engages family and community members in shaping a loved one's case (62). In addition to case-related stressors, we identified prevalent worsened mental health among residents that was attributed not only to fear of COVID-19 and unsanitary conditions but also to restrictive pandemic policies, corroborating prior qualitative work (45, 63–65). These mental health harms have likely only intensified with prolonged restrictions: all four jails suspended in-person visitation for over 10 months, and some continue to restrict recreation time and in-person programming over 2 years into the pandemic. While these measures can help mitigate transmission during major outbreaks, their prolonged and unnecessary use violates minimum human rights standards (3, 66, 67) and, as our findings warn, may be contributing to a second crisis of mental health among residents. Therefore, administrators should ensure prompt resumption and continuation of in-person visitation, programs, and standard recreation time, especially when facility and community transmission is low (68).

While this study focused largely on incarcerated individuals, we also identified various topics of interest relating to jail staff that merit future study. Male staff had significantly higher odds of antibody positivity even after adjusting for employment type; however, we were underpowered to identify other variables robustly associated with prior infection or undetected infection among staff. Additional research is needed on this topic given its implications for disease spread within carceral facilities and between carceral facilities and outside communities. In addition, the role of jail staff in contributing to or mitigating the deficiencies in infection prevention and control remains unclear. While staff generally felt able to protect themselves from COVID-19 at work, some still reported unsanitary conditions, worsened mental health due to the pandemic, and frequent fears of getting infected at work and bringing it home. These issues may contribute to critical staffing shortages occurring in prisons and jails across the U.S., which have had dire consequences for residents and staff alike (69). However, the pandemic has only further exposed and exacerbated the various threats to public health and human rights long posed by incarceration (1, 2, 14, 67, 70, 71); accordingly, efforts should focus on minimizing the population exposed to carceral settings rather than re-expanding the carceral workforce (15, 69).

This study had several limitations. All questionnaire data were subject to self-report biases; however, for incarcerated participants we validated demographic information and COVID-19 test history with custody records or the jail electronic health record (EHR) when available (**Supplementary Methods**). We also mitigated social desirability bias by administering questionnaires online for staff or via electronic tablet for incarcerated individuals when possible. Our participant population was likely a biased sample due to voluntary participation, language barriers for non-English or Spanish speakers, and exclusion of people in COVID-19 isolation, people in high security units, and people with severe mental illnesses; moreover, we were unable to track response rate. Therefore, our findings may not be representative of the entire resident or staff population and may have more qualitative value than quantitative precision. Due to small sample size, we did not analyze smaller racial/ethnic subgroups, such as Indigenous/Pacific Islander individuals or Hispanic/Latinx individuals of different races, but future studies should assess differences in infection risk or COVID-19-related perceptions across racial/ethnic subgroups. For logistic regression analyses we imputed missing data on age, length of incarceration, and number of cell mates; using imputed data led to trivial differences compared to excluding observations with missing data. Furthermore, our estimates of the extent of prior and undetected infection are affected by counteracting factors of imperfect test specificity vs. insufficient test sensitivity, lack of seroconversion, and antibody waning. However, these factors likely had similar effects on all strata that we compared. Finally, our findings may have limited generalizability to other carceral facilities but nonetheless reflect challenges that are shared across many carceral settings.

CONCLUSIONS

This study reveals significant practical barriers to achieving infection control in carceral settings. Reported deficiencies in preventive measures and the harmful conditions of medical isolation may foster mistrust and fears that in turn undermine symptom reporting, testing uptake, and vaccine acceptance. Concurrently, restrictive pandemic policies have resulted in heightened social isolation, deprivation, and case-related stress that exacerbate poor mental health and the already distressing experience of incarceration. In the short term, our findings warrant diligent efforts from custody and health officials to transform the conditions of medical isolation and to ensure periodic active mask provision and consistent, transparent responses to residents' reported illness. Custody officials should also prioritize prompt restoration of in-person visitation, programs, and services essential for the health and well-being of people living in carceral facilities. Ultimately, our findings highlight numerous obstacles to maintaining health and human rights in carceral settings and underscore the need for community-based investments to enable sustained decarceration during and beyond pandemic times (72).

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical and privacy concerns but may be made available in de-identified or aggregate form in the future, as allowed by the IRB. Requests to access the datasets should be directed to YL, yiranliu@stanford.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Stanford Institutional Review Board (#56169) and Santa Clara Valley Medical Center Institutional Review Board (#20-022). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL, CL, and JA contributed to conceptualization and study design. MRod, BS, and CT acquired the data. YL wrote the first draft of the manuscript and analyzed the data with critical input from CL and JA. All authors contributed to data interpretation, manuscript revision, and approved the submitted version.

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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.2022.854343/full#supplementary-material

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Assessing Vaccination Prioritization Strategies for COVID-19 in South Africa Based on Age-Specific Compartment Model

Chao Zuo, Zeyang Meng, Fenping Zhu, Yuzhi Zheng and Yuting Ling**

School of Management Engineering and E-Commerce, Zhejiang Gongshang University, Hangzhou, China

The vaccines are considered to be important for the prevention and control of coronavirus disease 2019 (COVID-19). However, considering the limited vaccine supply within an extended period of time in many countries where COVID-19 vaccine booster shot are taken and new vaccines are developed to suppress the mutation of virus, designing an effective vaccination strategy is extremely important to reduce the number of deaths and infections. Then, the simulations were implemented to study the relative reduction in morbidity and mortality of vaccine allocation strategies by using the proposed model and actual South Africa's epidemiological data. Our results indicated that in light of South Africa's demographics, vaccinating older age groups (>60 years) largely reduced the cumulative deaths and the "0–20 first" strategy was the most effective way to reduce confirmed cases. In addition, "21–30 first" and "31–40 first" strategies have also had a positive effect. Partial vaccination resulted in lower numbers of infections and deaths under different control measures compared with full vaccination in low-income countries. In addition, we analyzed the sensitivity of daily testing volume and infection rate, which are critical to optimize vaccine allocation. However, comprehensive reduction in infections was mainly affected by the vaccine proportion of the target age group. An increase in the proportion of vaccines given priority to "0–20" groups always had a favorable effect, and the prioritizing vaccine allocation among the "60+" age group with 60% of the total amount of vaccine consistently resulted in the greatest reduction in deaths. Meanwhile, we observed a significant distinction in the effect of COVID-19 vaccine allocation policies under varying priority strategies on relative reductions in the effective reproduction number. Our results could help evaluate to control measures performance and the improvement of vaccine allocation strategy for COVID-19 epidemic.

Keywords: COVID-19, vaccination strategy, social contact, age structure, compartment model

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****Correspondence:***
Chao Zuo
chaozuo1982@gmail.com
Yuting Ling
lingyuting999@gmail.com

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INTRODUCTION

The emergence of the novel coronavirus disease 2019 (COVID-19) has led to a global pandemic with serious implications for public health security. During this crisis, a large number of diagnostic protocols and treatment methods have been designed based on comprehension of the pathological characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). The vaccines are considered to be important for the prevention and control of COVID-19, so many countries are developing COVID-19 vaccines based on the infection mechanisms of SARS-CoV-2 and its effect on host immunity (3, 4). However, many countries have experienced insufficient access to vaccines and the major vaccine manufacturers find it hard to ramp up production in a short time. In particular, the variants of the SARS-CoV-2 (Beta, Delta, and Omicron variant) have reduced the effectiveness of existing vaccines, which prompts some counties to take COVID-19 vaccine booster shots (three doses) and develop new vaccines to prevent substantial morbidity and mortality. The development of effective vaccination strategies is critical given the limited availability of vaccines over the long term. It is well-known that vaccines should be allocated first to high-risk groups such as first responders and immunocompromised populations. What's worth exploring is the vaccine distribution of other groups after vaccination of high-risk groups.

One of the characteristics of COVID-19 is that the susceptibility, infectivity, severity, and mortality of the disease vary by age (5–7). Studies indicated that the susceptibility to infection usually increases with age, however, younger adults, especially those under 35, tend to experience the highest cumulative infection rates (6). Meanwhile, older adults have a higher mortality compared to younger individuals, mortality for those aged under 65 years range from 0% to 42%; and for those aged above 65 years range from 0% to 56% (7). Vaccination priority given to different age groups will affect the cumulative morbidities and mortalities. Moreover, the rate of infection relies on the social contact patterns (represented by the contact matrix), which depicts the contact degree between age groups, and is the linear combination of the location-specific matrices of household, school, workplace, and other locations (8). The epidemic can spread through the social network, which depends on pandemic contact pattern about the extent individuals interact with each other, and thus the contact patterns can effectively guide public health authority identify individual at high risk of infection and where an outbreak can be effectively prevented (9). Many studies consistently recommended that prioritizing younger populations who usually possess a higher contact rate exerts a greater effect on reducing morbidities relative to prioritizing older age groups (10, 11). Besides, the implementation of control measures, such as social distancing, lockdowns, and confinement on travel can slow the spread of pandemics and reduce morbidities (12). Several studies indicated that reasonable control measures substantially reduced the effective reproduction number in various regions (13). For example, relaxing restrictions can be considered to give priority to those less vulnerable age-brackets, which is presented because disease spread and mortality are apparently affected by the age distribution of the population (14). Daily testing volume is the mainstays of case finding, including asymptomatic and symptomatic infections, by identifying more infected people and then taking clinical treatment contributed to prevent the onward infection of others (15). In the absence of COVID-19 vaccine or shortage of medical resources, the implementation of large-scale rapid testing is an effective measure to curb transmission and death, particularly with asymptomatic transmission accountable for 44% of infections, thus increased testing volume is critical to the infection rates reduction (16). Vaccine availability and rollout speed can reflect the approximate time to vaccinate the target population, which promotes the vaccine coverage by continuous distribution to suppress the transmission of epidemics (17). Considering breakthrough infections resulted from the emergence of new variants, and waning immunity from primary COVID-19 vaccines, booster shots are an effective option for the prevention against COVID-19, which urges the adoption of more vaccines and faster rollout speed (18).

Thus, an effective vaccination priority strategy requires an understanding of the complicated interaction between age structure and age-specific social contact patterns and is combined with various hypothetical scenarios, such as the control measures, vaccine availability, detection rate, and rollout speed of vaccine, which also affect the spread of the COVID-19 epidemic. Meanwhile, the compartmental model is a very general modeling technique used for describing the flow patterns between the compartments of a system, which is often applied to the mathematical modeling of infectious diseases. Motivated by the above considerations, we construct an age-specific compartment model to evaluate the optimal distribution of limited COVID-19 vaccine availability across different age groups under various potential vaccine characteristics and hypothetical scenarios.

One of the dominant factors of the fourth wave in South Africa was the emergence of the Omicron variant. The public quickly understood that the Omicron variant had enhanced the infection rate of the delta virus (19). Accordingly, when the Omicron variant reached South Africa in November 2021, the number of cases and hospitalizations increased significantly. As of 6 February 2022, 27.92% of South Africans received two doses of vaccine, 4.99% of South Africans received one dose of vaccine, and only 1% had received the booster shot, the cumulative number of infections in South Africa reached 3.6 million (20). Therefore, we examine the effects of our proposed model and use pandemic contact matrices and actual epidemiological data in South Africa (1 November 2021–31 January 2022) to quantify and evaluate the effect COVID-19 vaccine prioritization policies have on cumulative morbidities and mortalities.

The study is organized as follows. In section model, we construct the age-specific compartment model. In section results, the numerical simulations are performed to assess the vaccination strategy. Finally, discussions are put forward in section discussions.

MODEL

Mathematical Modeling

To simulate the transmission and vaccination process of COVID-19, an age-specific compartment model is constructed, and the population is divided into compartments according to the characteristics of each age group: S_i = susceptible, E_i = exposed, R_i = recovered, Q_i = hospitalized intensive care, D_i = dead, I_i = infected, $V1_i$ = vaccinated first doses, $V2_i$ = vaccinated second doses, SV_i = susceptible and vaccinated, EV_i = exposed and vaccinated, *and* IV_i = infected and vaccinated. The age classes i = 1, 2, 3, 4, 5, and 6 represent individuals aged 0–20, 21–30,

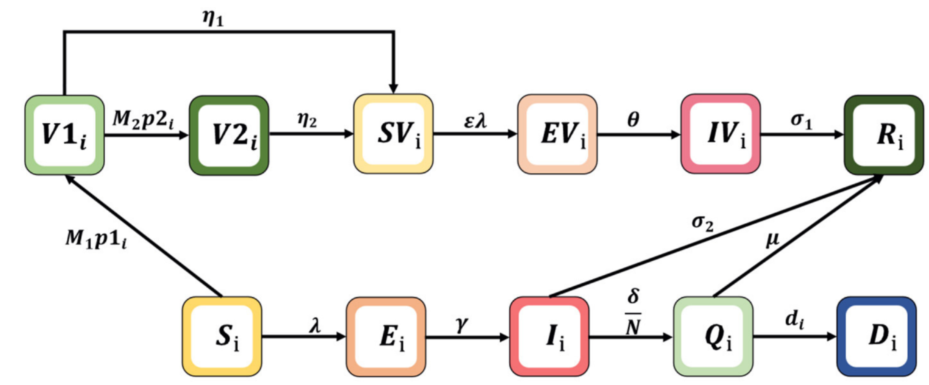

FIGURE 1 | Schematic diagram of the mathematical model.

31–40, 41–50, 51–60, and 60+ years, respectively. The schematic diagram of the model is shown in **Figure 1**.

The dynamic model is described by the following non-linear differential equation system:

$$\begin{cases} \frac{dS_i}{dt} = -S_i * \lambda_i - M_1 * p1_i \\ \frac{dE_i}{dt} = S_i * \lambda_i - E_i * \gamma \\ \frac{dI_i}{dt} = E_i * \gamma - I_i * \frac{\delta}{N} - I_i * \sigma_2 \\ \frac{dQ_i}{dt} = I_i * \frac{\delta}{N} - Q_i * \mu - Q_i * d_i \\ \frac{dD_i}{dt} = Q_i * d_i \\ \frac{dR_i}{dt} = Q_i * \mu + I_i * \sigma_2 + IV_i * \sigma_1 \\ \frac{dV1_i}{dt} = M_1 * p1_i - M_2 * p2_i - V1_i * \eta_1 \\ \frac{dV2_i}{dt} = M_2 * p2_i - V2_i * \eta_2 \\ \frac{dSV_i}{dt} = V1_i * \eta_1 + V2_i * \eta_2 - SV_i * \varepsilon * \lambda_i \\ \frac{dEV_i}{dt} = SV_i * \varepsilon * \lambda_i - EV_i * \theta \\ \frac{dIV_i}{dt} = EV_i * \theta - IV_i * \sigma_1 \end{cases} \quad (1)$$

Where λ_i is the infection force for each age group, $\lambda_i = \beta \times \sum_{j=1}^{6} \frac{C_{ij} \times (I_j + IV_j)}{N}$. The model parameters in Formula (1) are shown in **Table 1**, where N is the sum of the total population of each compartment; β is the potential of an individual being infected by contact once with an infectious person; and ε is reduced susceptibility. Note that C_{ij} represents an element in the contact matrix, reflecting the level of contact in the South African population, which is a 6×6 matrix (the detailed estimation of the contact matrix is shown in **Supplementary Section 1**). We assume that vaccines are rolled out M_1 and M_2 and doses are available each day, which are used for first and second injections, respectively. Vaccinated individuals may not be protected from infection due to immunity waning, we assume that individuals who received one and two doses lose vaccine protection with probabilities of η_1 and η_2, respectively. In addition, considering that the risk of severe disease of infection with Omicron is lower than that of Delta virus, the risk of hospitalization is also reduced; and patients who have been vaccinated and infected with the omicron variant can be cured through non-hospital treatment, such as the use of drugs and home isolation (21). We also assume that unvaccinated subjects moved to the recovered (R) compartment after they received intensive care (Q) or non-hospitalized treatment with probabilitiesμ and σ_2; vaccinated subjects are assumed to have no risk of intensive care and just recover at a given rate σ_1 (28).

In this study, the effective reproduction number that characterizes the mean number of secondary cases infected by a single infectious individual is calculated as $R_t = \rho(G)$, where ρ is the spectral radius of the next generation matrix G. $F(x)$ and $V(x)$ are derived as follows:

$$F(x) = \begin{pmatrix} S_i * \lambda_i \\ 0 \\ SV_i * \varepsilon * \lambda_i \\ 0 \end{pmatrix} \lambda_i = \beta \times \sum_{j=1}^{6} \frac{C_{ij} \times (I_j + IV_j)}{N} \quad (2)$$

$$V(x) = \begin{pmatrix} E_i * \gamma \\ -E_i * \gamma + I_i * \frac{\delta}{N} + I_i * \sigma_2 \\ EV_i * \theta \\ -EV_i * \theta + IV_i * \sigma_1 \end{pmatrix} \quad (3)$$

Hence, one can obtain the next generation matrix G as:$G = FV^{-1}$. **Supplementary Section 2** presents the detailed derivation of the above equation for R_t.

Vaccination Strategies

In our study, we separated the population into six age groups 0–20, 21–30, 31–40, 41–50, 51–60 and older (> 60 years) by 50% of the amount of vaccine followed by a priority strategy of distributing vaccination proportionally to the population of other age groups under vary case. We referred to the strategies for prioritizing vaccinations for the 0–20, 21–30, 31–40, 41–50, 51–60, and 60+ years age groups as "0–20 first" and "21–30 first." "31–40 first," "41–50 first," "51–60 first," and "60+ first," respectively. We simulated vaccine strategies under different vaccine supply plans, testing volumes, dose availability, infection rate, and other control measures (i.e., no control measures, moderate control measures, and strong control measures. In the absence of controls, the four positions are equally weighted. Under the strong control measures, the weights of the "at home," "at work," "at school," and "other"

TABLE 1 | Descriptions of parameters.

Variables	Description	Initial value	Resource
S_i	Susceptible population of age group *i*	22,563,300; 10,695,600; 8,949,400; 5,054,400; 4,861,900; 4,594,700	(21)
$V1_i$	Vaccinated first dose population of age group *i*	10,000; 90,000; 80,000; 80,000; 30,000; 10,000	Assumed
$V2_i$	Vaccinated second dose population of age group *i*	20,000; 600,000; 340,000; 270,000; 120,000; 80,000	(22)
$p1_i$	Proportion of vaccinated first dose of age group *i*	-	Estimated
$p2_i$	Proportion of vaccinated second dose of age group *i*	-	Estimated
M_1	Vaccinated first dose population daily	-	Estimated
M_2	Vaccinated second dose population daily	-	Estimated
N	The total contact possible population	59,300,000	(22)
Parameters	**Description**	**Value**	**Resource**
C_{ij}	Number of contacts made by a person in age group *j* with people in age group *i*	Appendix	(23)
β	Probability of infected individuals transmission per contact	0.1	(24)
$1/\gamma$	Latent period without vaccination	5	(25)
μ	Recovery rate	0.25	(25)
δ	Nucleic acid test done per day	100,000	(20)
$1/\sigma_1$	Self-recovery period after vaccination	21	(10)
$1/\sigma_2$	Self-recovery period without vaccination	21	Assumed
η_1	Probability of daily immune escape in individuals vaccinated first dose	0.129	(26)
η_2	Probability of daily immune escape in individuals vaccinated second dose	0.093	(26)
ε	Reduced susceptibility	0.8	(27)
$1/\theta$	Latent period after vaccination	5	Assumed
d_i	Case fatality rate	0.00002; 0.000339; 0.000339; 0.000339; 0.00252; 0.00644	(25)

In each cell for the fitted S_i, E_i, I_i, d_i and so on, the values from left to right are for the age groups of 0–20, 21–30, 31–40, 41–50, 51–60, and 60+, respectively.

matrices are 0.5, 1.2, 0, and 0.8, respectively, estimated from Google's mobile data during the lockdown (1 November 2021–31 January 2022). The weights under the moderate control measure are simulated by the average between the no control and strong control measure weights. Meanwhile, the effective reproduction number, cumulative infections, and deaths are the main indicators of infectious disease severity and public health problems, and can thus use to assess the effectiveness of different vaccination strategies.

RESULTS

First, since only about 1% of South Africans are currently vaccinated for the third dose, we considered two overall vaccination effects with all for the first dose (partial vaccination) and all for the second doses (full vaccination) for the sensitivity analysis and compared the influence vaccination priority strategies exerted on the estimated number of confirmed cases and cumulative confirmed deaths under different control measures and vaccine supply plans, as shown in **Figure 2**.

With the strengthening of control measures, the peak number of daily infections is reduced, and the outbreak time is relatively delayed. Our research showed that the outbreak of Omicron is basically under control in about 200 days, which is in line with Nicole Wolter's research published in the Lancet (29). Moreover, the "0–20 first" strategy turned out to be the most effective in terms of any vaccine supply plans and control measures to reduce infections. In addition, "21–30 first" and "31–40 first" strategies have also had a positive effect. In particular, the reduction rate difference is minimal under no control measures. Partial vaccination that confers sterilizing immunity appears to minimize the extent of infection waves compared with full vaccination. Meanwhile, the most effective strategy to reduce cumulative confirmed deaths was the "60+ first" strategy under strong control measures and partial vaccination. The "51–60 first" strategy also produced relatively benefits although not optimal, and other strategies resulted in relatively similar reductions in deaths. As the control measures tightened under the partial vaccination, the effect of reducing the number of deaths became more pronounced. Obviously, under the same control measures, partial vaccination was more effective in reducing cumulative confirmed deaths than full vaccination. In the context of a vaccine shortage in South Africa, partial vaccination resulted in lower numbers of infections and deaths under different control measures compared with full vaccination. All measures led to a reduction in deaths and infections, but the "60+ first" strategy exerted obvious benefits compared with other measures. Meanwhile, reduction in infections is substantially effective with the strategy "0–20 first."

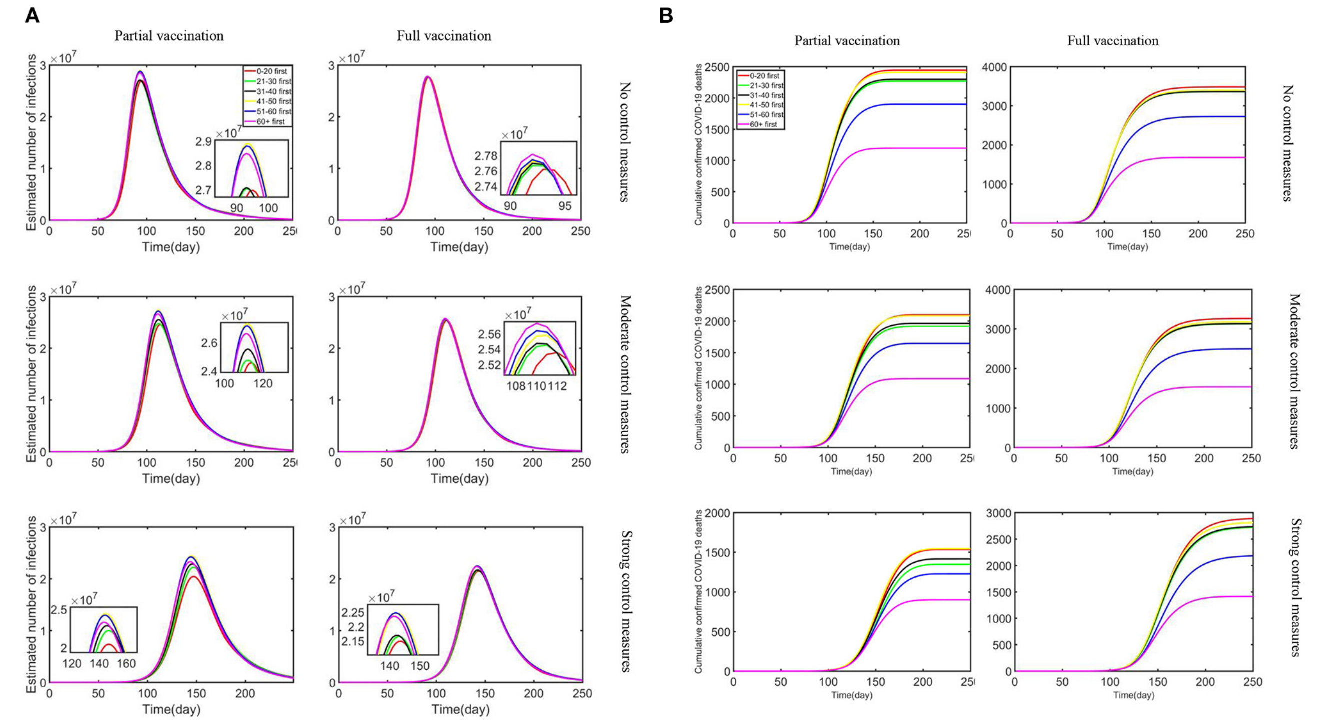

FIGURE 2 | The combined impact of different vaccine supply plans and control measures on reductions in the estimated number of infections and cumulative confirmed deaths: **(A)** estimated number of infections; **(B)** cumulative confirmed COVID-19 deaths.

Second, we investigated the effect of doses available each day on reducing the estimated number of infections and cumulative confirmed deaths under the combined effect of varying daily testing volume and infection rate. To research the fastest way to control the epidemic, we just studied the scenario with strong control measures and partial vaccination, which resulted in the maximum reduction in infections and deaths.

As shown in **Figure 3**, as doses available each day increased, the estimated number of infections and cumulative deaths decreased regardless of daily testing volume or infection rate. When the infection rate was relatively lower, prioritizing vaccine allocation among the 0–20 age group consistently resulted in the greatest reduction in infections, but with a higher infection rate, the "21–30 first" strategy was the best. When doses available each day were relatively limited, the difference in reduction rate of the six strategies was minimal. However, when doses available each day were increased, the "0–20 first" and "21–30 first" strategies accompanied by apparent differences compared with other age groups. On the other hand, under varying doses availability, testing volume, and infection rate, all vaccination strategies produced a significant reduction in death. Under lower infection rate, when doses available each day were relatively limited, the "60+ first" strategy was the most effective strategy in reducing cumulative confirmed deaths, but as supply increased, "51–60 first" was the best strategy. While under a higher infection rate, the "60+ first" strategy resulted in a relatively more obvious effect than the other strategies. We also observed that the number of confirmed deaths in the lack of daily testing volume is less than that in the plenty of testing volume, while as the amount of testing increased, the number of deaths increased on the contrary.

Third, considering "0–20 first" and "60+ first" were the most effective strategies to reduce infections and deaths under strong control measures. We studied the impact of the varying proportion of vaccination priority under varying strategies to minimize the cumulative morbidities and mortalities. After the target age group has been vaccinated the assumed vaccine proportion, vaccines are distributed to the remaining groups proportionally to the size of the remaining age groups. We used different priority vaccination rates in the simulations and assumed a fixed daily dose was available.

We assumed that, among different vaccination priority ratios, vaccines are initially vaccinated to the target age group by x% of the vaccine quantity, and then to other age groups in proportion to their population, where x ranged from 0 to 100%. Simulations were performed using a daily testing volume of sixty thousand under strong control (i.e., the infection rate is 0.1) with partial vaccination. From **Figure 4**, under the "0–20 first" strategy, as a proportion of priority vaccinations increased, the number of confirmed deaths increased by a certain margin because of the epidemic spread, but the number of confirmed cases decreased, and always had a favorable effect on reducing infections. As presented in the **Supplemental Section 3**, under the "21–30 first" and "31–40 first" strategies, increasing the proportion of priority vaccinations has a similar effect, but the "0–20 first"

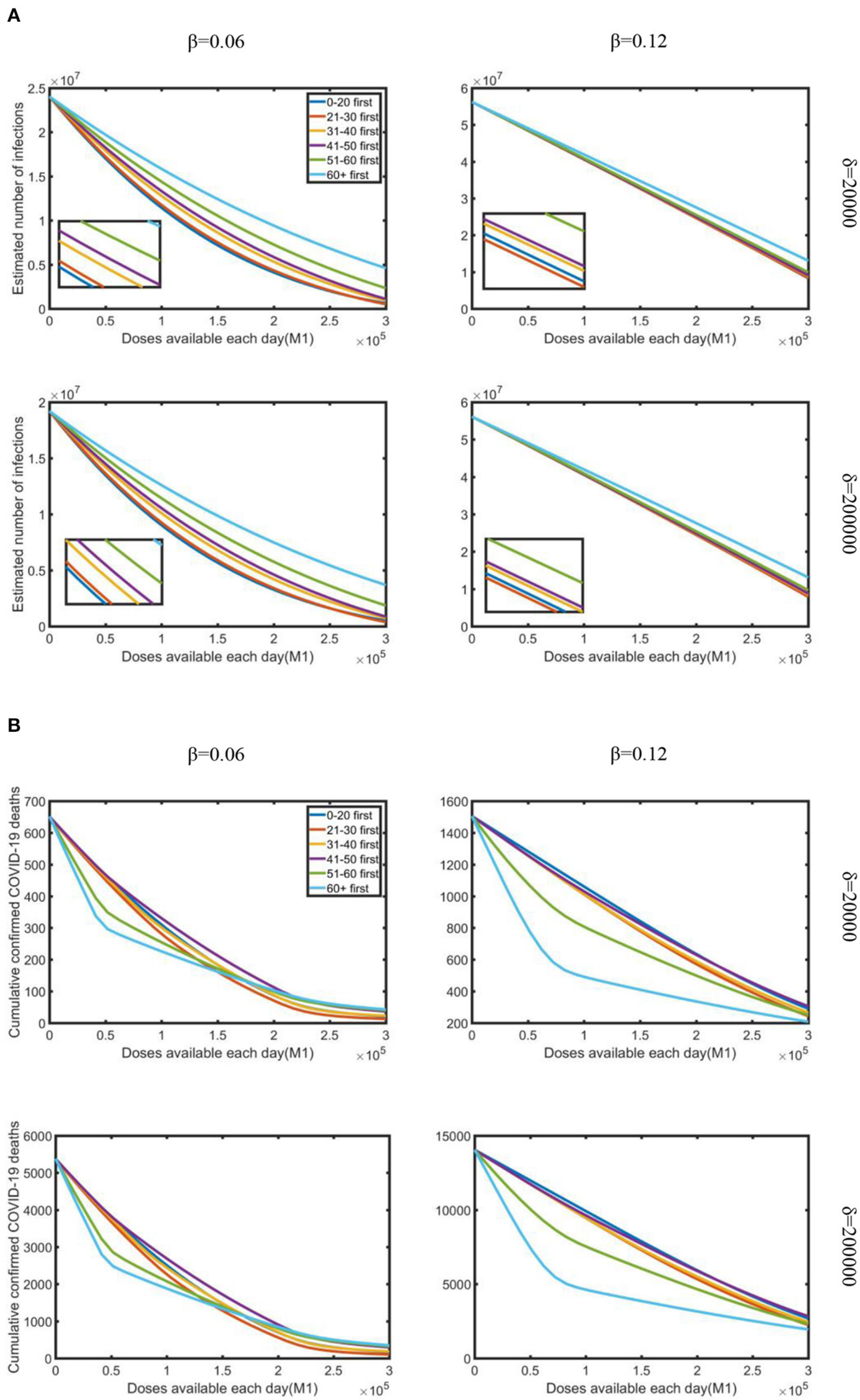

FIGURE 3 | Under strong control measures, the impact of doses available each day on the reduction in the estimated number of infections and cumulative deaths occurred for various daily testing volumes (δ) and infection rate (β): **(A)** estimated a number of infections; **(B)** cumulative confirmed COVID-19 deaths. Testing volume is 20,000 and 200,000, which represent the minimum and maximum testing volume in South Africa during the research period.

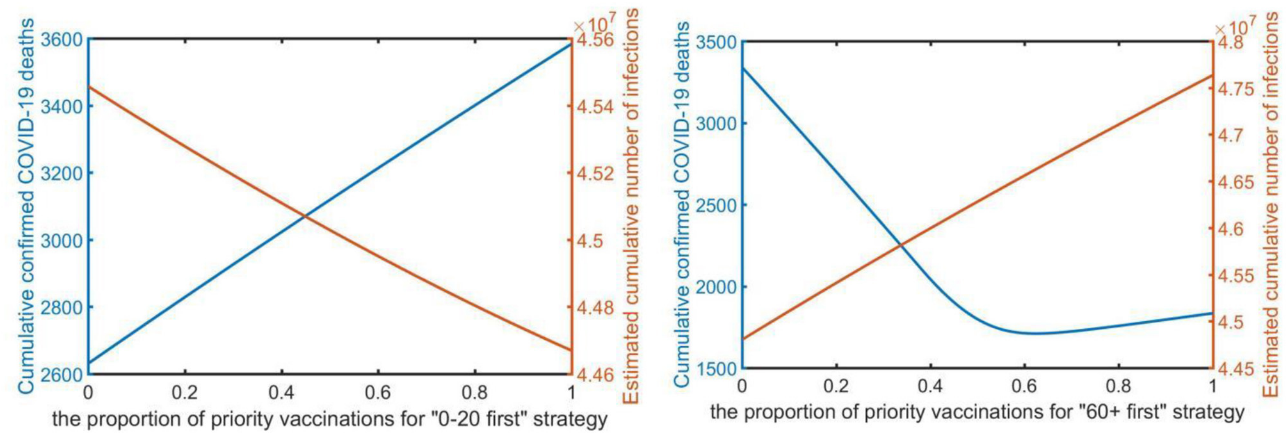

FIGURE 4 | The proportion of the vaccination priority under the "0–20 first" strategy and "60+ first" strategy (*x*-axis) to minimize the total number of infections and deaths (*y*-axis).

strategy has a more pronounced effect. However, under the "60+ first" strategy, as a proportion of priority vaccinations increased, the number of confirmed infections increased, which resulted in a noticeable impact on the decline in the number of confirmed deaths. In particular, when the proportion of priority vaccinations reached 60%, the "60+ first" strategy led to the greatest reduction in deaths. However, after reaching the 60% proportion in the vaccination priority strategy, the number of cumulative confirmed deaths slightly increased. **Figure 4** illustrates that prioritizing vaccine allocation among the 60+ age group with 60% of the total amount of vaccine consistently resulted in the greatest reduction in deaths. Overall reduction in infections is strongly limited by the vaccine proportion of the target age group, with 60% vaccine proportion leading to the most reduced mortality rate.

Lastly, we conducted a sensitivity analysis concerning the effect of each priority strategy on the effective reproduction number (R_t).

Figure 5 illustrates that all vaccination strategies were the best strategies to reduce the effective reproduction number, although all strategies resulted in similar reductions. However, in the early stage of Omicron, prioritizing vaccine allocation for the 0–20 age group resulted in the greatest reduction in effective reproduction number compared with other strategies; but in the later stage, more vaccines should be allocated to other age groups, such as the 60+ age group and the 51–60 age group. Our research showed that the effective reproduction number (R_t) was reduced to 1 at ∼150 days, which means that the epidemic would be controlled. Thus, we suggest that the government should prioritize vaccine allocation for the 0–20 age group, and then guarantee the vaccination of other age groups, to control the epidemic as soon as possible.

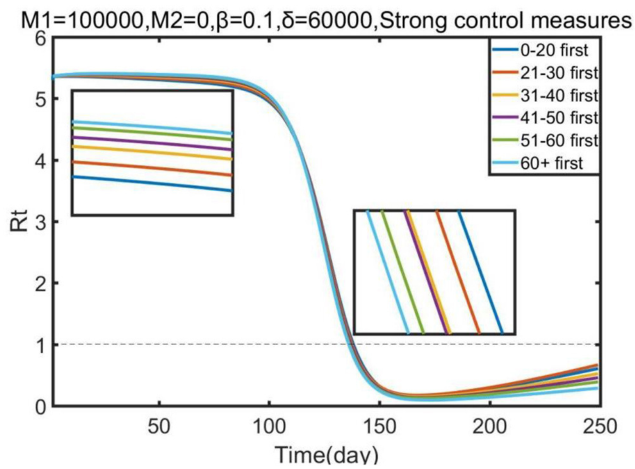

FIGURE 5 | Effect of each priority vaccination strategy on the reduction in the effective reproduction number (R_t).

DISCUSSIONS

Study on Omicron shows that it is high infectivity and has a greater ability to evade immunity than Delta (30). Moreover, Omicron appears to cause less severe infections and a higher chance of reinfection compared to previous variants (31). The reduction in hospital admissions and severity may be caused by previous high levels of infection, improved vaccination coverage and reduced pathogenicity or virulence of Omicron variant (32). Despite these, vaccination is still an important measure in protecting the population. This research lead to the adoption of an age-stratified modeling method to assess and compare vaccine prioritization strategies for COVID-19. The total population is separated into six age groups and the impact of prioritizing vaccination for target age groups on reducing the number of confirmed cases and deaths were compared under various potential vaccine characteristics and hypothetical scenarios, such as the control measures, vaccine availability, testing rate, and rollout speed of vaccine. It is worth noting that the choice of age group width will affect our results. Based on the assumption that the age distribution of morbidity and mortality are smooth, we divided South Africa's population into 10-year age groups. If ages were grouped too widely, it might hide actual age-specific case-fatality, social contacts and contact patterns differences (33).

Our results indicated that in light of South Africa's demographics, vaccinating older age groups (>60 years) largely reduced the cumulative deaths in all scenarios considered, and was in line with prior work also (13, 34). By contrast, prioritizing 0–20 age group who usually possess a higher contact rate exerts a greater effect on reducing morbidities relative to prioritizing older age groups. Furthermore, compared to the third wave, the data from Daily Hospital Surveillance (DATCOV) report showed a higher proportion of hospital admissions for patients under 20 in the early fourth wave (35). This is likely attributable to the fact that in the previous waves of the epidemic, the vaccination was mainly aimed at adults, and the distribution of vaccines to the adolescents was not advocated, which was mainly due to the lack of sufficient clinical data. Therefore, we recommend that the vaccine allocation strategy for the 0–20 age group should be refined based on actual clinical manifestations and characteristics. Some studies have advocated that the distribution of vaccines among young people should vaccinate 16-17 age group first, followed by 12–15 age group, and so on. However, there is no definite vaccination schedule with fixed age groups for young people (36). Our study didn't make too much subdivision discussion considering that adopting more complex division may incur unidentifiable issues caused by inadequate data in many involved compartments (37). Moreover, it is uncertain as to how susceptibility to children's infection changes with age (6).

Our analyses indicated that the combined effect of control measures and vaccine supply plan was the most effective way to reduce cumulative confirmed cases. We found that one dose of vaccine is more effective in minimizing severe COVID-19, which does not represent that the effect of vaccination of one dose is better than two-dose, while for the country with limited vaccine supply and low vaccination coverage, ensuring the first dose of vaccine supply will have a significant impact on severe disease. Correspondingly, in developed or developing countries where vaccine supply is unlimited, two-dose vaccines or even booster shots are significant to reduce disease (18).

We observed that, given the daily testing volume and infection rate, our model identified a few scenarios wherein prioritizing younger adults aged 0–20 and 60+ years would provide greater morbidity and mortality benefits, respectively. These scenarios were restricted to the conditions of inadequate vaccine supply and lower infection rates. We also found that the number of confirmed deaths in the lack of daily testing volume is less than that in the plenty of testing volume, while as the amount of testing increased, the number of deaths increased on the contrary. This could be explained by the fact that increasing the number of daily tests could identify more infected people, conversely, relatively inadequate testing rates will lead to more undetected infections among the susceptible, which may mislead our control measures of COVID-19. Thus, the symptomatic and asymptomatic patients must be tested to identify infectious individuals, and take clinical treatment to prevent the onward infection of others, which results in reducing the number of infected and deaths.

Besides, modeling for COVID-19 vaccination has discovered that the optimal balance between vaccine allocation and a total number of deaths depends on the proportion of priority vaccination, recommending the vaccination of the 60+ age group for 60% vaccine proportion. However, this recommendation is sensitive to the proportion of priority vaccination because, when the proportion of priority vaccination exceeds 60%, the effect shifts toward the opposite. These results can be illustrated by the features of the population ratio. If we continue to increase the proportion of priority vaccination to 60+ age group, it will reduce the proportion of other people who have the higher population ratio and higher contact rate, resulting in the increasing mortality in other age group. We also observed that the increase in the proportion of vaccines given priority to 0–20 groups always had a favorable effect on reducing infections. We then examined the effects of each priority strategy on the reduction of the effective reproduction number (R_t). We observed that significant distinction among COVID-19 vaccine allocation policies for relative reductions in R_t. The results suggest that the public health authorities should give priority to supplying the 0–20 age group, and then allocating vaccines for remaining age groups. The speed of COVID-19 vaccination is pivotal to rapid epidemic containment, however, vaccine hesitancy is a major barrier to speed up inoculation and improve vaccination coverage (38, 39). Therefore, the government needs to provide sustained health education and communication to strengthen individual vaccine willingness (40, 41).

Furthermore, our model can be modified to quantify and evaluate the effect of COVID-19 vaccine prioritization policies on cumulative incidence and mortality, facing the changes of the epidemic and s multitude of sequential waves in the case of COVID-19. Our study relies on actual epidemiological data and estimation of the related parameters (such as, infection force for each age group) and depends on pandemic contact patterns to the extent individuals interact with each other. Thus, within this framework, the model can incorporate epidemiological data in target areas and estimates of age-stratified contact rates to model future pandemic scenarios (42), and optimize the process for the evaluation of vaccine prioritization strategies against COVID-19. In particular, virus mutations characterized by increased contagiosity and relative capacity for immunological escape may trigger the decrease in vaccine effectiveness. The proposed model could provide an evidence-based rationale for prioritizing first-dose coverage and vaccination priorities based on the varying contributions of the vaccine effects. For example, in countries where vaccine coverage is constrained by supply, high first-dose coverage is important to minimize severe disease. Meanwhile, in high-income and high-middle-income countries, attention has turned to breakthrough infections and waning immunity (43).

Besides, our framework can be adapted to consider more possible goals of vaccination, such as minimizing hospitalizations, comorbidities, or economic costs (44) based on the development of future pandemic scenarios. Our studies could help evaluate control measures' performance and improve vaccine allocation strategy for COVID-19 epidemic.

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

CZ and YL proposed a framework and implemented the simulation experiments. ZM, FZ, and YZ contributed to model building, data analysis, and writing the article. All authors contributed to the article and approved the submitted version.

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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.2022.876551/full#supplementary-material

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Knowledge, Attitude, Practices, and Sources of Information (KAPS) Toward COVID-19 During the Second Wave Pandemic Among University Population in Qatar: A Cross-Sectional Study

Ibrahim Alkaabi[1], *Magdy Abita*[2], *Yousif Mahdi*[3], *Amr Ouda*[4] and *Mohammed Imad Malki*[4]*

[1] College of Arts and Sciences, Deanship of General Studies, Qatar University, Doha, Qatar, [2] Social Work Program, Department of Social Science, College of Arts and Sciences, Qatar University, Doha, Qatar, [3] Psycology Program, Department of Social Science, College of Arts and Sciences, Qatar University, Doha, Qatar, [4] College of Medicine, QU Health, Qatar University, Doha, Qatar

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***Correspondence:**
Mohammed Imad Malki
momalki@qu.edu.qa

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Background: The World Health Organization (WHO) declared COVID-19 as a pandemic on 11 March 2020. Many efforts were performed to contain the virus worldwide. People's knowledge and attitude should be directed toward strict preventive practices to halt the spread of the virus. We aimed to assess the knowledge, attitude, practices, and sources of information (KAPS) used by Qatar University (QU) attendees.

Methods: A cross-sectional web-based questionnaire was answered by 500 employees and students in the QU community. It included questions on KAPS toward COVID-19. Information on sociodemographics was collected and analyzed. This study was conducted during the second wave of COVID-18 in the state of Qatar (April–May 2021).

Results: A total of 475 participants aged between 18 and 68 years old consented to complete the survey questionnaire. The study involved 279 (58.7%) non-Qatari nationals and 196 (41.3%) natives, with 254 (53.5%) participants pursuing postgraduate studies and 221 (46.5%) undergraduates. Approximately two-thirds of the sample were employed (64.8%), while one-third were unemployed (35.2%). Knowledge scores on average were 66.4% ($M = 5.31$, $SD = 1.45$, and range: 0–8), with only significant differences were noted between nationalities (natives and non-natives) Participants' average score in practices was 69.72% ($M = 4.18$, $SD = 1.7$, and range 0–6) with a significant difference in safe COVID-19 practice scores based on the educational level. Adherence with COVID-19 policies and rules were 82% ($M = 2.46$, $SD = 0.7$, and range: 0–3) with no differences noted between groups. In addition, the population reported relying on governmental press conferences (76.0%) as their primary source of gaining details concerning COVID-19, followed by social media (64.4%). The least popular resources were information gained from family, relatives, friends, and coworkers (47.4%) and the news channels on TV (46.7%).

Conclusion: Overall, this study provides insights into Qatar's KAPS toward COVID-19 during the quarantine of the second wave of this pandemic. This study, being the first of its kind to be conducted in the state of Qatar, is expected to help the ministry of public health and the government communication office to establish a suitable measurement of response to the spread of COVID-19 and develop the best practices for any future epidemics that might occur.

Keywords: COVID-19, knowledge, attitude, practice, sources, Qatar

INTRODUCTION

The coronavirus (CoV) is a large single-stranded RNA virus known to cause many human and animal diseases (1). Many well-known disease epidemics, especially in the Middle East region, have been attributed to CoV (2). These include Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) (2). In December 2019, multiple cases of pneumonia were recognized in Wuhan, China (3). The pathogen responsible for causing these clinical conditions was later identified as a novel member of the coronavirus family that was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3). As the disease has since spread rapidly in China and globally, the World Health Organization (WHO) designated the disease as a pandemic in March 2020 (4). By the end of 2020, coronavirus disease 2019 (COVID-19) has infected ∼85 million people and led to more than 1.8 million deaths (5). The disease causes various symptoms, ranging from mild, unnoticeable symptoms to hospitalizing critical symptoms (6). Furthermore, a systematic review of population-based studies and cross-sectional surveys estimated that one-third of patients with COVID-19 are asymptomatic (7). This huge number of asymptomatic patients poses an additional challenge in controlling the spread of the disease, as it is believed that asymptomatic patients can transmit the disease as well (8).

Various safety measures were implemented internationally to fight against COVID-19. The goal of these measures was mainly to decrease the transmission of the disease and avoid overloading the healthcare system of countries (9). The severity of these actions ranged widely from non-mandatory social distancing recommendations to complete lockdowns with variable degrees of success (10). The state of Qatar has implemented multiple policies as soon as the first COVID-19 case was discovered in late February 2020 (11). These measures included travel restrictions, closure of restaurants, cafes, and public areas, and suspension of face-to-face education in schools and universities (11). Qatar then invested a lot in raising public awareness through educating the community about public preventive measures (12). These awareness campaigns were heavily spread through physical advertising banners and social media as well (13).

However, a clear understanding of the level of public awareness after such campaigns is crucial for policymakers in their fight against the upcoming waves of the COVID-19 pandemic (14). This study evaluates the awareness of the multi-cultural population residing in Qatar through a survey assessing the knowledge, attitude, practice, and sources of information (KAPS) toward COVID-19. Our study aims to assess the KAPS of the Qatari population toward COVID-19 and explore its relation to many factors, such as the demographics of the population. Unlike the commonly accepted KAP studies that have been published recently in different countries, the research team decided to include a "source of information" section in the survey. The aim of this was to assess where the public's awareness of the pandemic stems from in the country.

MATERIALS AND METHODS

A cross-sectional web-based questionnaire was developed to support the social work and psychology programs that are part of the department of social sciences and medical specialists in the College of Medicine to measure the KAPS.

The questionnaire made was distributed through the university's official email portal to faculty, students, and staff between April and May 2021. It was compromised of true/false, yes/no/sometimes, and checkbox types of questions. Every participant had the right to withdraw from the study even after completing it. Qatar University (QU)'s strict participant confidentiality policy was upheld throughout this research.

Participants

All included participants were older than 18 years and had to be enrolled in the QU either as students, staff, or faculty. The English language was necessary to answer the survey. Finally, a decision to only include residents in Qatar since at least February 2020 was taken by the research team to avoid information bias by new residents of the country.

The inclusion criteria were as follows:

- being older than 18 years of age
- currently a student, staff, or faculty at the QU
- capable of reading English
- has been in Qatar since at least February 2020.

The study's exclusion criteria were only:

- Full consent is not provided by the subject
- The subject does not fully complete all the questions.

The Survey

The developed survey was inspired by multiple similar COVID-19 questionnaires and input from behavioral scientists from the QU (as shown in **Supplementary Material**). The survey took approximately 8 min to be completed and was only sent in English. It was separated into five main components, each assessing a different aspect of the research. The first part was answered by checking a box that collected general demographic data about the participants, such as gender, age, nationality (Qatari or non-Qatari), an education level (undergraduate or postgraduate), and employment status. The second part, compromised of eight questions, assessed participants' knowledge through true and false statements regarding COVID-19. Statements started as general knowledge and got more specific each time.

Parts three, four, and five were all developed using the same yes/no/sometimes format, with each part targeting a different component of our research question. Part three focused on the practices of the public. Questions included the usage of hand sanitizer, washing hands with soap for 20 s, wearing facemasks in public, avoiding gatherings altogether, appropriate social distance, and attending social events or gatherings regardless of indoors or outdoors. Part four assessed the attitude of the population toward the COVID-19 laws introduced by the government of Qatar, which included questions, such as whether the national case tracking app (Ehteraz) was used, whether the participants reported suspicious symptoms of themselves, colleagues, friends, and family members to the government. Furthermore, whether QU's internal laws regarding COVID-19 were followed. Finally, and unlike a lot of other surveys on the matter of assessing the KAP only, the research team decided to include the sources of information most used by the public. The question asked participants to indicate with a yes/no or sometimes whether they use the following outlets as sources of information. The outlets included were news channels, direct governmental press conferences, social media or family, friends, relatives, and coworkers.

After the investigators developed the questionnaire, face-validity was confirmed by four public experts at the QU. They assessed and validated the instrument, providing several suggested modifications to improve the content and clarity of the questionnaire. Then, to measure the internal consistency (reliability coefficient) of the questionnaire and to detect any flaws with the survey, the link for the questionnaire was piloted on nine subjects. A Cronbach's alpha score of $\alpha = 0.715$ was found, which is a satisfactory internal validity score according to Bland and Altman (15).

Statistical Analysis

An independent sample t-test, one-way analysis of variance (ANOVA) test of significance, and multiple linear regression were used to examine the relation between the demographic characteristics and variables. A Pearson correlation analysis was used to compare correlations between variables. All statistical analyses were performed using IBM SPSS 28.

RESULTS

Demographics

Out of 491 participants who took part in this investigation, 475 participants consented to complete the survey questionnaire. Among the final sample, 308 (64.8%) were women, and 167 (35.2%) were men, aged between 18 and 68 years old. The study involved 279 (58.7%) non-Qatari nationals, and 196 (41.3%) natives. Further, 254 (53.5%) participants pursued postgraduate studies, and 221 (46.5%) were undergraduates. Approximately two-thirds of the sample were employed (64.8%), while one-third were unemployed (35.2%). Demographic characteristics are shown in **Table 1**.

TABLE 1 | Demographic characteristics of the subjects included in this investigation.

Characteristics		Numbers of participants (%)	
		N	**%**
Gender	Male	167	35.2%
	Female	308	64.8%
Age	18–29	215	45.3%
	30–49	188	39.6%
	50+	72	15.2%
Nationality	Qatari	196	41.3%
	Non-Qatari	279	58.7%
Education	Undergraduate	221	46.5%
	Postgraduate	254	53.5%
Occupation	Employed	308	64.8%
	Unemployed	167	35.2%
Total	–	475	100%

COVID-19 Knowledge

Regarding the participant's background knowledge of COVID-19 based on true or false questions, the subjects demonstrated a proficient level of understanding. The subjects scored on average 66.4% ($M = 5.31$, $SD = 1.45$, and range: 0–8). Based on independent sample T-tests (for gender, nationality, education, and occupation), and an ANOVA (for age), there was a significant difference in scores for nationality ($p \leq 0.01$), with findings suggesting that non-Qatari residents scored higher ($M = 5.61$, $SD = 1.0$) than Qatari nationals ($M = 5.31$, $SD = 1.2$) (as shown in **Table 2**). The correct answer rate across all the eight COVID-19 knowledge questions ranged between 18.3 and 96.2%. The most accurate and correctly answered question was "People who are older or have certain underlying medical conditions are at higher risk of getting more seriously ill from COVID-19" (97.9%). The least correctly answered question was "Supportive care is the current treatment for COVID-19" (15.4%) (as shown in **Table 2**).

Practice

Regarding the practice of COVID-19, most of the subjects indicated that they follow guidelines in keeping with safe COVID-19 practices across all six questions. As shown in **Table 3**, the participant's average score confirming full compliance with recommended COVID-19 practices was 69.72% ($M = 4.18$, $SD = 1.7$, and range 0–6). When stratifying the sample based on demographic characteristics, there was a significant difference in safe COVID-19 practice scores based on educational level ($p \leq 0.05$); with findings suggesting that undergraduates score

TABLE 2 | Coronavirus disease 2019 knowledge scores by demographic variables.

Characteristics		COVID-19 Knowledge Scores (mean ± standard deviation)	*p*-value
Gender	Male	5.56 ±0.9	$p > 0.05$
	Female	5.44 ±1.1	
Age	18–29	5.52 ±1.1	$p > 0.05$
	30–49	5.38 ±1.1	
	50+	5.67 ±0.9	
Nationality	Qatari	5.31 ±1.2	$p \leq 0.01$
	Non-Qatari	5.61 ±1.0	
Education	Undergraduate	5.41 ±1.2	$p > 0.05$
	Postgraduate	5.56 ±1.0	
Occupation	Employed	5.49 ±1.1	$p > 0.05$
	Unemployed	5.49 ±1.1	
Total	–	5.31 ±1.45	–

TABLE 3 | Coronavirus disease 2019 safe practice scores by demographic variables.

Characteristics		COVID-19 practice scores (mean ± standard deviation)	*p*-value
Gender	Male	4.16 ±1.8	$p > 0.05$
	Female	4.22 ±1.7	
Age	18–29	4.16 ±1.7	$p > 0.05$
	30–49	4.26 ±1.7	
	50+	4.19 ±1.8	
Nationality	Qatari	4.26 ±1.6	$p > 0.05$
	Non-Qatari	4.16 ±1.0	
Education	Undergraduate	4.38 ±1.6	$p \leq 0.05$
	Postgraduate	4.05 ±1.7	
Occupation	Employed	4.28 ±1.7	$p > 0.05$
	Unemployed	4.06 ±1.8	
Total	–	4.18 ±1.7	–

higher ($M = 4.38$ and $SD = 1.6$) than postgraduates ($M = 4.05$ and $SD = 1.7$). Responses kept in line with safe COVID-19 practices ranged between 67.5 and 73%. The most practiced COVID-19 factor was wearing a facemask in public places (90.5%). The least practiced indicator was attending large social gatherings indoors and outdoors (59.2%). Finally, the results revealed that participants mostly replied 'Sometimes' toward social distance by at least 1.5 m (27.5%) (as shown in **Table 3**).

Attitude

As illustrated in **Table 4**, the results showed a favorable attitude toward the laws regarding COVID-19 conduct in Qatar and within QU. Findings suggest that subjects' average score confirming full adherence with COVID-19 policies and rules was 82% ($M = 2.46$, $SD = 0.7$, and range: 0–3). When statistically compared using the T-test (for gender, nationality, education, and occupation) and ANOVA (for age), there was no significant difference in the attitude score. All COVID-19 laws in the questionnaire were abided similarly among all groups. Across the different groups included in this study, responses in full adherence to COVID-19 laws ("*Yes,*" response) ranged between 80.3 and 83.7%. The most practiced law by the participants was using the Ehteraz track and trace application (95.6%), while the least practiced law was reporting symptoms of COVID-19 for themselves, family members, friends, or colleagues (26.5%). More details are shown in **Table 4**.

TABLE 4 | Attitude toward COVID-19 laws and rules in Qatar by demographic variables.

Characteristics		COVID-19 attitude toward laws scores (mean ± standard deviation)	*p*-value
Gender	Male	2.46 ±0.8	$p > 0.05$
	Female	2.45 ±0.7	
Age	18–29	2.47 ±0.8	$p > 0.05$
	30–49	2.44 ±0.8	
	50+	2.47 ±0.8	
Nationality	Qatari	2.50 ±0.7	$p > 0.05$
	Non-Qatari	2.43 ±0.8	
Education	Undergraduate	2.51 ±0.7	$p > 0.05$
	Postgraduate	2.41 ±0.8	
Occupation	Employed	2.47 ±0.8	$p > 0.05$
	Unemployed	2.43 ±0.8	
Total	–	2.46 ±0.7	–

Source of Information

With regards to the most adopted means of getting information for COVID-19, data showed that the population in Qatar uses government press conferences (76.0%) as their primary source of gaining details concerning COVID-19, followed by social media (64.4%). The least popular resources were information gained from family, relatives, friends, and coworkers (47.4%) and the news channels on TV (46.7%) (as shown in **Supplementary Material** and **Table 2**).

Regression Analysis

Findings from the multiple linear regression analysis models of the key indicators of this investigation (gender, age, nationality, education level, and occupational status) are demonstrated in **Table 5**. The results showed that knowledge scores as predicted by nationality were significantly affected [$F_{(5,469)} = 2.343$, $p < 0.05$, and $R^2 = 0.014$]. This suggests that nationality explains and predicts a significant amount of the variance in knowledge toward COVID-19, with non-Qatari residents scoring higher than their Qatari counterparts (β: 0.308, and $p < 0.01$). Multiple regression was also carried out to investigate whether the demographic factors significantly predicted COVID-19 safety practice scores. The results of the regression indicated that the model was significant, as predicted by the education level and occupation status [$F_{(5,469)} = 3.769$, $p < 0.01$, and $R^2 = 0.028$]. Regarding educational level, postgraduates scored lower than their undergraduate counterparts (β: −0.896 and $p < 0.01$). In

TABLE 5 | Results of significant multiple linear regression on factors associated with COVID-19 knowledge and practices.

Variable	Coefficient (β)	Standard error	F	*p*	95.0% Confidence Interval	
					Lower bound	Upper bound
Knowledge			2.343	$p < 0.05$		
Nationality (non-Qatari)	0.308	0.115			0.082	0.535
Practice			3.769	$p < 0.01$		
Educational level (Postgraduate)	−0.896	0.230			−1.347	−0.445
Occupational status (Unemployed)	−0.717	0.238			−1.185	−0.249

addition, unemployed subjects scored lower than those who were employed (β: −0.717 and $p < 0.01$). Finally, a multiple linear regression was calculated for total attitude toward COVID-19 law scores as predicted by key participant features, which showed that the model was not significant [$F_{(5, 469)} = 1.462$, $p > 0.05$, and $R^2 = 0.005$].

DISCUSSION

This study is the first in Qatar during the COVID-19 pandemic that examines the KAPS among the general population. Similar articles examining KAP can be found in many countries, such as Syria, Bosnia and Herzegovina, and China (16–18). The research team decided to include the sources of information as well, considering its importance in the decision-making process.

Interestingly, the population of Qatar demonstrated a proficient level of understanding regardless of all factors (gender, age, education, nationality, and employment status), with a mean knowledge score of 5.31. Regardless, the only significant difference in knowledge scores was in nationality, as non-Qataris demonstrated a higher mean knowledge score than their Qatari counterpart. A possible explanation for this result could be that non-Qataris likely experienced previous pandemics, such as H1N1, SARS, or MERS in their native countries before. Qataris, on the other hand, have not been exposed much to such pandemics before as the country was never globalized like today ever before.

The knowledge score metric was overall very comparable among groups and relatively high with a mean score of 5.31 out of 8, which proves the success of Qatar's strategy of relaying information to the public as it was accessible to all people regardless of their age and education level, occupation status, and gender. Attitude toward the law across the population was similar regardless of gender, age, nationality, education, and occupation status. With a mean score of 2.46 out of 3, the population managed to impress with its adherence to laws. It is important to note that the severe penalties enacted by the government against COVID-19 lawbreakers might have introduced some bias to this study. While all participants were assured of complete anonymity, we cannot discredit the possibility of bias affecting the results, especially in the attitude toward laws section. This might explain why more than 92% of participants answered that they follow instructions issued by QU while only 90.5% reported wearing a face mask in public which is considered the main instruction provided by QU health. Regarding the practice toward COVID-19, most of the subjects indicated that they follow guidelines in keeping with safe COVID-19 practices, across all six questions. With a mean score of 2.46 out of 3, the population demonstrated a very mature approach toward COVID-19, with the only significant difference being among the education group, whereas postgraduates were less likely to follow the rules compared with undergraduates. It must be noted that Qatar's approach to face masks was probably why it was the most practiced indicator. Qatar's strategy, which included non-tolerable fines, constant surveillance, and continuous availability of PPE, seems to have proved successful.

In fact, compared with the data reported in many countries, such as Syria, Thailand, and China, the population in Qatar has shown a considerably high knowledge score compared with the population in these counterparts (16, 17, 19). For example, in Thailand, 73.4% had poor knowledge of COVID-19 (19). This underlines the importance of the Qatar national health authorities providing relentlessly clear updates and information about the emerging virus and the need to continuously assess and monitor whether their messages are being understood within the community. Furthermore, the vast majority of the population in Qatar is in agreement that all the preventive measures taken by the government is effective against COVID-19.

Our hypothesis was that social media would be the main source of information used by the public. Surprisingly, however, approximately three-quarters of the survey fillers noted that they get information directly from governmental press conferences. This result, when compared with the rest of the world, is unique (20, 21). The Qatari government has proved to be a leader in information campaigns regarding this pandemic. Therefore, their strategy deserves a closer and deeper look, perhaps in another article.

Over the past 2 years, many countries in the world have conducted the COVID-19 KAP study, as the results provide invaluable insight into prevention control and population management. In 2004, a similar article examined the KAP of the population in relation to SARS. In line with our article, the 2004 study also found that Qataris scored significantly lower than non-Qataris. In this regard, Qataris scored 31.7% in knowledge, while non-Qataris scored 68.3% (22). The explanation cited was that the Arabic-speaking community lacks information about SARS due to the vast majority of news coverage in English (22). This article is interesting to note because Dr Abdelatif Al Khal, the second author, is the Executive Director of Hamad Medical Corporation's Division of Infectious Diseases and Chair of the National Health Strategic Group on COVID-19 and all his governmental conferences are being conducted live, interactively, and in Arabic, a strategy that might have helped the Qatari governmental conferences to displace both social media and traditional news outlets as the main sources of information in the pandemic.

Another KAP article was published in Qatar during the COVID-19 pandemic. It measured the KAP of paramedics toward Personal Perspective Equipment than the disease itself (23). As the only study in Qatar that addressed the general population and used the KAPS tool, our article is the first of its kind in Qatar during the COVID-19 pandemic.

It is important to note that our study does not represent the university's population over the whole country. While QU is the biggest and the first national university in Qatar, other universities do exist in the country, and they were not added to the study. Therefore, the research team recommends that wider scale studies are conducted in the country to truly assess the population's KAPS and reduce the survey bias by increasing the number of participants.

CONCLUSION

Overall, the population of the state of Qatar has demonstrated favorable results compared with the rest of the world and the region, especially regarding mask-wearing. These results explain how the country achieved an astonishing 0.18% death ratio from COVID-19. Only 8.14% of the total population ever contracted the virus regardless of over five million tests being made by January 2022 in the country of less than three million people (24–26). Qatar's response to the COVID-19 pandemic was excellent and deserved a closer look in a follow-up article. The results of this study might be generalizable to other regional countries in the Gulf Cooperation Council (GCC) that have experienced similar second wave of COVID-19 pandemics. This study presents a unique reference for pandemic cautious behavioral response to COVID-19 in a well-developed health system.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Qatar University Institutional Review Board (QU-IRB) Number: 1727764-1. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM conceived and supervised the study. IA, MA, and MM designed the questionnaire, obtained IRB approval, and distributed the survey. YM analyzed the data. AO and MM drafted the manuscript. All authors revised the final manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.906159/full#supplementary-material

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MINI REVIEW
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Hypertonic Solution in Severe COVID-19 Patient: A Potential Adjuvant Therapy

Matheus Gennari-Felipe[1†], Leandro Borges[1†], Alexandre Dermargos[1], Eleine Weimann[1], Rui Curi[1,2], Tania Cristina Pithon-Curi[1] and Elaine Hatanaka[1]*

[1] *Instituto de Ciências da Atividade Física e Esportes, Universidade Cruzeiro do Sul, São Paulo, Brazil,* [2] *Seção de Produção de Imunobiológicos, Centro Bioindustrial, Instituto Butantan, São Paulo, Brazil*

Coronavirus disease 2019 (COVID-19) features hyper-inflammation, cytokine storm, neutrophil function changes, and sodium chloride (NaCl) homeostasis disruption, while the treatment with NaCl hypertonic solutions (HS) controls electrolytic body homeostasis and cell functions. HS treatment is a simple, popular, economic, and feasible therapy to regulate leukocyte function with a robust anti-inflammatory effect in many inflammatory diseases. The purpose of this narrative review is to highlight the knowledge on the use of HS approaches against viral infection over the past years and to describe the mechanisms involved in the release of neutrophil extracellular traps (NETs) and production of cytokine in severe lung diseases, such as COVID-19. We reported the consequences of hyponatremia in COVID-19 patients, and the immunomodulatory effects of HS, either *in vitro* or *in vivo*. We also described the relationship between electrolyte disturbances and COVID-19 infection. Although there is still a lack of clinical trials, hypertonic NaCl solutions have marked effects on neutrophil function and NETs formation, emerging as a promising adjuvant therapy in COVID-19.

Keywords: coronavirus, leukocytes, neutrophils, immune system, NETs, NETosis, NaCl

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***Correspondence:**
Elaine Hatanaka
elainehatanaka@gmail.com

† *These authors have contributed equally to this work*

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INTRODUCTION

The World Health Organization (WHO) determined the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) as a pandemic in March 2020. Even after efficient vaccines are made available, the new variants of SARS-CoV-2 may reduce their effectiveness, and COVID-19 caused by different variants can still affect the respiratory tract (1).

COVID-19 patients have also been reported to have superinfections and coinfections with SARS-CoV-2 (2) and a recent meta-analysis found coinfections (19%) and superinfections (24%) of these patients, both being related to the risk of higher mortality (3). In this sense, superinfections and respiratory coinfections in SARS-CoV-2-positive patients were more prevalent in critically ill COVID-19 patients (4) and Paolucci et al. found a correlation between elevated viral load (especially Epstein-Barr virus) and lymphopenia, which demonstrates the relationship between viral prevalence and immunosuppression (5). Thus, alternative practices are needed to prevent hyper-inflammation and the respective worsening of severe respiratory illness in COVID-19 patients.

The vaccine minimizes the risk of coronavirus infections and reduces the severity of the disease, while the heterologous and homologous sera treatments block the virus. In general, antivirals block the activity of a specific enzyme/protein needed for the virus to replicate. In the chronology of disease, vaccine administration must be before contamination, thus, treatment with serums is effective in the high viral load.

The evolution of COVID-19 to lung inflammation results in severe cases. At pulmonary complications, anti-inflammatory drugs (cortisone/dexamethasone) are administrated to patients and, theoretically, in a critical inflammatory period, hypertonic saline could be a potential adjuvant therapy. Hypertonic sodium chloride solution (HS) has hemodynamic and electrolyte homeostasis maintenance properties. It improves blood viscosity, causes fast distension of intravascular volume, and decreases endothelial and tissue edema (6, 7). HS also regulates leukocyte function and exhibits an anti-inflammatory effect to improve inflammatory disease conditions such as sepsis and cystic fibrosis (8, 9).

Sputum induction by HS inhalation has been suggested for use in chronic obstructive pulmonary disease (10), while HS inhalation enhances the effectiveness of respiratory physiotherapy in patients with bronchiectasis (11). HS also stimulates mucociliary clearance in healthy individuals and patients with asthma, bronchiectasis, and cystic fibrosis (12, 13).

Recent studies reported that hyponatremia is associated with poor outcomes in COVID-19 patients as an independent predictor of in-hospital mortality (14, 15). Kimura et al. studied outpatients with COVID-19 without acute respiratory distress syndrome, one of the leading causes of mortality in COVID-19 patients, and suggested considerable symptom resolution with HS administration (16). However, they only enrolled patients who could self-isolate and perform irrigation in a bathroom separate from other household contacts and similar precautions would need to be taken by any COVID-19 patient considering this type of intervention in other studies. It is also worth noting that their study had a reduced number of participants (only 14 participants in the hypertonic saline group; 16). Therefore, despite the positive HS effects in other inflammatory diseases (17, 18), it has not been used in COVID-19 patients, and the mechanisms by which HS regulates mucociliary clearance and neutrophil functions remain unknown. We explored how HS modulates leukocyte function and attenuates severe respiratory illness aggravation in COVID-19 patients. We also discuss how HS may regulate neutrophil functions and NETosis formation in the interaction with SARS-CoV-2.

DISCUSSION

Hyponatremia in Coronavirus Diseases 2019 Patients and Hypertonic Solution Administration Approaches

The infection of human cells by SARS-CoV-2 occurs through virus Spike protein binding to angiotensin I-converting enzyme 2 (ACE2) receptor (19). ACE-2 is one of the major anti-regulatory proteins of the main axis of the renin-angiotensin system (RAS), a fundamental determinant for the regulation of electrolyte balance and blood pressure. The binding of SARS-CoV-2 to ACE2 results in increased angiotensin II activity, as well as inflammation, and reduces the counter-response of ACE2 on RAS, which influences electrolyte control and elevates blood pressure (20). Moreover, approximately 60% of COVID-19 patients with watery diarrhea have moderate hyponatremia (21). As a result, SARS-CoV-2 infection promotes disturbances in the homeostasis of pH and electrolytes *in vivo*.

Hyponatremia is the most common electrolyte disturbance and, even when mild, is related to higher mortality (22). This electrolyte disorder is as high as 30% in inpatient settings (23). It is categorized in euvolemic, hypovolemic, and hypervolemic hyponatremia, each managed differently (24). Regarding severe acute respiratory syndrome (SARS), retrospective research in 77 medical, surgical, and mixed intensive care units showed that hyponatremia is described as an independent predictive indicator of poor outcomes in critically ill patients (25) and it is associated with poor prognosis (26). In addition to the impact on lung function, the clinical evolution of patients with COVID-19 can be unpredictable, leading to systemic complications and affecting different organs, as shown in **Supplementary Table 1**.

Direct endothelial cell infection by SARS-CoV-2 and the following endothelitis can induce platelet activation, high vascular permeability, raised thrombin generation, and reduced fibrinolysis, leading to a hypercoagulable state (27). In severe COVID-19, the high concentration of cytokines is related to systemic and local endothelial dysfunction and injury (28). In turn, endothelial activation induces downregulation of thrombomodulin expression, elevated tissue factor expression, and loss of heparin sulfate – all defensive mechanisms against thrombosis (29), contributing substantially to mortality and morbidity (30). Moreover, unregulated inflammatory markers production can induce blood-brain-barrier disruption, hence favoring the entry of cytokines, (or even SARS-CoV-2) into the central nervous system (31), promoting neurologic damage through either the complement or macrophages (32).

Extra-pulmonary manifestations such as gastrointestinal (GI) symptoms are also common in patients with COVID-19. Since ACE2 is expressed by various tissues, including epithelial cells of the GI tract (33), GI symptoms are usual in COVID-19 and the most ordinary GI presentation in COVID-19 patients is diarrhea, followed by vomiting and/or nausea and abdominal pain (34). Other usual GI symptoms reported in COVID-19 patients are anosmia, anorexia, and dysgeusia (35).

Since SARS-CoV-2 moves into the mucous membranes, it can access the biliary system through the portal vein. Thus, SARS-CoV-2 can induce direct immune injury to hepatocytes (cytopathic effect). In this sense, direct viral cytopathy with micro-vesicular steatosis, mild lobular, or portal implication has been observed in other studies (36). Elements that may influence the hepatic involvement in COVID-19 include exacerbated immune responses/systemic inflammatory response syndrome (37), direct viral cytopathic effects, hypoxia-induced alterations, endothelitis (38), vascular changes due to coagulopathy, and drug-induced liver injury (37). Regarding the severity, the prevalence of liver damage in severe COVID-19 cases (74.4%) was higher than that of patients with mild disease (43%), while the prevalence of liver injury in COVID-19-related deaths was 58% (39).

The etiology of hyponatremia seems to have multiple causes in COVID-19 patients, possibly including the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and digestive losses of sodium by vomiting or diarrhea (40). COVID-19 aggravation has been related to the reduction in potassium, calcium, and sodium serum levels (41, 42). Berni et al. (43) reported that hyponatremia is related to a more severe outcome in COVID-19 patients (43).

Hyponatremia may also be a consequence of the increased inflammatory biomarkers and interleukin (IL)-6 being one of the most relevant cytokines involved in COVID-19 infection (43). IL-6 may induce hyponatremia by causing vasopressin release (44). Besides, the proposed mechanisms for SIADH in COVID-19 patients involve inflammatory cytokine production (45). This issue requires prospective multicenter research and search for chronic underlying hyponatremia and evaluation of cytokines associated with urinary osmolarity to find out the mechanisms involved in the SIADH and COVID-19 linkage.

In vitro assays show that intracellular energy deprivation and membrane depolarization are potential pathways by which the HS usefully avoids virus replication. This possibility was recently raised by Machado et al., who studied non-human primate kidney cell line Vero and found that 1.2% NaCl restrained virus replication by 90%, achieving 100% restraining at mildly HS (1.5%). They also found that 1.1% NaCl was enough to restrain virus replication by 88% in human epithelial lung cell line Calu-3 (46).

In addition to the possible protection against viral replication, several NaCl solutions promote clear patient clinical improvements. HS improves the efficacy of respiratory physiotherapy in patients with bronchiectasis or cystic fibrosis (47, 48), stimulating cough (49), and restraining epithelial sodium channels (6).

Ho et al. investigated a case of SARS-CoV-2 induced SIADH manifesting as new-onset seizures using a pro-active desmopressin strategy (3% HS infusion with concomitant fluid restriction). On day 4, the authors found a clinical recovery with resolution and normalization of natremia. They suggested that high cytokine concentrations promote osmoregulation impairment, leading to hyponatremia (50). Nevertheless, this research is a case study without a control group and based on just one patient's clinical and biochemical data. A randomized controlled trial (RCT) also reported the efficiency of HS (3, 2.5, 2.0, and 1.5%; nasal irrigation and gargle versus standard care) as therapy on adults within 48 h of the upper respiratory tract infection (URTI) onset. The authors found a reduction in the time of illness, transmission within household contacts, over-the-counter medications use, and viral shedding (51). Accordingly, the analysis from the Edinburgh and Lothians Viral Intervention Study RCT demonstrated that HS (gargling and nasal irrigation) decreases the time of URTI by an average of two-and-a-half days (52), however, since the results are a *post hoc* secondary analysis of data from a pilot RCT, they need to be interpreted with caution. In a systematic review, Singh et al. pointed out that HS with gargles and nasal wash may be beneficial in the prevention and care of COVID-19 patients (53).

Hypertonic Saline as an Immunomodulatory Agent

During SARS-CoV-2 infection, hyper-inflammation and pulmonary edema are the most worrying clinical conditions (54). COVID-19 in the severe phase presents a cytokine storm with increased plasma concentrations of tumor necrosis factor (TNF)-α, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, chemokine ligand 2 (CCL2), chemokine C-C motif ligand 3 (CCL3), granulocyte colony-stimulating factor (G-CSF), interferon (IFN)γ, and IFNγ-inducible protein 10 (55, 56). High plasma concentrations of cytokines and chemokines in patients with COVID-19 are associated with the aggravated state of the disease compared to non-severe patients (57). Huang et al. reported that COVID-19 patients in the intensive care unit, compared with non-intensive care unit patients, have increased plasma levels of CCL2, CCL3, interferon-inducible protein 10, TNF-α, IL-2, IL-7, IL-10, and G-CSF (58). Patients with COVID-19 and hyponatremia have a worse prognosis than individuals without electrolyte disbalance (59).

The reduction in cytokine production by leukocytes may be a supplementary beneficial effect of HS on the exacerbated immune response in COVID-19 patients. The HS modulates the expression and release of adhesion molecules, such as beta2-integrins and intercellular adhesion molecule (ICAM)-1, and cytokines (e.g., TNF and IL-10) in leukocytes (60–62).

Aerosolized HS elevates IL-8 release by cystic fibrosis gland cells *via* nuclear factor (NF)-κB pathway (63) and IL-8 expression *via* p38 mitogen-activated protein kinases in human bronchial epithelial cells (64). On a cellular level, the favorable outcomes of aerosolized HS were also reported regarding suppressing mTOR activity in mononuclear cells (65) and the decreased arachidonic acid leukotriene-B4-induced priming of the respiratory burst in neutrophils (66). Oreopoulos et al. reported that HS decreases TNF and increases IL-10 stimulated by lipopolysaccharide (LPS) at the gene expression level, independent of NF-κB signaling. HS treatment might exert its effects by independently modulating pro- and anti-inflammatory molecules, explaining the reduced degree of injury in multiple organs after HS administration (62).

The potential anti-inflammatory effects of HS are still unconcluded in humans. Paff et al. carried out a double-blind RCT study on the impact of HS inhalation (7%, twice daily) in 22 patients with primary ciliary dyskinesia. The authors evaluated inflammatory parameters [serum C-reactive protein, erythrocyte sedimentation rate, white blood cell count and cell differentiation, sputum cell differentiation, sputum neutrophil elastase (NE), IL-1β, IL-6, IL-8, IL-10, TNF-α, myeloperoxidase, IFN-α, and –β] and the quality of life (QoL) of the patients. The authors reported that the QoL-bronchiectasis health perception scale improved with HS. However, there was no alteration in the inflammatory measurements even after 12 weeks of treatment (67). Similarly, Aitken et al. did not find a reduction in IL-8 levels after sputum induction (3% HS at 5-time points over 20 min) in 10 clinically stable patients with cystic fibrosis (68). Elkins et al. also did not find differences in pro-inflammatory cytokines (IL-10, IL-6, IL-8, and TNFα) in the sputum of 164 patients with stable cystic fibrosis (7% HS inhaled twice daily) after 48 weeks of intervention (69). Nevertheless, it is essential to mention that all samples from Aitken et al. and Elkins et al. studies were in the post nebulization condition. There was no direct comparison between participants pre and post-nebulization (68, 69). In contrast, Reeves et al. found that HS reduces neutrophil chemotaxis and IL-8 levels in the sputum of 18 cystic fibrosis patients (nebulized 7% HS) compared to 14 non-cystic fibrosis control subjects, thereby assisting resolution of inflammation in the lower airways (18).

Consensus opinions of experts in hyponatremia by the Hyponatremia Treatment Guidelines (24) indicate that the treatment of hyponatremia depends on two factors: (a) etiology and (b) the volume status and comorbidities of the patient. Besides, usual saline therapies involve two different approaches: fluid restriction treatment and electrolytic substitution treatment. In the first scenario, the fluid limitation is necessary in the case of hyponatremia secondary to SIADH, and the HS administration may be associated in this case (depending on the stage of neurological impairment). This approach is recommended to prevent iatrogenic problems, such as lung injury aggravation secondary to SARS-COV-2 infection and pulmonary edema. On the other hand, general guidelines establish the beginning of electrolyte replacement treatment in the case of hypovolemic hyponatremia secondary to GI fluid losses and decreased fluid intake (24). Therefore, personalized pathophysiological judgment is crucial in this pandemic since there are no official clinical guidelines for treating hyponatremia in COVID-19 patients.

As discussed above, the ideal concentrations of NaCl solutions in the different stages of COVID-19 and the associative consequences of NaCl unbalance and clinical relevance in COVID-19 patients remains unestablished. The ongoing RCTs on COVID-19 and HS approaches are summarized in **Table 1**. All trials are being applied to adults (≥18) or older adults among the RCTs. Three studies (NCT04465604, NCT04382131, and NCT05104372) are with the status of "recruiting" and one study had the status of completed (NCT04755972), whereas two others are in the level of "not yet recruiting" (**Table 1**).

Hypertonic Saline and Neutrophils

Neutrophils' altered responsiveness is likely to be a risk factor for severe COVID-19 considering increased mortality in the elderly, diabetic, and obese patients. These patients exhibit leukocyte dysfunction and chronic inflammation that predispose them to an excessive release of cytokines (70, 71). Impaired leukocyte function and reduced cell number are indicators of the progress from mild to severe clinical disease phases (72), and hyponatremia was recently associated with the high neutrophil count in SARS-CoV-2 patients (15).

The primary role of neutrophils in infections is the clearance of pathogens and debris through phagocytosis (73). The liberation of neutrophil-chemoattractant agents and the consequent recruitment of neutrophils is a vital host action against viral infection (74). Barnes et al. described an extensive lung infiltration of neutrophils in an autopsy specimen from a patient who succumbed to COVID-19 (75). Moreover, a high neutrophil-to-lymphocyte ratio indicates a poor prognosis for these patients (76).

Hypertonic solutions resuscitation has been reported as a potential strategy to decrease tissue damage and neutrophil activation in trauma patients (77), which mechanisms for neutrophil adhesion and sequestration vary with the inflammatory state. Chen et al. found that HS resuscitation has anti-inflammatory effects on panx1, CD39, CD73, and other ectonucleotidases. The authors also reported adenosine production induced by HS blocks neutrophil function through

TABLE 1 | Summary of ongoing randomized controlled trials that included hypertonic saline approaches in the COVID-19 treatment.

Identifier	Therapy	Primary outcome measures	Last update posted	*n*	Prim. Purp.	Start date	Estim. study compl. date	Age	Status
NCT04465604	Surgical face mask sprayed with HS	Improvement of respiratory symptoms and respiratory signs	Mar 2021	50	T	Feb 2021	May 2022	≥18	Recruiting
NCT04382131	HS; nasal irrigation and gargling	Time to resolution of symptoms	Sep 2020	405	T	Jun 2020	Oct 2020	≥18	Recruiting
NCT04842721	HS; mouth Rinse Active Arm	Number of Participants with Negative COVID-19 PCR test results	May 2021	20	T	Jul 2021	Dec 2021	≥18	Notyet recruiting
NCT04341688	HS; gargle and nasal lavage	Intraoral viral load	Jul 2021	50	SC	Dec 2021	Jul 2022	≥18	Notyet recruiting
NCT04755972	HS; inhalation (active comparator)	Ventilator-associated pneumonia rate	Feb 2021	40	P	Jan 2021	Aug 2021	≥18	Completed
NCT05104372	HS; nasal irrigation and gargling	Time to resolution of symptoms	Nov 2021	405	T	May 2021	Nov 2021	≥18	Recruiting

The studies were selected from the United States National Library of Medicine (assessed at ClinicalTrials.gov) by the descriptors "COVID-19 | NaCl Solution | Hypertonic saline". Studies using only normal saline (until 0.9% sodium chloride) were excluded. n, estimated enrollment of participants; prim. purp., primary purpose; estim.compl. date, estimated completion date; T, treatment; SC, supportive care; P, prevention; HS, hypertonic saline; and PCR, polymerase chain reaction.

A2a receptors (78). Rizoli et al. investigated the effect of HS resuscitation on the progress of lung injury in a hemorrhagic shock model. They found suppression of LPS-stimulated activation and expression of CD11b. They demonstrated that CD11b integrin could be essential for neutrophil–endothelial interactions under the conditions studied (79). Reports also indicate that HS decreases lung injury by avoiding neutrophil adhesion to endothelium and suggests a mechanism for HS resuscitation. HS resuscitation decreases neutrophil margination by suppressing neutrophil L-selectin expression (80) and HS not only reduces post-shock mesenteric lymph release but also suppresses neutrophil priming by mesenteric lymph (81).

Hypertonic solutions may have clinical relevance by decreasing neutrophil-mediated intestinal damage. Tillinger et al. investigated HS treatment of neutrophils *in vitro*. They noted a dose-dependent effect involving decreased cell migration and the disruption of T84 monolayers compared with untreated control cells (82). Compared with physiological saline, Oreopoulos et al. found inhibition of ischemia/reperfusion-induced hepatic expression of ICAM-1 mRNA with HS from *in vivo* model of hepatic ischemia-reperfusion and *in vitro* model from the activated endothelial cell. The authors postulated hypertonicity minimizes neutrophil-mediated injury by regulating endothelial ICAM-1 expression (61).

Hatanaka et al. reported that hypertonic NaCl solution strongly inhibits LPS-mediated cytokines released by neutrophils and mononuclear cells *in vitro* (83). These findings were corroborated by research showing that the blockage of surface integrins or selectin molecules expression by HS prevents the accumulation of neutrophils in the sites of inflammation (17). Besides, HS inhibits neutrophil's function regarding the expression of adhesion molecules (84), reactive oxygen species (ROS) production (7), neutrophil migration (85), and exocytosis (86). However, the mechanism by which HS stimulates mucociliary clearance is not fully clarified yet. In addition, investigations on the effects of hypertonic NaCl solution on neutrophil death and ROS production should be encouraged. **Figure 1** illustrates the possible beneficial effects of hypertonic saline solution decreasing neutrophils' hyperresponsiveness in the coronavirus disease.

Neutrophil Extracellular Traps: A Promising Path?

Neutrophil extracellular traps (NETs) play a role in immune defense, autoimmunity, and sepsis (87). NETs are constituted of antimicrobial agents and decondensed chromatin, including myeloperoxidase (MPO) and NE, which capture and kill bacteria, parasites, and fungi (88). Considering the high production of ROS and the cytokine storm, COVID-19 cases can be greatly worsened by the tissue-damaging actions of NETs (89). Conditions closely associated with NETosis are coagulopathy, severe tissue damage, and barrier dysfunction of the lungs (90). For an in-depth look at the subject, Borges et al. previously described the mechanisms related to NETs formation in the pathophysiology of COVID-19 (91).

Hypertonic solutions induces water to come out from the cell, activating various cellular processes (92), such as dehydration of neutrophils that mitigate their role to restrain ROS and sequential NETosis. Nadesalingam et al. described that HS usually used in therapies (509 mM or 3% saline) restrains NOX2-dependent NETosis promoted by phorbol-12-myristate-13-acetate (PMA) and LPS. They also reported that the suppressive action of HS on NETosis is in part controlled by restraining liberation of ROS, which is mainly exerted by an elevation in osmolarity (93).

Myeloperoxidase has been closely associated with hyper-inflammation tissue damage (94). Although the role of MPO in SARS-CoV-2 is still uncertain, NaCl on MPO may be clinically

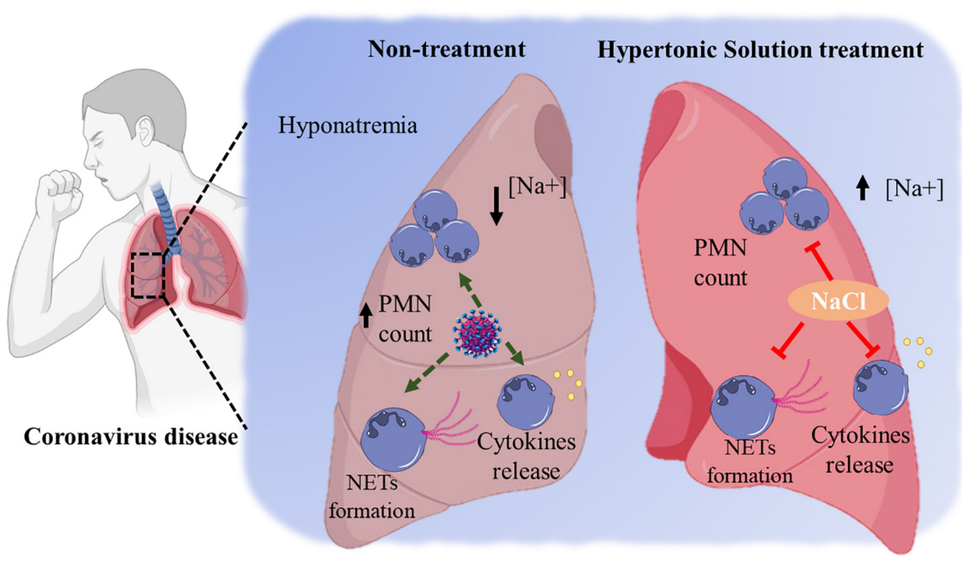

FIGURE 1 | The possible beneficial effects of hypertonic saline solution decreasing neutrophils' hyperresponsiveness in the coronavirus disease.

associated with less severe conditions. Delgado-Enciso et al. investigated ambulatory COVID-19 patients and therapy efficacy with nebulized and/or intravenous neutral electrolyzed saline (containing hypochlorous acid) associated with usual medical care versus routine medical care only. They found no adverse severe symptoms and showed an increased effect on SARS-CoV-2 clearance (95). The authors hypothesized that increased osmolarity influences oxidative processes related to the death and health deterioration of COVID-19 patients. However, the precise MPO mechanism still requires specific in-depth research to establish the effect of saline regarding the regulation of SARS-CoV-2 infectivity by MPO. This knowledge could assist the planning of novel salt approaches in intensive care unit-related inflammatory illnesses, such as COVID-19, in different stages of the disease.

FINAL CONSIDERATIONS

Although the relationship between the electrolyte disturbances and COVID-19 infection is not fully clear yet, the electrolytic imbalance is often reported among COVID-19 patients, and hyponatremia is associated with a bad prognosis. HS therapies are simple, popular, economic, and feasible therapy to regulate leukocyte function with a robust anti-inflammatory effect in many inflammatory diseases, such as sepsis and cystic fibrosis. However, the potential anti-inflammatory action of HS *in vivo* requires more studies, the mechanisms by which HS stimulates mucociliary clearance are not fully clear and the cause-and-effect relationship of these events in patients with COVID-19 can only be confirmed by RCT. Therefore, there is a compelling need to investigate the effects of HS on neutrophil function and NETs formation in COVID-19 as promising targets for pharmacological treatment of the disease in the current pandemic scenario.

AUTHOR CONTRIBUTIONS

MG-F and LB developed the idea and wrote the manuscript. AD, EW, RC, and TP-C collected and prepared the study data. EH reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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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.2022.917008/full#supplementary-material

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Molecular Epidemiology of AY.28 and AY.104 Delta Sub-lineages in Sri Lanka

Diyanath Ranasinghe[1†], Deshni Jayathilaka[1†], Chandima Jeewandara[1†], Dumni Gunasinghe[1], Dinuka Ariyaratne[1], Tibutius Thanesh Pramanayagam Jayadas[1], Heshan Kuruppu[1], Ayesha Wijesinghe[1], Fathima Farha Bary[1], Deshan Madhusanka[1], Pradeep Darshana Pushpakumara[1], Dinuka Guruge[2], Ruwan Wijayamuni[2], Graham S. Ogg[3] and Gathsaurie Neelika Malavige[1,3]*

[1] Allergy Immunology and Cell Biology Unit, Department of Immunology and Molecular Medicine, University of Sri Jayewardenepura, Nugegoda, Sri Lanka, [2] Colombo Municipal Council, Colombo, Sri Lanka, [3] MRC Human Immunology Unit, Radcliffe Department of Medicine, MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom

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***Correspondence:**
*Gathsaurie Neelika Malavige
gathsaurie.malavige@ndm.ox.ac.uk*

† These authors have contributed equally to this work

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Background: The worst SARS-CoV-2 outbreak in Sri Lanka was due to the two Sri Lankan delta sub-lineages AY.28 and AY.104. We proceeded to further characterize the mutations and clinical disease severity of these two sub-lineages.

Methods: 705 delta SARS-CoV-2 genomes sequenced by our laboratory from mid-May to November 2021 using Illumina and Oxford Nanopore were included in the analysis. The clinical disease severity of 440/705 individuals were further analyzed to determine if infection with either AY.28 or AY.104 was associated with more severe disease. Sub-genomic RNA (sg-RNA) expression was analyzed using periscope.

Results: AY.28 was the dominant variant throughout the outbreak, accounting for 67.7% of infections during the peak of the outbreak. AY.28 had three lineage defining mutations in the spike protein: A222V (92.80%), A701S (88.06%), and A1078S (92.04%) and seven in the ORF1a: R24C, K634N, P1640L, A2994V, A3209V, V3718A, and T3750I. AY.104 was characterized by the high prevalence of T95I (90.81%) and T572L (65.01%) mutations in the spike protein and by the absence of P1640L (94.28%) in ORF1a with the presence of A1918V (98.58%) mutation. The mean sgRNA expression levels of ORF6 in AY.28 were significantly higher compared to AY.104 ($p < 0.0001$) and B.1.617.2 ($p < 0.01$). Also, ORF3a showed significantly higher sgRNA expression in AY.28 compared to AY.104 ($p < 0.0001$). There was no difference in the clinical disease severity or duration of hospitalization in individuals infected with these sub lineages.

Conclusions: Therefore, AY.28 and AY.104 appear to have a fitness advantage over the parental delta variant (B.1.617.2), while AY.28 also had a higher expression of sg-RNA compared to other sub-lineages. The clinical implications of these should be further investigated.

Keywords: delta variant, sub lineages, epidemiology, COVID-19, sub genomic RNA, AY.28, AY.104

INTRODUCTION

The SARS-CoV-2 virus continues to result in outbreaks in many geographical regions, with the number of cases exponentially increasing in many countries due to the rapid transmission of Omicron (1). Of the five variants of concern (VOCs) that have been identified so far, the delta variant is associated with more severe disease compared to other variants (2, 3). Until Omicron emerged, the delta variant was the most transmissible variant and rapidly displaced all other VOCs and variants of interest (4). Due to the higher transmissibility and increased virulence of the delta variant, outbreaks due to the delta wave were associated with the highest mortality, intensive care admissions and hospitalizations so far in all countries (1).

As the delta variant was the dominant variant globally before emergence of Omicron for the longest time period during the COVID-19 pandemic, it gave rise to over 100 sub lineages. Phylogenetic Assignment of Named Global Outbreak (PANGO) nomenclature has currently assigned 122 sub lineages of delta (AY.1 – AY.122) that are distributed in different geographical regions (4). The sub-lineages of the delta variants have not shown to be functionally different to the parental delta variant (B.1.617.2) and have shown to have a similar susceptibility to neutralizing antibodies (5). However, some of these sub lineages such AY.4.2 have been assigned as a variant of interest due to its possible higher transmissibility compared to B.1.617.2 the parental delta variant (6). While certain mutations such as the presence of A222V has shown to cause slightly higher viral titers, which is thought to result in a higher transmissibility (7), mutations such as the E484K have a possibility of enhanced immune evasion (8). Therefore, it is important to study the evolution and spread of different delta sub lineages to understand their transmission and to detect possible changes associated with virulence and immune evasion.

Sri Lanka experienced 3 major outbreaks since the identification of patient zero in March 2020. The first large outbreak, which occurred from October 2020 to January 2021 was driven by B.1.411 which peaked at 800 cases/day until it was completely replaced by B.1.1.7 (alpha) in mid-April (9). The outbreak due to the alpha variant, which began in April 2021 to June 2021, with the reported number of daily cases as high as 9,950 (10). During this time period (October 2020 to June 2021), apart from 9 imported B.1.351 (Beta) and B.1.525 (Eta) cases which were identified in overseas visitors in quarantine facilities (11), Sri Lanka did not experience any outbreaks due to other VOCs.

The largest Sri Lankan SARS-CoV-2 outbreak was due to the delta variant and its sub lineages from July to end of October 2021 (12). During the peak of this 'delta wave' the PCR positivity rates rose above 30% with case fatality rates reaching 6.35% (12). Apart from the delta parental lineage B.1.617.2, two other delta sub lineages AY.28 and AY.104 were the predominant variants observed during this time period (4). The AY.28 and AY.104 were assigned as Sri Lanka delta sub-lineages as they were found to originate in Sri Lanka and to be transmitted to all continents in the world (13, 14). In this study, we discuss lineage defining mutations, sub genomic RNA expression, relative frequency over time and clinical disease severity of individuals infected with either AY.28, AY.104 or B.1.617.2 in Sri Lanka.

METHODS

Identification of AY.28 and AY.104 Lineages in Sri Lanka

A total of 1,091 sputum or nasopharyngeal swab samples collected from individuals who presented to government and private hospitals with a COVID-19 like illness, and samples collected as a part of the sentinel surveillance of influenza-like illness (ILI) or acute respiratory infection (ARI) from mid-May to November 2021 were sequenced using Illumina ($n = 188$) and Oxford Nanopore ($n = 903$) platforms.

705/1,091 delta sequences with > 70% genome coverage were included in the analysis. Details of RNA extraction, library preparation, and analysis are given in **Supplementary Methods**. Of these 335/705 (47.5%) were assigned to AY.28 and 217/705 (28.5%) were assigned to AY.104, while 68/705 (9.6%) were assigned to B.1.617.2. The rest of the sequences were assigned to various AY sub-lineages of Delta (<24) by pangolin v3.1.16 (https://github.com/cov-lineages/pangolin) with the pangoLearn model released on 2021-11-25. In order to analyze the frequency of infections caused by these sub-lineages over time, we analyzed the relative change in the frequencies of AY.28 and AY.104 in the Colombo district from 15th July to 30th November 2021. As the frequency of delta was <50% of the SARS-CoV-2 viruses that were sequenced before 15th July 2021, they were not included in the analysis. Metadata and statistical analysis of all the 705 samples are included in the **Supplementary Table 1**.

The clinical disease severity and vaccination status of 440/705 individuals who were found to be infected with the delta variant during this time period were further analyzed in order to determine if infection with either AY.28 or AY.104 was associated with more severe disease or with the type of vaccination. Those who were not hospitalized or who were hospitalized and were not given oxygen were considered as having mild illness, whereas those who were given oxygen or required intensive care admission were classified as moderate/severe based on the WHO guidelines in COVID-19 clinical disease classification (15). Pearson's Chi-squared test was used to determine the associations between categorical variables (gender, vaccination, vaccine dose, and disease severity) and sub-lineages while pairwise T-tests with Bonferroni correction to compare means of age and hospitalization period. All statistical tests were done using R version 4.1.2.

Mutational and Phylogenetic Analysis of AY.28 and AY.104

In addition to the delta variants sequenced by us, all the AY.28 ($n = 519$) and AY.104 ($n = 493$) sequences available at GISAID were downloaded from the GISAID database and aligned to the reference sequence using Nextalign (https://github.com/neherlab/nextalign). Amino acid mutations and their frequencies for Spike, ORF1a, ORF1b, and N proteins were calculated, and frequencies of ambiguous amino acids derived from ambiguous nucleotides were removed using in-house python scripts. The phylogenetic tree was inferred by Maximum Likelihood in IQ-Tree (version 1.6.12) using the GTR+G model of nucleotide substitution and 1000 replicates of ultrafast bootstrapping (-B 1000) and SH-aLRT branch test (-alrt 1000). The ML tree was then time stamped with TreeTime (16) (version 0.7.5) using least-squares criteria and the evolutionary rate of $1.1^{*}10^{-3}$ subs/site/year as described by Duchene et al. (17). Six sequenced with inconsistent temporal signal were removed from the analysis. The tree was rendered using ggtree in R version 4.1.2.

Sub-genomic RNA Expression of AY.28 and AY.104

Sub-genomic RNA expression of 705 delta genomes (335 AY.28, 217 AY.104 and 68 B.1.617.2) were analyzed using periscope (https://github.com/sheffield-bioinformatics-core/periscope). This algorithm aligns raw reads against the SARS-CoV-2 reference genome (MN908947.3) and identifies reads that contain the leader sequence at their start position. Depending on the amplicon position, the sgRNA detected reads were counted and classified into each ORF of the virus. Means of sgRNA counts normalized to per 1000 genomic RNA reads, were then compared individually for each of the ORFs using the unpaired Wilcoxon test by adjusting p-values with the Holm method. Statistical analysis results are presented in **Supplementary Table 2**.

Structural Analysis of AY.28 and AY.104

The PyMOL Molecular Graphics System v.2.4.0 (https://github.com/schrodinger/pymol-open-source/releases) was used to map the location of the mutations defining the AY.28 and AY.104 onto the closed-conformation spike protein (PDB: 6ZGE).

RESULTS

We have previously described the changes in the SARS-CoV-2 variants from the onset of the pandemic to May 2021 in Sri Lanka (9). The first delta variant was identified in Sri Lanka on 22nd May (AY.28), and the relative frequency of delta and sub lineages in Sri Lanka is shown in **Figure 1A**. By the first week of December 2021, out of all the delta variants sequenced from Sri Lanka, 481/974 (49.4%) belonged to AY.28 lineage, while only 320/974 (32.9%) were AY.104. Only 140/974 (14.4%) belonged to the parental delta variant, B.1.617.2, while 33/974 (3.39%) belonged to the AY.95 delta sub lineage that is thought to have originated in Maldives.

Mutational and Structural Analysis of AY.28 and AY.104

AY.28 had three lineage defining mutations in the spike protein: A222V (92.80%), A701S (88.06%), and A1078S (92.04%). ORF1a of AY.28 consists of seven lineage defining mutations: R24C, K634N, P1640L, A2994V, A3209V, V3718A, and T3750I with prevalence between 97.83% to 87.96%, and A1918 (96.59%) in ORF1b, and G215 (96.21%) in the N protein, which is present in the SARS-CoV-2 wild-type virus (**Figure 1B**). AY.104 was characterized by the high prevalence of T95I (90.81%) mutation and T572L (65.01%) mutation in the spike protein, A1918V (98.58%) in ORF1a, G215C mutation (98.98%) in N protein. In addition, it is characterized by the absence of P1640L (94.28%) in ORF1a as seen in the wild-type virus (**Figure 1B**).

The pre-fusion (closed-conformation) surface representation of the SARS-CoV-2 B.1.671.2 spike trimer (PDB: 6ZGE) mapped by PyMOL v.2.4.0 is shown in **Figure 1C**. The receptor-binding domain (RBD) is colored in orange while the N-terminal and S2 subunit are shown in gray. Amino acid substitutions and deletions that correspond to each delta sub-lineage are shown in two separate diagrams. Ribbon diagram view of the spike trimer common to both AY.28 and AY.104 of the same is shown on the top right (**Figure 1C**).

Changes in the Relative Frequency of B.1.617.2 and the two Delta sub Lineages Over Time

In order to understand the possible transmissibility of each of the delta sub lineages in comparison to each other, we assessed the relative frequency of B.1.617.2 and the two sub-lineages of delta (AY.28 and AY.104), in the Colombo district. We could not extend this to an island wide analysis, as samples were sequenced infrequently from other districts. Of the 705 delta variants sequenced by us from 15th July to 18th October 2021, 440 were from the Colombo district. From July 2021 to October 2021, AY.28 accounted for 251/440 (57%) of the delta genomes, while AY.104 accounted for 109/440 (24.8%) and B.1.617.2 accounted for 39/440 (8%) of the genomes sequenced from the Colombo district. The changes in the absolute and relative frequencies of the B.1617.2, AY.28 and AY.104 sequenced from the Colombo district are shown in **Figures 2A,B**. AY.28 was the most prevalent variant until mid-August 2021 and since August 2021, an almost equal prevalence of AY.28 and AY.104 were seen.

The time resolved maximum likelihood tree of global AY.28 and AY.104 sequences compared to the parent B.1.617.2 sequences reported in Sri Lanka suggests the time of the most recent common ancestor (tMRCA) of AY.28 emerged around 20th of January 2021. According to the analysis of tMRCA, AY.104 appears to have originated around 20th April 2021. Interestingly, a separate node of AY.28 predominantly sampled in USA appears to have originated in mid-January 2021. The tips are color annotated according to the country where the sequences were identified, which shows Sri Lanka as the likely country of origin (**Figure 3**). Majority of the AY.28 and AY.104 sequences detected outside of Sri Lanka were reported from the United Kingdom, India, Japan, Canada and Australia (**Figure 3**).

Sub-genomic RNA Expression of Delta Sub-lineages

We analyzed 335 AY.28 genomes and 217 AY.104 and 68 B.1.617.2 for expression of sgRNA. The highest sgRNA expression was observed in the spike protein of B.1.617.2 and the sub-lineages followed by ORF7a (**Figure 4**). The mean sgRNA expression levels of ORF6 in AY.28 was significantly higher compared to AY.104 ($p < 0.0001$) and B.1.617.2 ($p < 0.01$). Also, ORF3a showed significantly higher sgRNA expression in AY.28 compared to AY.104 ($p < 0.0001$). However, AY.104

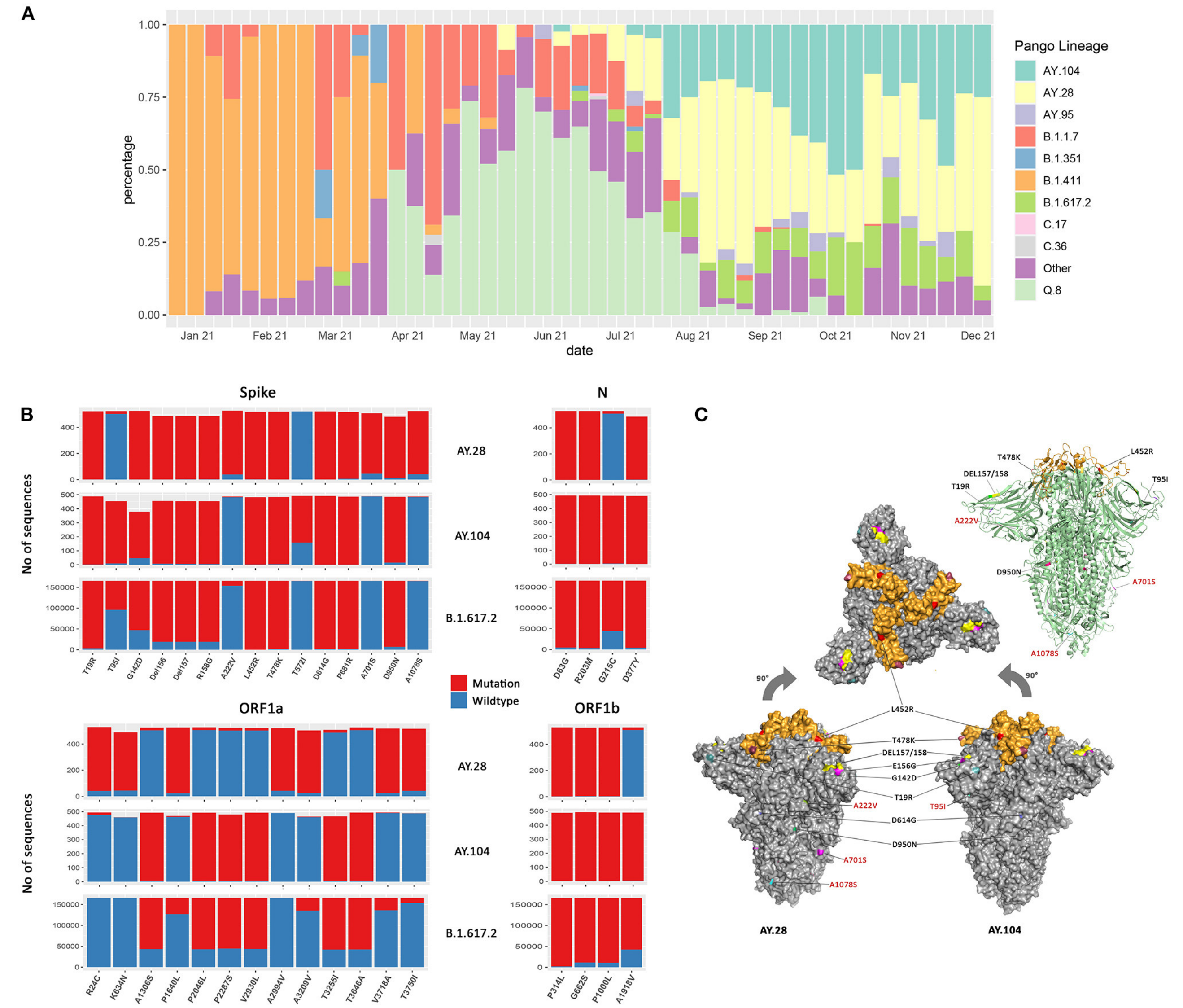

FIGURE 1 | The mutation and structural changes of AY.28 and AY.104 sequences in comparison with B.1.617.2 (Delta) lineage. **(A)** Weekly lineage frequencies of the sequenced cases in Sri Lanka since January 2021 were retrieved from the GISAID EpiCoV database. **(B)** The frequency of mutations in the spike, ORF1a, ORF1b, and N proteins of AY.28 and AY.104 compared to those of the parental B.1.617.2 (Delta) lineage. The bar height represents total unambiguous amino acids at each position, mutated (red) and wildtype (blue) based on the analysis of the global sequences deposited in the EpiCoV database. **(C)** The structural modeling of the pre-fusion surface representation of the SARS-CoV-2 B.1.671.2 spike trimer (PDB: 6ZGE) and the mutations in the structure in AY.28 and AY.104 are shown. The receptor-binding domain (RBD) is colored in orange while the N-terminal and S2 subunit are shown in gray. Amino acid substitutions and deletions are colored on the surface and labels of the mutations specific for AY.28 and AY.104 are colored in red. On the right, a ribbon diagram is shown of the same.

had significantly higher sgRNA expression in ORF8 compared to AY.28 ($p < 0.0001$), and B.1.617.2 ($p < 0.0001$). Also, the mean sgRNA expression of the nucleocapsid (N) in AY.104 was significantly higher compared to AY.28 ($p< 0.01$) and B.1.617.2 ($p<0.05$). Interestingly, ORF7a of AY.104 expressed significantly lower sgRNA compared to AY.28 ($p < 0.0001$) and B.1.617.2 ($p < 0.001$) (**Figure 4**). During the peak of the outbreak which lasted from August to September, AY.28 accounted for 128/189 (67.7%) of the infections sequenced.

Clinical Characteristics and Vaccination Status of Patients Infected With AY.28 and AY.104

We retrieved the clinical details of 440 patients infected with B.1.617.2 and the sub lineages from the Colombo district (Colombo Municipality Council area) and investigated if infection with different sub lineages associated with clinical disease severity. 97/440 patients were home quarantined, 320/440 were treated at quarantine centers and 23 were treated at hospital.

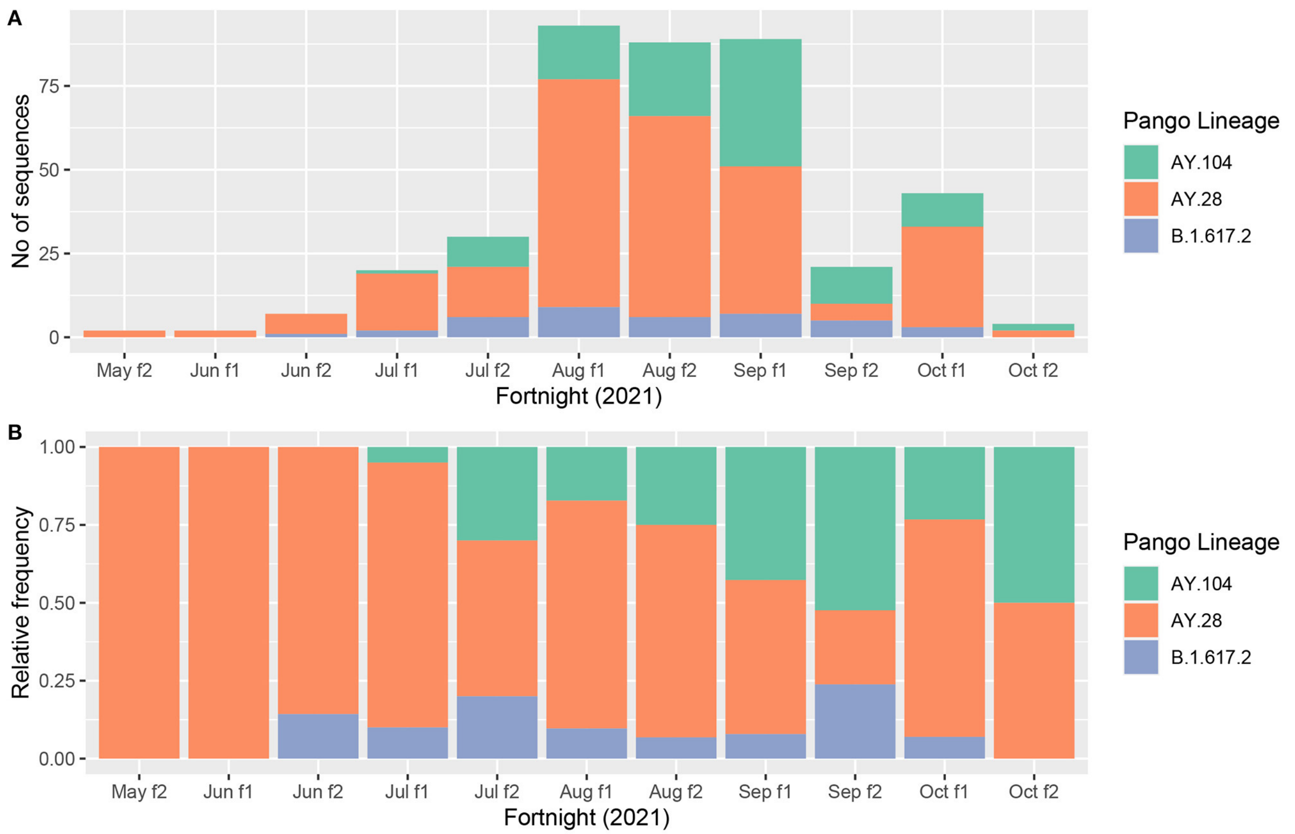

FIGURE 2 | Prevalence of AY.28 and AY.104 against the original Delta (B.1.617.2) in Colombo district. **(A)** Absolute prevalence of main delta sub-lineages (AY.28, AY.104 and B.1.617.2) sequenced in Colombo district ($N = 440$) since mid-May to November 2021 is shown for each fortnight, month and week. **(B)** Relative prevalence of AY.28, AY.104 and parental B.1.617.2 sequenced in Colombo district ($N = 440$) since mid-May to November 2021.

Of the 440 individuals who were infected with the delta variant, the mean age of those infected with AY.28 was 38.39 (SD ± 15.32) and AY.104 was 38.27 (SD ± 17.36) and therefore was not significantly different ($p = 0.86$). There was no difference in the gender of those who were infected with different delta sub-lineages ($p = 0.39$). 156/160 (98%) individuals infected with AY.28 had mild infection, while 3/160 (1.88%) had moderate/severe illness and one individual succumbed to the illness. Of those who were infected with AY.104 all 63/63 (100%) patients developed mild illness. All those who were infected with B.1.617.2 18/18 (100%) also developed mild illness and there were no deaths. However, there was no significant difference between clinical disease severity in these three groups ($p = 0.72$). Individuals were hospitalized between an average of 3 to 60 days. The mean duration of hospitalization of those infected with AY.28 was 13.91 (SD ± 5.88) days, for AY.104 a mean of 14.33 (SD ± 5.93) days and for B.1.617.2 infection a mean of 18.13 (SD ± 11.94) days. The duration of hospitalization was only significantly different between AY.28 and B.1.617.2 ($p = 0.0417$).

In our cohort, 166/228 (72.8%) had received Sinopharm/BBIBP-CorV, while Covishield/ AZD1222 was taken by 61/228 (26.8%) individuals. Only one patient had received the Pfizer vaccine. 225/309 (72.8%) were vaccinated with at least one dose of either Sinopharm/ BBIBP-CorV, Pfizer, or the Covishield (AZD1222) vaccine while 84/309 (27.2%) were unvaccinated. Even though we observed more vaccinated people with AY.28 infection 142/309 (46%), the association was not significant ($p = 0.35$). Although 178/228 (78.0%) were fully vaccinated while 50/228 (21.9%) had only one dose, we did not observe any significant association between the number of vaccine doses and infection with different sub-lineages ($p = 0.69$). Association between vaccine and sub-lineage was insignificant ($p = 0.83$). Among the 84 unvaccinated individuals, AY.28 infection was seen in 60/84 (71.4%) individuals, AY.104 in 17/84 (20.2%) And B.1.617.2 in 7/84 (8.3%).

DISCUSSION

In this study we have described the molecular epidemiology of the delta variant and its sub lineages during a massive outbreak in Sri Lanka, which occurred from July to November 2021. We detected the first delta variant in the community in the Colombo Municipality Council area in the third week of May 2021. This initial cluster which originated in Colombo belonged to AY.28 sub-lineage, while the first AY.104 infection was detected in the 2nd week of June. By the first week

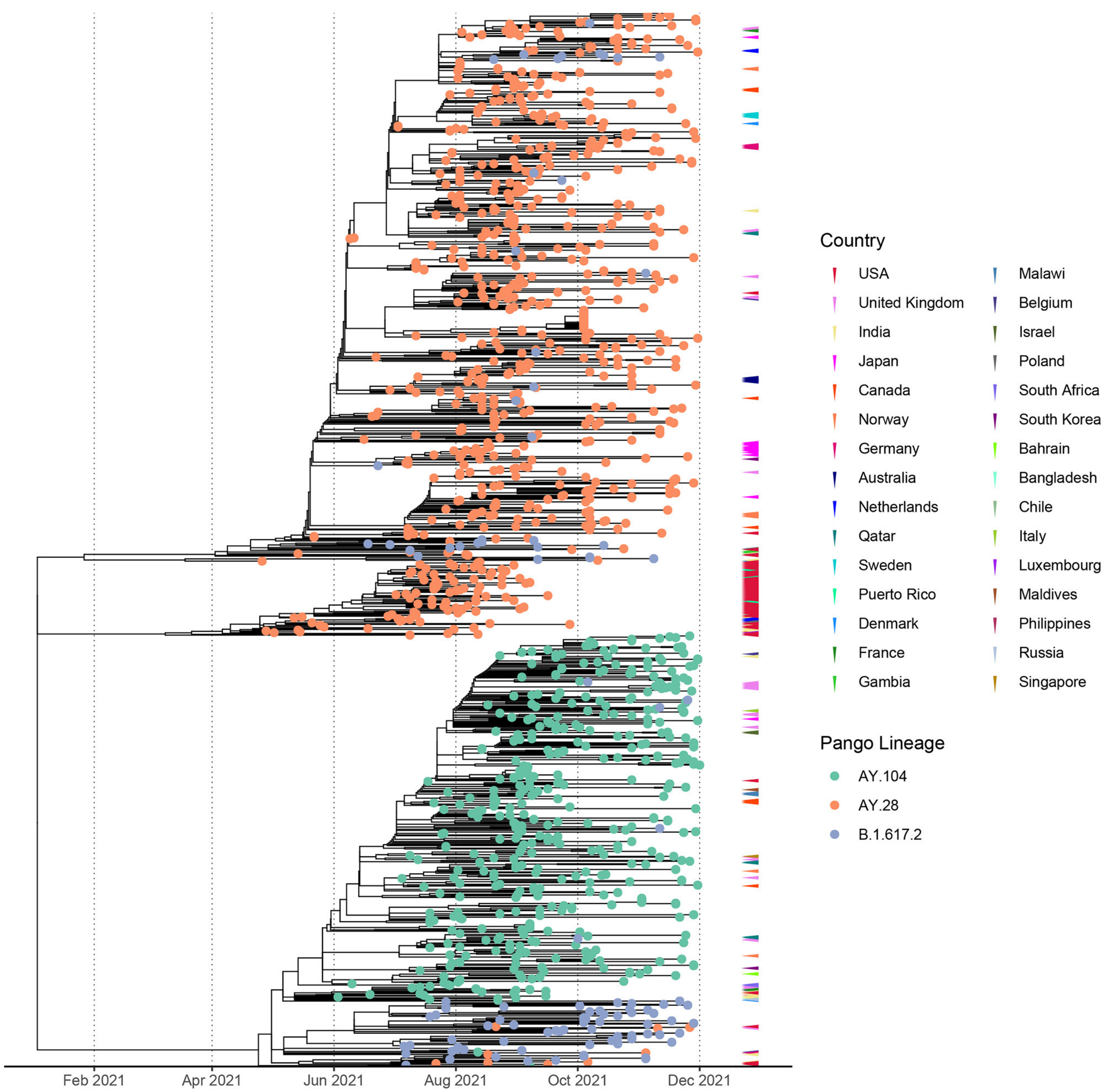

FIGURE 3 | Divergence times of the phylogenetic trees of the global AY.28 and AY.108 viruses using molecular clock. Time-resolved maximum-likelihood phylogenetic tree of AY.28 and AY.104 cases sequenced globally and B.1.617.2 sequences only originating from Sri Lanka. The molecular clock was inferred using TreeTime with an evolutionary rate of 1.1×10^{-3} substitutions/site/year with a standard deviation of 0.00004. Non-local cases of AY.28 and AY.104 are color-coded according to the originating country on the outer layer.

of December, of the delta variants sequenced, 46.3% were of the AY.28 sub lineage, while only 33.6% were of AY.104 sub lineage. AY.28 was seen to dominate over the parental B.617.2 lineage, possibly due to the presence of the A222V mutation, which has been previously suggested to associate with higher transmissibility (7). It was shown that the presence of the A222V mutation promotes an increased opening of the receptor binding domain (RBD) and slightly increases binding to ACE2 compared to the D614G SARS-CoV-2 variant (18). However, although AY.28 was the dominant variant during a major part of the outbreak, an equal prevalence of AY.104 and AY.28 was seen since September 2021, after AY.104 was first detected in June 2021. Although it is not known if the T95I mutation in spike seen in AY.104 gave it a fitness advantage in transmission over the parental delta variant, AY.104 is also likely to be more transmissible than B.1.617.2 as [ref]as this only

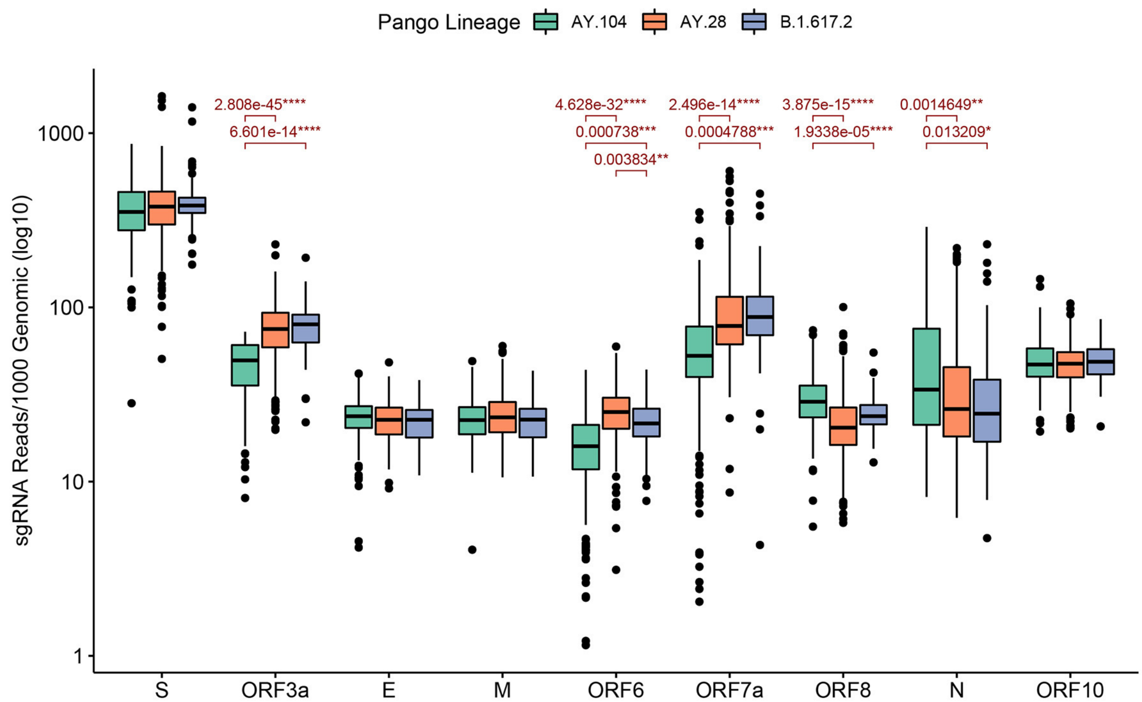

FIGURE 4 | Sub-genomic RNA expression of the delta sub-lineages sequenced in Sri Lanka. Sub-genomic RNA (sgRNA) expression levels of AY.28 ($n = 335$), AY.104 ($n = 217$) and B.1.617.2 ($n = 68$) viruses sequenced in Sri Lanka. SgRNA reads containing the leader sequence are normalized to per 1000 genomic reads for each open reading frame (ORF) of SARS-CoV-2 using Periscope. Significant differences of mean expression levels are indicated with a p value calculated using an unpaired Wilcoxon test adjusting *p*-values of multiple comparisons with the Holm method (**** < 0.0001, *** < 0.001, ** < 0.01, * < 0.05).

accounted for 3.39% of the sequenced variants by the first week of December.

The spike protein of AY.28 has 13 mutations (>75% prevalence) while AY.104 and the parental delta variant (B.1.617.2) have only 11 and 10 mutations respectively. Furthermore, the ORF1a of AY.28 has 7 mutations, whereas AY.104 and B.1.617.2 have 6 mutations. However, AY.28 has fewer mutations in ORF1b and nucleocapsid (N) proteins compared to the other two lineages. Mutations in the N protein has shown to increase infectivity, virulence, and fitness of the virus, with the R203K/G204R mutations being associated with more severe disease in hamster models (19). The R203K/G204R mutations were shown to inhibit GSK-3 kinase and therefore, resulted in increased viral replication (20). The R203M mutation is seen in AY.28, AY.104 and the parental delta lineage and the R203M was shown to enhance immune evasion by the delta variant along with the L452R mutation (21). In addition to the mutations in the R203 region, G215C, which is a lineage defining mutation in AY.104 has shown to improve viral assembly leading to higher viral loads (22). Therefore, in addition to the mutations in the spike protein, certain mutations in the N protein appear to lead to increased viral virulence, infectivity and immune evasion. Unfortunately, due to the non-availability of biosafety 3 level laboratory facilities, we could not isolate these viruses and further characterize the significance of these mutations. Our analysis of clinical disease outcomes and duration of hospitalization in a sub cohort of individuals infected with AY.28, AY.104 and B.1.617.2 showed that there was no difference in the clinical disease severity or duration of hospitalization in individuals infected with these sub lineages. However, only 3 individuals in those cohort developed severe disease, while only one individual succumbed to the illness. Therefore, since only 4/440 (0.9%) individuals (all infected with AY.28) had adverse disease outcomes, the sample size is unlikely to be adequate to determine if infection with these sub lineages associate with more severe disease.

Structural proteins of coronaviruses are first transcribed into sgRNA before translation (23). Although the presence of sgRNA per se does not indicate the presence of actively replicating virus, the relative abundance of sgRNA indicates the relative expression of different ORFs of the virus (23, 24). Many ORFs of the SARS-CoV-2 have shown to suppress interferon gene transcription, interferon production and recognition by innate immune responses, thereby inhibiting innate immune antiviral responses (25). Although our data showed that there were no significant differences in the total sgRNA levels between the two sub-lineages and the parental delta, sgRNA expression was significantly lower in AY.104 for ORF3a, ORF6 and ORF7a compared to the other two lineages. All these ORFs play an important role in evading the host interferon responses by suppressing STAT1 and STAT2 phosphorylation, inhibiting STAT1 complex nuclear translocation and interacting with STING and preventing nuclear translocation of NFκβ (25–27). Therefore, increased expression of sgRNA of ORF3a, ORF6 and ORF7a by AY.28 and parental B.1.617.2 compared to AY.104, may associate with increased virulence due to suppression of host IFN responses. On the contrary, AY.104 had a higher sgRNA expression of ORF8 and the N genes compared to the other lineages. ORF8 has shown to inhibit IRF3 nuclear translocation and N protein has shown to inhibit RIG-1 signaling (25). However, these sgRNA analysis data are only suggestive of such a possibility and isolation of these viruses and further studies *in vitro* and *in vivo* would be required to draw further conclusions.

The AY.28 and AY.104 delta sub lineages that originated in Sri Lanka, spread to several countries within a few weeks. AY.28 was detected in 42 countries by now, while it has predominantly been reported in USA, Japan, India and United Kingdom, reflecting the main travel destinations of Sri Lankan individuals (13). Large divergent cluster of AY.28 seen in USA appears to be a spread of an individual case from early days of the lineage according to the most recent common ancestor (tMRCA) in late January 2021. AY.104 is currently detected in 22 countries, while again predominantly been reported in United Kingdom, India, Canada and Qatar (14). One of the main other sub lineages reported in Sri Lanka was AY.95 (8.2%), which in thought to have originated from the Maldives (28). Therefore, this sub lineage appears to have been introduced due to frequent travel between Sri Lanka and Maldives.

In conclusion, the massive outbreak due to the delta variant in 2021 was predominantly due to two delta sub lineages AY.28 and AY.104. These two Sri Lankan sub lineages accounted for over 80% of the sequenced delta variants in Sri Lanka from July to December, while AY.28 was the cumulatively predominant sub lineage. Although the A222V mutation and significantly higher sgRNA expression in certain ORFs possibly contributed to an enhanced suppression of interferon genes in AY.28 thereby giving it a fitness advantage over AY.104, similar frequencies of AY.28 and AY.104 at the later stage of the outbreak suggest that both sub lineages may have comparable transmissibility. It would be important to further investigate the relevance of the findings by isolating these viruses, in order to understand the evolution and virulence of SARS-CoV-2 variants during this pandemic.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Committee, University of Sri Jayewardenepura. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: DR, CJ, and GM. Study design: DR, CJ, DJ, GO, and GM. Experiments and assays: DJ, DGun, DA, TJ, HK, AW, FB, DM, and PP. Project administration: CJ, DGur, and RW. Data curation: DGur, CJ, and DR. Formal analysis: DR. Writing the manuscript: DR, GM, and GO. Funding: CJ, GO, and GM. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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OPINION
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Is Endemicity a Solution for the COVID-19 Pandemic? The Four E's Strategy for the Public Health Leadership

Leonardo Villani[1]*, *Maria Rosaria Gualano*[2] *and Walter Ricciardi*[1]

[1] Section of Hygiene, University Department of Life Sciences and Public Health – Università Cattolica del Sacro Cuore, Rome, Italy, [2] Department of Public Health Sciences, University of Turin, Turin, Italy

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Correspondence:
Leonardo Villani
leonardovillani92@gmail.com

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INTRODUCTION

In recent times the debate about the possibility, and in some cases the hope, that the COVID-19 disease will become endemic has gained momentum. Indeed, in some cases, public opinion and scientists have proposed and enthusiastically welcomed this evolution, indicating a change of phase of the pandemic and a possible resolution of it.

Infectious diseases can evolve in four scenarios, in relation to their biological characteristics (mutations that arise as a result of specific selective pressures might determine the occurrence of variants) and the Public Health measures implemented to contain the spread of the pathogen. Incidence, prevalence and geographical distribution of the disease, in fact, identify the conditions of extinction (the pathogen no longer exits, both in nature and in the laboratory, on a global scale), eradication (permanent zero incidence globally, so as not to require further interventions of Public Health: there is no risk of reappearance of the disease), elimination of the pathogen and the disease (zero incidence in specific geographic areas, following continuous Public Health interventions) and endemicity (constant presence and/or habitual prevalence of an infectious agent in a population within a geographic area with coexistence between human and the pathogen) (1, 2). The latter, therefore, requires a constant control of the epidemiological trend of the disease, in order to maintain acceptable levels of incidence, prevalence and mortality. While there are no examples of extinction, smallpox, and rinderpest represent examples of eradication, while polio and measles of elimination.

That stated, is the evolution toward endemicity really desirable with a disease with high transmission and mortality rates such as the COVID-19? is the evolution toward endemicity really desirable? In this context, it is important to point out a few considerations about the health, social and economic burden of endemicity and the possible impacts of COVID-19 endemicity, summed up in the 4 E's strategy, as follows.

THE 4 E's STRATEGY

Estimating the Health and Healthcare Services Impact of Endemicity

Endemic infectious diseases have a huge health impact, as they are responsible for the deaths of millions of people each year. Tuberculosis and malaria, for example, as well as HIV/AIDS, are responsible of about 1.5 million, 600,000, and 700,000 deaths each year, respectively, with high mortality rates (about 20/100,000, 15.3/100,000, and 10/100,000, respectively) (3–5). By comparison, in 2021, there were about 3.5 million deaths due to COVID-19 worldwide with a mortality rate of about 50/100,000, despite the spread of vaccines and the availability of new diagnostic and therapeutic tools.

Moreover, endemic diseases (such as malaria, tuberculosis, and AIDS) have an important impact on the quality of life of people, and can lead to the development of chronic conditions, reducing life expectancy and increasing the years lived with disability, so as to be among the top leading causes of Disability-adjusted life year (DALYs) (6). Increasing literature is showing the impact of COVID-19 in terms of DALYs (7, 8) and reduction of life expectancy (9, 10), with a burden that might persist and worsen in the coming years. Likewise, the long-term effects of the COVID-19 are partially known, although early evidence from long-COVID are associated with the persistence of more than 50 clinical conditions in patients (11). This may have a huge impact on population health in long-term period, with an important health, social and economic burden on health systems. These considerations are even more true if we consider the pediatric age: it is well-established that infectious diseases (i.e., pneumonia) contracted in childhood or adolescence might have important sequelae on organ function in adult life (12) and the same pattern could be observed in COVID-19 pediatric patients (13). In addition, the healthcare services will continue to have a large number of patients to assist in the next years, since the burden of the disease continue to exist. In this context, many countries made a great effort by increasing healthcare spending in order to provide more beds, medical personnel, drugs and technologies needed to counter the pandemic. However, this effort may not be sustainable in the future, and in any case, it may decrease attention toward the management of other diseases (14). Indeed, the pandemic caused and is still causing a disruption in all healthcare settings in both low- and high-income countries, increasing the burden of other diseases, especially chronic degenerative and oncological, with a delay in diagnosis and treatment, making people unable to access care at the primary care and community care levels (15).

Encountering the Social Impact of Endemicity

Endemic infectious diseases have a devastating impact in social terms, causing negative consequences both at individual (divorces, low household income and poverty, stigmatization, social exclusion) and country level (permanent condition of poverty, reduced economic growth, and discouraging investments and tourism) (16–18).

The COVID-19 pandemic has resulted in school closures, disruption of education, and interruption of social and recreational activities (19). These closures, necessary to contain the spread of the virus, have and will have a devastating impact on people's mental health, especially children, and adolescents (20, 21). The trend toward an endemic condition, which does not exclude the appearance of new epidemic waves, as happened with influenza viruses (22), could lead to new closures, with unacceptable damage to the population. In this context, the persistence of the virus in the population guarantees the spread of variants, whose evolution in terms of lethality and transmission capacity cannot be predicted (23). Thus, it is important to take caution and remember that the pandemic is still ongoing. Maintaining public health containment measures (hand hygiene, proper ventilation of rooms, mask use, and physical distancing) are important conditions that should not be avoided. At the same time, it will be necessary to ensure social recovery mechanisms and investment in order to prevent the immediate and long-term impact of the pandemic on wellbeing, poverty, and the onset of inequality (24).

Evaluating the Economic Impact of Endemicity

Endemic infectious disease has a significant economic impact, both in terms of direct (personal and public expenditures on both prevention and treatment of the disease) and indirect costs (lost productivity associated with illness or death). For example, it is estimated that tuberculosis will have a cost of about 1 trillion USD in the period 2015–2030 (25), while the global cost of malaria is estimated of about 12 billion USD per year (26). Moreover, the economic impact can be observed in countries with endemic diseases that remain in a condition of poverty and reduced economic growth, contributing to lifelong disadvantage in an already disadvantaged group and establishing a vicious circle from which it is difficult to find a way out (27).

Considering the COVID-19, in 2020 the pandemic resulted in a contraction of global GDP of 3.2%, with a projected cumulative output loss during 2020 and 2021 of about USD 8.5 trillion (28) with a slow economic recovery for the next years (29). Moreover, COVID-19 has an important impact in terms of costs related to healthcare assistance: indeed, in the US it was estimated a total cost that range between about USD 11,000 and 47,000 per hospitalization (30), and same results are reported in Europe (31, 32), highlighting that it can be particularly difficult to address these costs in all health services, especially universal health services.

Enhancing the Attention of Endemicity Impacts in Low-Income Countries

Endemic diseases, such as tuberculosis and malaria, often remain in the most disadvantaged areas of the world (such as African countries), which have reduced access to care and treatment and vaccination. Thus, there is a real risk that the evolution toward endemicity will be borne more by low-income countries, where an additional serious disease would be added. The most disadvantaged areas of the world are currently unable to cope with diseases that are already present. It is therefore essential to prevent a new disease from becoming endemic in these territories. This condition would further increase the economic, social, and health burden on countries already severely damaged by these diseases. In particular, although in Africa the reported prevalence of the SARS-CoV-2 is lower than expected, it is necessary to carefully consider possible explanations for this evidence: while it could be due to the presence of other diseases and related therapies in use in these countries (33), it should be noted that the epidemiologic surveillance systems in these countries are weak, and therefore a strong underestimation of the number of cases and deaths is possible (34–37), with an estimated 97 times as many confirmed cases as reported (38). Moreover, drugs used in malaria prophylaxis, such as hydroxychloroquine, have been shown to be ineffective and even harmful in the treatment of COVID-19, thus ruling out a possible protective action of such drugs (39, 40). In addition, the absence of structured epidemiological surveillance systems is associated with lack of professional skills and capacities, absence of facilities, diagnostic tools, and the presence of other epidemics to be monitored, which make it difficult to manage the pandemic, in addition to the difficulties in reaching patients living in rural areas (41).

DISCUSSION

Are we really willing to accept the evolution of the disease toward endemicity with optimism? And above all, is it really right, in terms of Public Health, to favor this evolution? The tools to contain the infection, such as diagnostic tools, vaccines and specific drugs, are available: it is therefore necessary a strong international leadership that can really lead the fight against the virus, through three key actions.

First, it is necessary making treatments and vaccines available to all. Equity in access to treatment and vaccines is and must be a priority for all in order to counteract the trend toward endemicity and facilitate the conclusion of the pandemic. Currently, only 15% of the population living in low-income countries is vaccinated, against an average of 70/80% in high-income countries (42). These data reflect the accessibility to vaccination: in high-income countries, in fact, although the availability of COVID-19 vaccines, ignorance, miscommunication, and in some cases the absence of a strong central leadership that follow the scientific evidence, have caused vaccine hesitancy (43, 44). On the contrary, in low-income countries there is a lack of vaccines due to several aspects such as the absence of infrastructure and technology for vaccines production and maintenance, and the problem of the suspension of patent protections (45). In this context, despite the commitment made by the high-income countries and the World Health Organization (46), it could be difficult to ensure a total and above all continuous vaccination campaign (i.e., with booster doses) (47).

Moreover, in addition to vaccine availability worldwide, it is important to provide vaccine updates as frequent SARS-CoV-2 mutations are decreasing vaccine efficacy (48), always considering that vaccination, for both COVID-19 and other types of diseases, is one of the most cost-effectiveness intervention in healthcare, even in relation to high need for doses (49–51).

Second, create strong international scientific leadership that can guide, and direct government choices based on scientific evidence. In particular, multidisciplinary scientific research contributed enormously to the rapid identification of drugs and vaccines, as well as providing evidence about the mechanisms of action of the virus and consequently also of the effectiveness of containment measures. Basic research, clinical trials and epidemiological studies have helped to expand knowledge about COVID-19 with unprecedented rapidity (52–54). However, in some cases policymakers, discouraged from making unpopular decisions, have ignored scientific evidence, with devastating effects in their countries (55–57). Thus, albeit science cannot replace the integrity of public leadership, it is necessary to build bridges between research and politics in order to cooperate and support policy decisions and help policymakers make unpopular decisions, increasing people's confidence in science and politics (58, 59). In this context, it is worth noting the apparent incongruence between science, based on evidence, and politics, which is required to take swift action during emergency situations. Evidence-based medicine is a lengthy process derived from the sum of the knowledge's, so it may be difficult to apply to new emergency situations. However, it is possible to rethink it in these kinds of settings, recognizing, for example, the role of experts and fostering their involvement and cooperation in policy decision making (58, 60), including through the creation of national and international agencies, such as the new European Health Emergency Preparedness and Response Authority (HERA) (61). In this way, scientists can provide important policy decision support, based, in the absence of solid evidence, on appropriateness, reasonableness, and evidence from similar contexts.

Third, there is a need to work on the education and cultural aspects of the population, and, often, of policymakers. Mistrust in science, which has become more acute in some segments of the population in some countries, represents a major issue in the management of both the current and future emergencies. This condition might be fixed by a univocal communication adherent to scientific evidence at international and national institutional level, which has often been lacking during the pandemic (the management of communication about Vaxzevria adverse reactions is a cogent example).

In conclusion, although the epidemiological evolution shows a trend toward endemicity, it is necessary to make public opinion and policymakers understand that this may have significant long-term effects in health, social, and economic terms. It is therefore necessary to increase the commitment to ensure vaccination at the global level (with the production of increasingly specific, updated, and effective vaccines), which currently represents the strongest tool to contain the spread and severe symptoms of the disease. On one hand the example of diseases of the past (smallpox and rinderpest) show how the eradication of the virus is possible, on the other endemic diseases show the huge burden at global level and especially in low-income countries. Public health has the opportunity and the capacities to support governments in their policy activities and to advocate for evidence-based strategies at national and international levels to build a common front in response to the pandemic: let's use them, not give in to endemicity.

AUTHOR CONTRIBUTIONS

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

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COVID-19 Inpatient Deaths and Brought-in-Dead Cases in Malaysia

Poh Ying Lim[1*†], *Salmiah Md Said*[1†], *Hayati Kadir Shahar*[1,2†], *Ahmad Zaid Fattah Azman*[1†], *Siti Aisah Mokhtar*[1†] and *Aidalina Mahmud*[1†]

[1] Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia,
[2] Malaysian Research Institute of Ageing (MyAgeing), Universiti Putra Malaysia, Serdang, Malaysia

Coronavirus disease 2019 (COVID-19) deaths can occur in hospitals or otherwise. In Malaysia, COVID-19 deaths occurring outside of the hospital and subsequently brought to the hospital are known as brought-in-dead (BID) cases. To date, the characteristics of BID COVID-19 cases in Malaysia are not clear. The objectives of this study are 2-fold: to explore the characteristics of 29,155 mortality cases in Malaysia and determine the factors associated with the high probability of BID, using the multilevel logistic regression model. Data on COVID-19 mortality cases from the entire country between March 17, 2020 and November 3, 2021 were retrieved from a national open data source. Of the 29,155 COVID-19 mortality cases, 5,903 (20.2%) were BID. A higher probability of BID ($p < 0.05$) was seen among individuals aged between 18 and 59 years, non-Malaysians, had no comorbidities, did not receive COVID-19 vaccination, and the interval between the date of death and diagnosis. A high prevalence of BID is an alarming public health issue, as this may signal health system failure at one or several levels and, hence, need urgent attention from relevant stakeholders. Based on the findings of this study, increasing the intensity of the vaccination campaign, addressing any issues faced by noncitizens about to COVID-19 management in- and out-of-hospital, increasing the awareness of signs and symptoms of worsening COVID-19 and, hence, the significance of self-monitoring, and determining the potential gaps in the health system may contribute to their increased risk of deaths.

Keywords: COVID-19, mortality case, brought-in-death, inpatient death, Malaysia

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Correspondence:
Poh Ying Lim
pohying_my@upm.edu.my

†These authors have contributed equally to this work

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INTRODUCTION

As of December 2021, Coronavirus disease 2019 (COVID-19) mortality cases in the world reached approximately 5.33 million. Many factors contribute to the survival, and, hence, death rates, of patients with COVID-19. Among them are inadequate human resources and inadequate medical supplies such as medicines, equipment, and facilities such as intensive care beds (1–3).

In Malaysia, the first COVID-19 death was reported on 17 March 2020. Since then, the country has recorded fluctuating numbers of COVID-19 deaths and by December 2021, there were approximately 30,000 people died of COVID-19 in the country. From the beginning of the COVID-19 pandemic, several measures have been implemented by the Malaysian government in reducing the spread of COVID-19 and its related morbidity and mortality. Among these measures was the Movement Control Order (MCO), which ranged from total movement restrictions (lockdown) to partial restrictions (such as allowing crucial sectors and businesses to operate) (4). In addition to controlling the movement of the population, the government consistently urged the public, especially the vulnerable groups (children, elderly, unvaccinated individuals, and people with comorbidities), to stay away from crowded places and to strictly adhere to the national COVID-19 standard operating procedure (SOP) because high infection and mortality rates have been reported among these vulnerable groups (2, 5–9).

In general, COVID-19 mortality cases can be classified into two categories based on the location of death: within the hospital or out-of-hospital (5). Studies show that the percentage of COVID-19 cases, which occurred out-of-hospital, namely, at home, in several developed nations (England, Wales, Scotland, Northern Ireland, and the United States of America) ranged between 4.0% and 8.1% (1, 6, 7). A study in Zambia, however, showed that the out-of-hospital deaths were almost 10 times higher at 72.5% in August 2020 (10).

In Malaysia, COVID-19 deaths occurring out-of-hospital are referred to as brought-in-dead (BID) cases and must fulfill several criteria set by the Ministry of Health (MOH) Malaysia (5). The criteria include confirmation of COVID-19 diagnosis through laboratory tests such as rapid test (RT) and PCR, the presence of an epidemiological link between the deceased and other COVID-19 cases, or the presence of radiological changes suggestive of COVID-19 infection, if an autopsy was not conducted (5). To date, the sociodemographic and clinical characteristics of COVID-19 deaths, particularly the BID COVID-19 cases, remain unclear.

As knowledge of the sociodemographic and clinical characteristics of patients who died due to COVID-19 is needed for a better understanding and proper management of the disease, this study aims to explore these characteristics and determine the factors associated with the high probability of BID COVID-19 cases in Malaysia.

Data Source and Methodology

This study was a retrospective record review. All the patients confirmed to have died due to COVID-19 in Malaysia, between March 17, 2020 and November 3, 2021, were included in this study. Data retrieved from the national open data database were on the date of death date of confirmed COVID-19 diagnosis (from which the interval between the date of death and confirmation of COVID-19 was determined), vaccination status (no vaccination, 1 dose and 2 doses of vaccination), date of vaccination(s), type of vaccine, comorbidity status (yes or no), nationality (Malaysian or non-Malaysian), age, gender (female or male), place of death (inpatient death or BID), and state [Johor, Kedah, Kelantan, Melaka, Negeri Sembilan, Pahang, Perak, Perlis, Pulau Pinang, Sabah, Sarawak, Terengganu, Wilayah Persekutuan Kuala Lumpur (WP Kuala Lumpur), Wilayah Persekutuan Labuan (WP Labuan), and Wilayah Persekutuan Putrajaya (WP Putrajaya)] (https://github.com/MoH-Malaysia/covid19-public/tree/main/epidemic).

Descriptive analysis was conducted to determine the profile of all the COVID-19 mortality cases. The profiles of inpatient mortality cases and the BID cases were also compared. The trend of COVID-19 mortality cases was demonstrated based on the epidemiological weeks (also known as the Epid Week). A multiple multilevel logistic regression analysis was conducted to investigate the factors associated with places of death: inpatient death was coded as zero and BID cases were coded as one.

TABLE 1 | Distribution of the COVID-19 mortality cases ($N = 29,155$).

		Frequency (*n*)	Percentage (%)
Year	2020	514	1.8
	2021	28641	98.2
State	Johor	3679	12.6
	Kedah	1995	6.8
	Kelantan	1054	3.6
	Melaka	905	3.1
	Negeri Sembilan	1239	4.2
	Pahang	664	2.3
	Pulau Pinang	1611	5.5
	Perak	1130	3.9
	Perlis	118	0.4
	Selangor	9620	33.0
	Terengganu	468	1.6
	Sabah	2540	8.7
	Sarawak	1399	4.8
	W.P. Kuala Lumpur	2563	8.8
	W.P. Labuan	149	0.5
	W.P. Putrajaya	21	0.1
Age	0–11	70	0.2
	12–17	45	0.2
	18–59	12810	43.9
	60+	16230	55.7
Gender	Female	12391	42.5
	Male	16764	57.5
Malaysian	Non–Malaysian	3703	12.7
	Malaysian	25452	87.3
Comorbidity status	No comorbidity	6779	23.3
	Comorbidity	22376	76.7
Vaccination status	No vaccination	19698	67.6
	1 dose	5339	18.3
	2 doses	4118	14.1
Type of vaccination received ($n = 9457$)	Pfizer	2991	31.6
	Sinovac	5692	60.2
	AstraZeneca	767	8.1
	Others	7	0.1
Place of death	Inpatient death	23252	79.8
	BID	5903	20.2
Interval after confirmed to death (days)	0	8710	29.9
	1–3	4481	15.4
	4–7	5558	19.1
	8–14	6560	22.5
	15–21	2602	8.9
	22–28	764	2.6
	29–35	245	0.8
	36–42	93	0.3
	43–49	57	0.2
	50 above	85	0.3

A multiple multilevel logistic regression model with two levels, individual mortality cases nested within each state, was used as follows:

$$y_{ij} = \alpha_{ij} + \beta_{ij}X_{ij} + \mu_j$$
$$\mu_j \sim N(0, \sigma^2)$$

where y_{ij} was the binary outcome with zero (inpatient death) or one (BID), α_{ij} was an intercept of the equation, and i and j represented the *ith* mortality cases of the *jth* state, respectively. β_{ij} was the coefficient of variables X_{ij} and μ_j was the random effect of state level, which the variation σ^2. The model was set up using MLwiN version 2.25 (the Centre for Multilevel Modelling, University of Bristol), estimated using quasi-likelihood methods. Variables with $p < 0.05$ were retained in the final model. Confounder, multicollinearity between variables, and interaction terms between variables were also checked.

RESULTS

As of November 3, 2021, there were 29,155 COVID-19 mortality cases in Malaysia (**Table 1**). The majority of the cases were from Selangor ($n = 9,620$, 33.0%), the most populous state in the country, followed by Johore (3,679, 12.6%) and WP Kuala Lumpur (2,563, 8.8%), both of which are also major cities, located in the West Coast and Southern Region of Peninsular Malaysia, respectively. The majority of the deceased

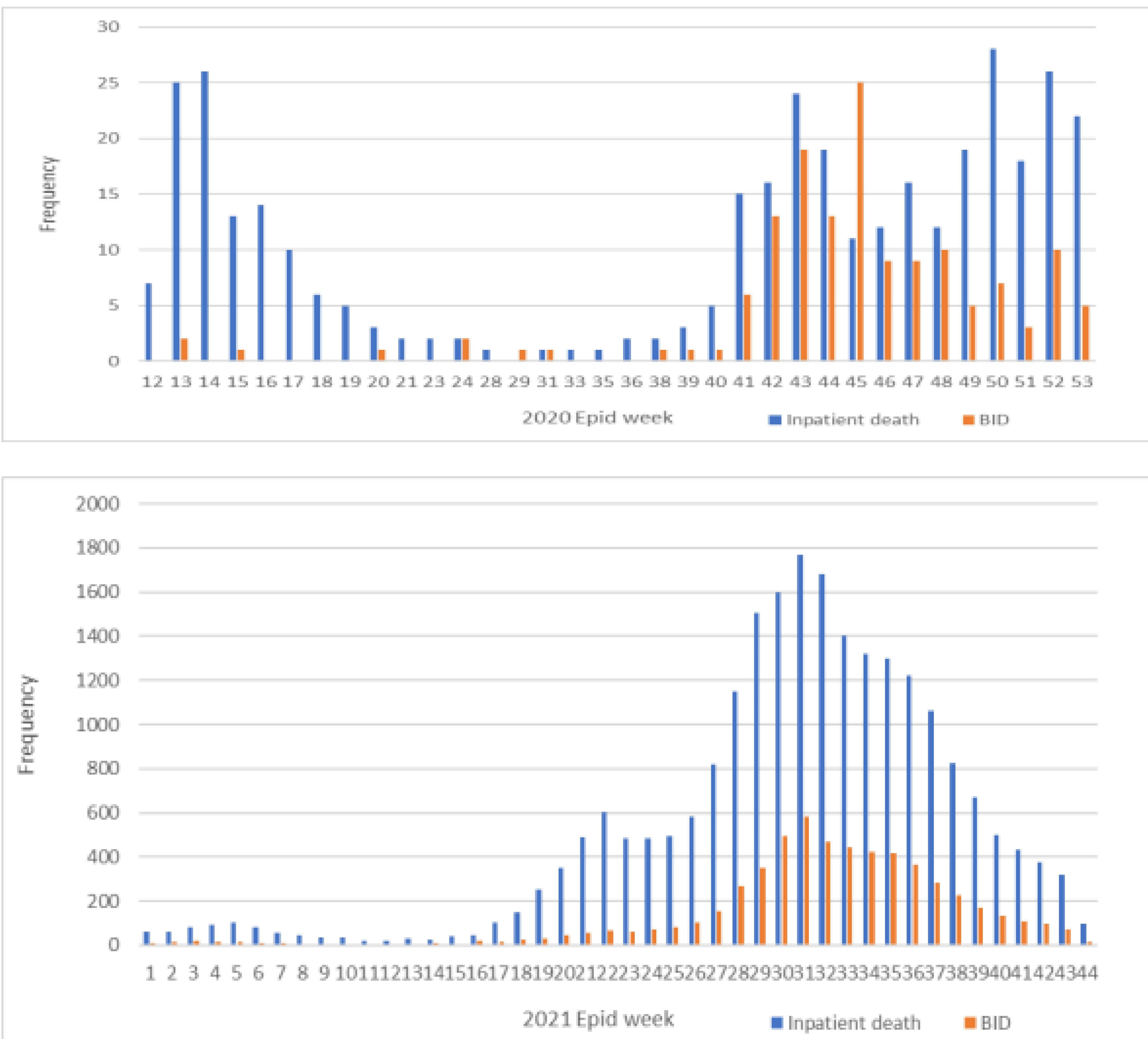

FIGURE 1 | Distribution of inpatient death and the brought-in-dead (BID) COVID-19 mortality cases between the years 2020 and 2021.

were not vaccinated (19,698, 67.6%), had one or more comorbidity (22,376, 76.7%), and were aged 60 years and more (16,230, 55.7%).

Of the total mortality cases, 20.2% of them were BID cases (5,903). The majority of cases with the interval between the date of death and the confirmation of COVID-19 status ranged between 1 and 14 days (16,599, 57.0%). Of these, 15.4% (4,481) of cases were confirmed as COVID-19 positive between 1 and 3 days, 19.1% (5,558) of cases were confirmed as COVID-19 positive between 4 and 7 days, and 22.5% (6,560) of cases were confirmed as COVID-19 positive between 8 and 14 days. There were 8,710 cases (29.9%) that were confirmed COVID-19 positive on the same date of death. These cases were tested for COVID-19 upon arrival at the hospital, if the status was not already known.

The distribution of inpatient deaths and the BID COVID-19 deaths in the years 2020 and 2021 is shown in **Figure 1**. The majority of the cases were in the year 2021, which peaked between the 30th and 32nd Epid Week (25 July—14 August 2021).

As with the data on the overall COVID-19 death, the majority of BID cases were also noted in Selangor (34.7%) and Kuala Lumpur (11.3%). However, a large number of BID cases was also detected in Sabah (16.7%), which is a state located on the island of Borneo and is one of the less developed and has lower socioeconomic status compared to the other states in the country.

The adult BID cases were of higher proportion among those in the younger age group, where more than half (54.5%) were aged 18–59 years, compared to those in the same age group who died in hospital (41.3%). The inpatient COVID-19 deaths were more common among patients aged 60 years or more, who constituted almost 60% of these deaths. Similarly, in the pediatric age group (0–11 years), the proportion of those who were BID was higher than those who died at the hospital (0.4 vs 0.2%).

The data also showed that more than 60% of BID cases had comorbidities compared to a higher proportion of inpatient death cases with comorbidities (80.8%). Approximately one-third (31.9%) of the BID cases were non-Malaysians. The majority of the BID cases (79.3%) were confirmed as COVID-19 at the same date of death (**Table 2**).

The univariate multilevel logistic regression model was used to investigate the association of each independent variable associated with the probability of BID. The results showed that associations between all the independent variables and BID status were statistically significant, except for gender (**Table 3**). All the variables were tested in multiple multilevel logistic regression model to identify the factors associated with the probability to BID, using the stepwise variable selection method. Variable with $p > 0.05$ was not retained in the multiple multilevel logistic regression model.

The results show that higher probabilities of BID were related to the young age groups (0–11 and 18–59 years), being non-Malaysian, and having no known comorbidities, whereas lower probabilities of BID were related to having had at least one dose or two doses of COVID-19 vaccine and having the longer interval between death and confirmation of COVID-19 diagnosis (**Table 4**).

DISCUSSION

Characteristics of COVID-19 Deaths in Malaysia

In Malaysia, the prevalence of COVID-19 cases was higher in the year 2021 compared to the previous year. This higher prevalence in 2021 compared to the year 2020 was probably due to the year-long movement control order in 2020 compared to a shorter duration of movement control order in 2021. For example, between March 18, 2020 and May 3, 2020, the Malaysian population underwent a full lockdown. People were strictly ordered to stay home, and schools, businesses, and offices were closed. Only essential services were allowed during this period. Following this period, the Conditional Movement Control Order (CMCO) was implemented from May 4, 2020 to June 9, 2020 and then the Recovery Movement Control Order (RMCO) was implemented from June 10, 2020 to March 31, 2021, during which time movement of the people was gradually eased and everyday activities returned to almost normal. In contrast, during 2021, there was only one period of total lockdown, which was between June 1, 2021 and June 28, 2021, following which the country resorted to having the National Recovery Plan (NRP) from June 15, 2021 to December 31, 2021, when again social and business activities were almost as per usual. Therefore, in the year 2021, the contact rate between the population of Malaysia was higher compared to the year 2020, hence this could explain why the number of cases was higher in 2021.

The results of this study also noted that most of the COVID-19 cases were reported in the central region of Malaysia (Selangor, Kuala Lumpur, and Putrajaya) (8). This geographical preponderance could be because the central region is the most developed and populous area of the country. According to the Department of Statistics, Malaysia, Selangor are the most populous states, while the most densely populated states are Kuala Lumpur (7,188 persons per square kilometer) and WP Putrajaya (2,354 persons per square kilometer). Higher population density can result in an increased contact rate, hence explaining the high incidence of COVID-19 in Selangor, Kuala Lumpur, and Putrajaya. A recent local study also showed that the central region had the strongest correlation between the COVID-19 cases and population density ($r = 0.912$; 95% CI 0.911, 0.913; $p < 0.001$). The propagation effect and the spread of disease were greater in urbanized districts or cities (9). Understandably, due to the high prevalence of cases, the number of deaths due to COVID-19 was also highest in these three states (Selangor, Kuala Lumpur, and Putrajaya) (1, 2, 8).

The results of this study showed that the proportion of patients who died from COVID-19 was not vaccinated, concurring with other studies (11, 12). Indeed, vaccination plays one of the most significant roles in reducing the infection risk and the severity of COVID-19 in humans (10, 13, 14). Malaysia began a massive nationwide COVID-19 vaccination program on February 2, 2021. The vaccination program, however, was not compulsory. Citizens and people living in Malaysia were encouraged to get themselves vaccinated. Civil servants and healthcare workers were highly encouraged, as they were workers

TABLE 2 | Comparison characteristics of mortality cases between inpatient death and brought–in–dead (BID).

Variable		Place of death				Total	χ^2 value	P-value
		Inpatient death		BID				
		n	%	n	%			
Year	2020	369	1.6	145	2.5	514	20.547	<0.001*
	2021	22883	98.4	5758	97.5	28641		
State	Johor	3213	13.8	466	7.9	3679	975.180	<0.001*
	Kedah	1689	7.3	306	5.2	1995		
	Kelantan	827	3.6	227	3.8	1054		
	Melaka	789	3.4	116	2.0	905		
	Negeri Sembilan	1107	4.8	132	2.2	1239		
	Pahang	581	2.5	83	1.4	664		
	Pulau Pinang	1260	5.4	351	5.9	1611		
	Perak	981	4.2	149	2.5	1130		
	Perlis	112	0.5	6	0.1	118		
	Selangor	7570	32.6	2050	34.7	9620		
	Terengganu	419	1.8	49	0.8	468		
	Sabah	1557	6.7	983	16.7	2540		
	Sarawak	1125	4.8	274	4.6	1399		
	W.P. Kuala Lumpur	1895	8.1	668	11.3	2563		
	W.P. Labuan	107	0.5	42	0.7	149		
	W.P. Putrajaya	20	0.1	1	0.0	21		
Age	0–11	44	0.2	26	0.4	70	354.561	<0.001*
	12–17	33	0.1	12	0.2	45		
	18–59	9595	41.3	3215	54.5	12810		
	60+	13580	58.4	2650	44.9	16230		
Gender	Female	9904	42.6	2487	42.1	12391	0.413	0.520
	Male	13348	57.4	3416	57.9	16764		
Malaysian	Non-Malaysian	1820	7.8	1883	31.9	3703	2460.288	<0.001*
	Malaysian	21432	92.2	4020	68.1	25452		
Comorbidity status	No comorbidity	4463	19.2	2316	39.2	6779	1059.51	<0.001*
	Comorbidity	18789	80.8	3587	60.8	22376		
Vaccination status	No vaccination	15414	66.3	4284	72.6	19698	10.488	<0.001*
	1 dose	4511	19.4	828	14.0	5339		
	2 doses	3327	14.3	791	13.4	4118		
Type of vaccination received ($n = 9457$)	Pfizer	2488	31.7	503	31.1	2991	17.349	0.001*
	Sinovac	4669	59.6	1023	63.2	5692		
	AstraZeneca	675	8.6	92	5.7	767		
	Others	6	0.1	1	0.1	7		
Interval after confirmed to death (days)	0	4029	17.3	4681	79.3	8710	8762.688	<0.001*
	1–3	4007	17.2	474	8.0	4481		
	4–7	5237	22.5	321	5.4	5558		
	8–14	6308	27.1	252	4.3	6560		
	15–21	2530	10.9	72	1.2	2602		
	22–28	733	3.2	31	0.5	764		
	29–35	215	0.9	30	0.5	245		
	36–42	86	0.4	7	0.1	93		
	43–49	43	0.2	14	0.2	57		
	50 above	64	0.3	21	0.4	85		

$P < 0.05$; χ^2 value, chi square test value.

TABLE 3 | Factors associated with probability to BID using the univariate multilevel logistic regression model.

Variable	Unadjusted coefficient	SE	Crude OR	95% CI of OR		P–value
Vaccination status						
No vaccination	Ref.					
1 dose	−0.480	0.045	0.619	0.567	0.676	<0.001*
2 doses	−0.201	0.047	0.818	0.746	0.897	<0.001*
Age						
18–59	0.531	0.031	1.701	1.600	1.807	<0.001*
0–11	0.954	0.263	2.596	1.550	4.347	<0.001*
12–17	0.582	0.353	1.790	0.896	3.575	0.099
60+	Ref.					
Gender						
Female	Ref.					
Male	0.001	0.031	1.001	0.942	1.064	0.974
Malaysian						
No	1.622	0.039	5.063	4.691	5.465	<0.001*
Yes	Ref.					
Comorbidity status						
No comorbidity	0.955	0.033	2.599	2.436	2.772	<0.001*
Comorbidity	Ref.					
Interval after confirmed to death (days)[a]						
1–3	Ref.					
4–7	−0.644	0.078	0.525	0.451	0.612	<0.001*
8–14	−1.074	0.083	0.342	0.290	0.402	<0.001*
15–21	−1.420	0.133	0.242	0.186	0.314	<0.001*
22–28	−1.042	0.198	0.353	0.239	0.520	<0.001*
29–35	0.107	0.213	1.113	0.733	1.690	0.615
36–42	−0.363	0.408	0.696	0.313	1.548	0.374
43–49	1.084	0.318	2.956	1.585	5.514	0.001*
50 above	1.053	0.264	2.866	1.708	4.809	<0.001*

$P < 0.05$, SE, Standard Error; CI, Confidence Interval; OR, Odd Ratios; Ref, Reference group.
[a] *There was 8710 cases (29.9%) had the same date of confirmed positive and date of death, which might be these cases were tested COVID−19 upon arrival at the hospital. Therefore, interval between actual confirmed positive with death date remain unknown and were not included in the analysis.*

of the essential services group. People who had contraindications for the vaccine, such as being allergic to the vaccine or its components, were exempted from this campaign. Although COVID-19 vaccination was not compulsory, those who have been vaccinated were given several privileges such as the ability to do interstate traveling or attend congregational prayers at religious sites. The COVID-19 vaccines in Malaysia were administered free of charge at numerous vaccination centers nationwide. In remote areas of the country or among people with disabilities and poor access, mobile vaccination teams were deployed to deliver the vaccines at home. Vaccination was also given at workplaces such as factories. The program was a success because by October 10, 2021, just 8 months after it began, approximately 90% of the adult population had received at least one dose of the COVID-19 vaccine. Consequently, the number of COVID-19 deaths decreased dramatically. Nonetheless, despite the good coverage of the vaccination program, there were still individuals who were not vaccinated against COVID-19 and these individuals make up the majority of the BID cases in Malaysia.

The data also showed that the majority of patients with COVID-19 in Malaysia had comorbidities and were among the elderly, both the findings concur with other global studies (8, 11, 15, 16). Many studies have demonstrated that people with diabetes, hypertension, obesity, and the elderly are vulnerable to COVID-19 (8, 11, 15, 16). As Malaysia is one of the countries with a high prevalence of non-communicable diseases [the prevalence of diabetes in the population was 36.6%, hypertension (30.0%), high cholesterol (38.0%), one in four people were physically not active, and one in two people was overweight or obese (17)], it could explain why those who had comorbidities make up a large proportion of those who died from COVID-19 in Malaysia during this study period.

Brought-in-Dead Cases in Malaysia

Of the mortality cases during this study period, one in five (20%) were BID cases, the majority had no history of COVID-19 vaccination, non-Malaysian, were aged 18–59 years, and had no comorbidities.

TABLE 4 | Factors associated with probability to BID using the multiple multilevel logistic regression model.

Variable	Adjusted coefficient	SE	Adjusted OR	95% CI of OR		P–value
Intercept	−2.540	0.058				
Malaysian						
No	0.939	0.051	2.557	2.314	2.826	<0.001*
Yes	Ref.					
Vaccination status						
No vaccination	Ref.					
1 dose	−0.203	0.052	0.816	0.737	0.904	<0.001*
2 doses	0.076	0.055	1.079	0.969	1.202	0.167
Age						
18–59	0.198	0.040	1.219	1.127	1.318	<0.001*
0–11	0.639	0.327	1.895	0.998	3.596	0.051
12–17	0.494	0.428	1.639	0.708	3.792	0.248
60+	Ref.					
Comorbidity status						
No comorbidity	0.707	0.042	2.028	1.868	2.202	<0.001*
Comorbidity	Ref.					
Interval after confirmed to death (days)[a]						
1–3	Ref.					
4–7	−0.635	0.078	0.530	0.455	0.617	<0.001*
8–14	−1.069	0.083	0.343	0.292	0.404	<0.001*
15–21	−1.423	0.132	0.241	0.186	0.312	<0.001*
22–28	−1.05	0.194	0.350	0.239	0.512	<0.001*
29–35	0.098	0.213	1.103	0.727	1.674	0.645
36–42	−0.364	0.4	0.695	0.317	1.522	0.363
43–49	1.125	0.321	3.080	1.642	5.779	<0.001*
50 above	0.993	0.269	2.699	1.593	4.573	<0.001*

$P < 0.05$; SE, Standard Error; CI, Confidence Interval; OR, Odd Ratios; Ref, Reference group. Random effect for state level: 0.279 (0.031), stepwise variable selection method.
[a]There was 8710 cases (29.9%) had the same date of confirmed positive and date of death, which might be these cases were tested COVID−19 upon arrival at the hospital. Therefore, interval between actual confirmed positive with death date remain unknown and were not included in the analysis.

The high prevalence of BID may be due to several factors, one of which could be the home quarantine measures. In Malaysia, at the beginning of the COVID-19 pandemic, all patients with COVID-19 were hospitalized. However, as the number of cases increased and the resources were limited, home quarantine for stable cases was implemented. The Malaysian government used the following classification of the COVID-19 clinical stages: (1) asymptomatic; (2) symptomatic, no pneumonia; (3) symptomatic, pneumonia; (4) symptomatic, pneumonia, and requiring supplemental oxygen; and (5) critically ill with multiorgan involvement. Individuals diagnosed with COVID-19 categories 1 and 2 were allowed to be quarantined out-of-hospital, either at their own homes, or, if the home situation is not suitable, the individual can be lodged at mass quarantine centers. Those who were hospitalized comprised patients in categories 3–5. The out-of-hospital quarantine measures began in early 2021, when the COVID-19 Assessment Centers (CACs) were setup in every district to assess which COVID-19 cases can undergo isolation at home. As of January 22, Malaysia had established 213 CACs nationwide (18). COVID-19 home isolation criteria include: the case is not displaying any COVID-19 symptoms, the case does not belong to the high-risk group (e.g., senior citizens, patients with chronic illness), the case has a suitable caretaker, and the residence is suitable for self-isolation. In addition, there were basic guidelines for patients placed under home isolation: the patient must stay alone in separate rooms, preferably with an attached toilet. If toilets must be shared, all the surfaces touched by the patient must be cleaned thoroughly, windows should be opened to ensure proper ventilation, and cases should not receive any visitors. In addition, face-to-face interactions with others in the household must be avoided and the person placed under isolation must report their status daily through the nation's COVID-19 mobile phone application called MySejahtera or to the medical officer in charge.

After the nationwide home quarantine measures, several factors could have led to the high prevalence of BID. For example, ignorance of the patient and/or the family members/caregivers of the COVID-19 disease progression could be a contributing factor. This ignorance may have made them unaware of the danger signs of COVID-19 and, consequently, succumbed to the infection at home, instead of going to the hospital. Another possibility was that the patient may not have known how to get to the hospital when the symptoms got worse, for example, not knowing that he can call for an ambulance for help. Another possible factor was that young patients did not know that they suffered from a chronic disease such as diabetes or hypertension and, hence, when they were infected with the COVID-19 virus, the patient deteriorated very quickly and did not get to the hospital in time. Inappropriate or delayed healthcare-seeking behavior has been shown to reduce the chances of getting immediate treatment, resulting in unfavorable outcomes (19).

The results of this study also showed that the majority of BID cases in Malaysia during this study period were among those who were relatively young (18–59 years old) similar to another nationwide study in the USA, which found that the percentage of out-of-hospital deaths among the elderly was low (only 33%) (18). This phenomenon could be because elderly patients were mostly hospitalized. Nonetheless, it is unclear exactly why a large proportion of BID victims in Malaysia are younger.

The data showed that non-Malaysians were more likely to be BID compared to Malaysians. Non-Malaysians can be categorized into legal vs. illegal workers/migrants. Legal workers, including students, are usually covered by medical insurance and are usually free to travel within the country without fear of getting arrested or detained. However, workers who are in the country illegally may not have any financial coverage for medical care and they are usually afraid of traveling albeit to a medical facility for fear of being arrested or detained. To address these issues, in January 2020, the Ministry of Health, Malaysia indicated that migrant workers who were suspected of positive COVID-19 or with close contact with patients with COVID-19 were exempted from paying the fees (i.e., registration, examination, treatment, and ward fees) at government facilities. In addition, in March 2020, the government assured that undocumented migrant workers who were seeking care and medical test at government health facilities will not be arrested and detained (20). However, in May 2020, hundreds of undocumented migrant workers and refugees were arrested in a massive raid operation conducted in Kuala Lumpur where they were rounded up and subsequently detained in immigration detention centers (21). These turn of events could have contributed to these migrant workers not coming forth to the hospital, if their condition deteriorated. In addition, access barriers to healthcare services could have contributed to a high probability of BID among non-Malaysians. A local study by Loganathan, Rui, Ng, and Pocock (2019) found that healthcare services in Malaysia are often inaccessible to migrant workers due to financial constraints, the need for legal documents such as valid passports and work permits, discrimination and xenophobia, physical inaccessibility, and employer-related barriers. In addition, language barriers may affect the quality of care received by migrant workers, by inadvertently resulting in medical errors, while preventing them from giving truly informed consent (22).

As far as the author is aware, this is the first study comparing the characteristics of inpatient deaths and BID cases using national data in Malaysia. Apart from highlighting the factors associated with the higher likelihood of BID, it is also important to emphasize that the percentage of BID cases in Malaysia during this period was higher than those reported in the USA and the UK (4%−8%) as mentioned earlier (1, 6, 7). The high percentage of BID cases is alarming and calls for urgent attention by the government, as it can signal the presence of gaps or weaknesses in the country's health system, either in the upstream state (access to vaccination) or downstream (access to medical care after being infected with COVID-19). Further studies should be conducted to explore in more depth the factors contributing to BID cases.

There are several limitations to this study. First, the comorbidity status of certain BID cases was not readily known, hence rendering the prevalence of comorbidity in the BID sample lower than that of the inpatient deaths. Second, it was not apparent in the database used in this study, whether the positive diagnosis of COVID-19 among the cases was done before or after postmortem examination. Hence, more detailed investigations on the characteristics of the BID and inpatient death cases should be carried out in the future to enhance an understanding of why BID occurred. This study is descriptive and could not show any causal relationship between the variables analyzed. Last but not least, the exogenous variable such as the policy of COVID-19 and hospital-related variables is suggested to include in the analysis, which might affect the BID occurred.

CONCLUSION

One in five COVID-19 deaths in Malaysia between March and November 2021 was brought-in-dead (BID) cases. These cases were more likely to be among the younger age group, having no comorbidities, non-Malaysian, not vaccinated, and the interval between the date of death and diagnosis.

This high prevalence of BID is an alarming public health issue, which needs urgent attention by all the parties involved in the management of patients with COVID-19, namely, the patients themselves, the patients' families and caregivers, the community, healthcare workers, and even non-governmental organizations. Based on the findings of this study, there is a need to increase the intensity of the vaccination campaign, address any issues faced by non-citizens concerning COVID-19 management in- and out-of-hospital, increase the awareness of signs and symptoms of worsening COVID-19 among the population, emphasize the significance of self-monitoring among the patients especially those who undergo home quarantine, and determine the potential gaps in the health system that may contribute to their increased risk of deaths.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here:

github.com/MoH-Malaysia/covid19-public; https://github.com/CITF-Malaysia/citf-public/tree/main/vaccination.

AUTHOR CONTRIBUTIONS

Conceptualization and writing—reviewing and editing: PYL, SAM, SMS, HKS, AZFA, and AM. Methods: PYL, SAM, SMS, HKS, and AZFA. Formal analysis: PYL, SAM, and AM. Writing—original draft preparation: PL and AM. All the authors have read and agreed to the published version of the manuscript.

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Disease Characteristics, Care-Seeking Behavior, and Outcomes Associated With the Use of AYUSH-64 in COVID-19 Patients in Home Isolation in India: A Community-Based Cross-Sectional Analysis

***Narayanam Srikanth*[1], *Adarsh Kumar*[1], *Bhogavalli Chandrasekhararao*[1], *Richa Singhal*[1], *Babita Yadav*[1], *Shruti Khanduri*[1], *Sophia Jameela*[1]*, *Amit Kumar Rai*[1], *Arunabh Tripathi*[1], *Rakesh Rana*[1], *Azeem Ahmad*[1], *Bhagwan Sahai Sharma*[1], *Ankit Jaiswal*[1], *Rajesh Kotecha*[2] and *State Level Collaborators*[2]**

[1] *Central Council for Research in Ayurvedic Sciences, New Delhi, India,* [2] *Ministry of Ayush, Government of India, New Delhi, India*

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***Correspondence:**
Sophia Jameela
drsophia9754@gmail.com

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Background: During the second wave of the COVID-19 pandemic in India, the Ministry of Ayush conducted a community study to provide therapeutic care to patients with asymptomatic, mild, and moderate COVID-19 in home isolation based on the empirical evidence generated on the efficacy of AYUSH-64 in COVID-19.

Objective: To document disease characteristics, care-seeking behavior, and outcomes in patients with asymptomatic, mild, or moderate COVID-19 in home isolation who used AYUSH-64 for COVID-19.

Methods: Cross-sectional analysis of the data generated through a community study conducted in India from 08 May to 31 August 2021 was performed to study the disease characteristics, care-seeking behavior during home isolation, clinical outcomes, adverse events, and the association between various risk factors and clinical recovery during the study period. The data were collected through semi-structured questionnaires, available in electronic data collection format at the baseline, 7, 14, and 21 days. A logistic regression was performed to explore the relationship between relevant variables and clinical recovery.

Results: Data from 64,642 participants were analyzed for baseline assessment, and final analysis was done for 49,770 participants. The mean age of the enrolled participants was 38.8 ± 11.7 years, and 8.4% had co-morbidities. AYUSH-64 was utilized as an add-on to the standard care by 58.3% of participants. Comparable clinical outcomes were observed in participants utilizing AYUSH-64 either as a standalone or as an add-on to standard care, in terms of clinical recovery, disease progression, the requirement for oxygen supplementation, hospitalization, ICU admission, and need for ventilator support. Younger age, having no co-morbidities or substance abuse, and having been vaccinated were associated with early clinical recovery than those who were older and not vaccinated.

Conclusions: The study findings suggest that AYUSH-64 use, either standalone or as an adjunct to standard care, in asymptomatic, mild, or moderate COVID-19 is associated with good clinical outcomes. Ayush services and interventions can be effectively integrated into the mainstream public health architecture to serve public health goals.

Keywords: Ayurveda, Ayush, AYUSH-64, COVID-19, community study, home isolation

INTRODUCTION

The global impact of COVID-19 triggered an unprecedented and heterogeneous response from governments, and the ability of governments to act decisively and effectively was cast under public scrutiny. The timely allocation of infrastructure, human resources, and budget across different sectors and beneficiaries took a considerable risk-benefit analysis to simultaneously balance public health and economic considerations (1). Owing to the catastrophic pandemic nature and its high transmissibility, the majority of the countries targeted effective containment strategies and measures to equip themselves for effectively managing the burden of hospitalization and mortality associated with COVID-19. While quarantines, lockdowns, prophylactic medical care, and social distancing played a critical role in reducing the disease transmission, the stress on the health care system was too large, especially in countries with modest resources and health care capacity. Ensuring adequate capacity and resources to provide rapid and effective health care to the masses had a substantial economic impact on developing nations. The most effective way of handling the pandemic has been a matter of great discourse on its social, ethical, and economic aspects. It may have a potential role in policy-making decisions when it leads to community-based mass interventions. India has a rich heritage of traditional systems of medicine, including Ayurveda, Yoga, Unani, Siddha, and Homeopathy (currently regulated through the Ministry of Ayush in India), which are effectively utilized in delivering a pluralistic type of health care. The Ministry of Health and Family Welfare (MoHFW) has issued proactive guidelines from time to time in line with the global approaches and national protocol to tackle this unprecedented pandemic, and the Ministry of Ayush (MoA) has issued guidelines for the prevention and management of COVID-19 (2).

AYUSH-64 is a poly-herbal Ayurveda formulation developed by the Central Council for Research in Ayurvedic Sciences (CCRAS), MoA, Government of India, and was repurposed for the symptomatic management of COVID-19 based on the evidence generated through a clinical study on Influenza-like illness (ILI) and also a molecular docking study that revealed that phytoconstituents isolated from AYUSH-64 demonstrated anti-viral activity against SARS-CoV-2 (3, 4). The experimental studies also demonstrated immunomodulating and anti-inflammatory activities of the constituents of AYUSH-64 (5–10). Based on the clinical evidence on the therapeutic potential of AYUSH-64 in COVID-19 generated through multiple clinical trials, AYUSH-64 was positioned as a potential adjunct to standard care in COVID-19 management (11–16). It was recommended for the management of asymptomatic and mild COVID-19 in the National Clinical Management Protocol based on Ayurveda and Yoga issued by the MoA, India (2).

Pre-existing health inequalities and the burden of communicable and non-communicable diseases in India compelled the diversification of health care resources to contain COVID-19, and with the call for lockdown, health care services were prioritized for COVID-19 care. The lack of pandemic preparedness strategies resulted in all preventive and curative services, and services requiring a continuum of care, coming to a halt in the public sector (17). With the view to ensure some measure of equitable access, as well as to reduce the hospital burden in COVID-19 patients, the MoA undertook an initiative to dispense AYUSH-64 at the doorstep through Ayush health care centers in patients with asymptomatic, mild, or moderate COVID-19 who were in home isolation along with the standard care. This decentralized, participatory people-centered program was designed and executed by establishing local partnerships and networks to obtain maximum penetration within the community. The involvement of local volunteers, Ayurveda professionals, including doctors, medical students, and others, and establishing a satisfactory framework for implementation were the key highlights.

The primary objective of the study was to document disease characteristics, such as disease progression, disease severity, and clinical outcomes in asymptomatic, mild, or moderate COVID-19 patients in home isolation who used AYUSH-64. The secondary objectives of the study were to assess the care-seeking behavior (AYUSH-64 as stand-alone/or with standard care) and adverse events reported. The association between various demographic and clinical variables with clinical recovery at day 21 and the factors that may have a role in the participant's preference for using AYUSH-64 either as a standalone or as an adjunct to standard care was also included as a study objective.

MATERIALS AND METHODS

Study Design

This is a cross-sectional analysis of data generated through a community-based distribution of Ayurvedic intervention, AYUSH-64, as standalone or as an add-on to standard care for patients patients with asymptomatic, mild or moderate COVID-19 disease in home isolation as per the guidelines issued by the MoHFW, India (18).

Study Setting

The community-based distribution was implemented nationwide from 08 May 2021 to 31 August 2021 through 87 Ayush research and academic institutes across India.

Study Participants

Patients with asymptomatic, mild, or moderate COVID-19, in the age group 18–60 years, with SpO_2 levels, ≥ 94%, in home isolation as per the national guidelines, and provided consent were the study participants. The diagnosis of COVID-19 was based on a positive RT-PCR/ RAT assay or based on the presence of symptoms suggestive of clinically compatible COVID-19 illness (at least one of the following symptoms: fever, cough, difficulty in breathing, myalgia, headache, sore throat, new olfactory or taste disorder, or diarrhea) (19), or in home isolation along with any of the following criteria, i.e., those residing or working in a setting with a high risk of transmission of the virus or in an area with community transmission anytime within the 14 days before symptom onset, working in a health setting, history of contact with a probable or confirmed case, or is linked to a COVID-19 cluster.

Patients with COVID-19 in home isolation, requiring oxygen support or with SpO_2 levels below 94%, on immunosuppressive medications, not willing to provide consent or unable to take oral medicines, and pregnant and lactating women were not included.

Informed Consent and Ethical Consideration

The Central Ethics Committee of the CCRAS approved the study. Informed consent was obtained from all the participants who expressed willingness to participate in the study and data collection after adequate information disclosure. Due to the communicability of SARS-CoV-2, limited resources, the need to protect study personnel from infection, the methodology of door-to-door medicine distribution, and the potential for a more extensive spread through fomites such as paper, informed consent was obtained through different methods. In people using a smartphone, the image of the signed consent form was asked to be shared with the study personnel. In the areas without internet coverage or those without a smart phone the content of the study information sheet and consent were shared as an SMS, to which their consent was instructed to be sent as “I agree” or “Yes.” An image of the signed informed consent document was taken without contact from those without access to a mobile. The obtained consent was then printed and stored with other study documents or scanned into the electronic format and stored. In the case of a caregiver visiting the Ayush facility for the collection of AYUSH-64, the signature of the caregiver was obtained in the consent form. Confidentiality was maintained throughout the study, from data collection to the dissemination process.

Framework for Implementation of the Community Study

The framework was built upon the network of Ayush institutes (both research and academic) catering to public health care services under the MoA across India. The CCRAS had designed and implemented the community study aligning with the existing advisories and guidelines issued by the MoHFW and MoA. A total of 203 Ayush professionals, including research officers, academicians, and medical officers from the 87 selected institutes, were identified as nodal officers to devise the distribution plan; establish liaisons with the directorate of health services/COVID-19 cells/ COVID care centers; provide training to non-governmental organizations (NGOs) and study personnel dispensing the medicines on procedures to be followed, systematic data collection, and data entry in electronic formats; and coordinate the daily activities. The coordinating institute also provided training on the modalities of execution and standard operating procedures (SoP) to the nodal officers. Letters seeking cooperation from stakeholders were sent to state authorities, and the nodal officers in the concerned area conducted visits initially with health authorities and local government bodies to garner cooperation and finalize the plans to enable a seamless distribution and data collection. Local NGOs were engaged with dispensing the medicine to the patients with COVID-19 in home isolation, identified through local health care directorates/ COVID-19 response cells, etc. NGOs with broad reach within the community were identified, and volunteers with enough experience and interest in working as part of the community study were contacted to volunteer. Concerned nodal officers trained them through virtual sessions to handle the medicine distribution as per the plan. During the training, the volunteers were made familiar with the methodology to be followed while dispensing AYUSH-64, including physical distancing, sanitization techniques, PPE, and other preventive measures. The medical personnel, such as doctors and nurses in the study team, were also made familiar with the selection of eligible participants and preliminary health and symptom evaluation. All the study personnel were trained on the methodology for getting informed consent, data collection, and data sharing. The baseline data was collected through face-to-face interviews, and the follow-ups on days 07, 14, and 21 were done through telephonic interviews by the study personnel at each nodal institute.

Intervention

Patients with asymptomatic COVID-19 were advised to use two tablets of AYUSH-64 (500 mg each) twice daily with warm water after meals, while symptomatic patients (mild/moderate) were advised to use two tablets of AYUSH-64 (500 mg each) thrice daily. The intervention was advised to be used along with standard conventional care suggested by the MoHFW on clinical management of COVID-19 as per the disease severity status, assessed by the local health care provider (20). Quality-assured AYUSH-64 was procured from GMP certified manufacturer, Indian Medicines Pharmaceutical Corporation Limited (IMPCL) (Batch no.:19-APM-LDA-289; Manufacturing date: May 2021; Expiry date: April 2024). AYUSH-64 is a polyherbal formulation containing *Saptaparna* (*Alstonia scholaris* R. Br.), *Katuki (Picrorhiza kurroa* Royle ex. Benth), *Kiratatikta* (*Swertia chirata* Pexbex. Karst), and *Kuberaksha (Caesalpinia crista* L.).

Data Sources and Data Collection Methods

The requisite information was collected through semi-structured questionnaires designed in consultation with domain experts in English language, to be filled by Ayush practitioners. Due to the community nature of the study, the questionnaire was concise, easily understandable, and structured, utilizing close-ended or dichotomous questions.

The data was collected through four different questionnaires designed for data collection at each time point as per the study design, *viz.*, baseline, day 7, day 14, and day 21.

The e-version of the questionnaire finalized through iterative consultations was made available through Google forms to furnish the data. After obtaining the consent, the field personnel filled the baseline data through direct interviews. The research team at the nodal institutes filled the specific questionnaire at follow-ups through telephonic interviews at the scheduled time points. The participant reports, such as RT-PCR/RAT assay for COVID-19, other laboratory investigations, and consent, were stored electronically.

Outcomes Measures

Primary Outcome

The primary outcome was to document the data on the patient characteristics, such as demographics, vaccination status (recorded as not vaccinated, fully vaccinated, and one dose vaccination done along with the name of vaccine), SARS-CoV-2 testing (whether or not testing was done, the reason for testing, testing method and date of testing), and disease characteristics (days since onset of symptoms, asymptomatic or symptomatic, if symptomatic, disease severity recorded as mild or moderate, and symptoms present). The parameters associated with disease outcomes such as the proportion of participants who attained clinical recovery (criteria of "clinical recovery" defined as normal body temperature, absence of cough or mild cough, absence of dyspnea on routine activity, absence of any other symptom/sign attributed to COVID-19, and recovery should be sustained for at least 48 h as reported by the participant), progression of the disease (from asymptomatic to symptomatic, mild/moderate disease to severe disease), the proportion of participants who achieved SARS-CoV-2 clearance defined as a single negative RAT/RT-PCR assay on day 7, 14, and 21, and the proportion of participants who required hospitalization, mechanical ventilation, oxygen supplementation, or succumbed to disease, were also assessed.

Secondary Outcomes

The care-seeking behavior was assessed as the utilization of AYUSH-64 as standalone (those who were not taking any standard care as per the personal preference) or add-on to standard care, and the incidence of adverse events reported was included as secondary outcome measures. The association between various risk factors and clinical recovery was also assessed as a secondary outcome measure.

Study Size

Data was generated from 64,642 patients diagnosed with asymptomatic, mild, or moderate COVID-19 in home isolation and who participated in the community study.

Statistical Analysis

The data obtained from the questionnaires were entered into the MS-Excel sheet and were numerically coded. This coded Excel file was then imported into STATA 16.1 (Stata Corp LLC) and used for statistical analysis. The categorical data related to the patient's demographic and disease characteristics are presented as frequency (percentage). Univariate and multivariate logistic regression was performed to explore the relationship between clinical recovery and the other demographic and clinical variables. This regression model included clinical recovery as the dependent variable, and variables like age, gender, substance abuse, co-morbidities, and vaccination status of the patients as dependent variables. The logistic regression analysis results are displayed as odds-ratio (OR) and 95% confidence intervals. A $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Participants

The baseline characteristics of 64,642 participants in home isolation, diagnosed as having asymptomatic, mild, or moderate COVID-19, were documented and analyzed (**Table 1**). Data of only those participants (49,770) who were available for at least any of the scheduled follow-up visits on days 07, 14, or 21 were included in the final analysis. A total of 14,872 participants (23%) who could not be contacted at any of the scheduled follow-ups after the baseline visit were excluded from the analysis. The flow of study is given in **Figure 1.** The mean age of the enrolled participants was 38.8 ± 11.72 years, 37,027 (57.3%) were male and a small proportion of participants (6,560, 10.1%) had reported substance abuse. Overall, 85.9% of the study population reported to have not undergone vaccination for COVID-19. A vast majority of the participants, 49,234 (76.2%) had no history of working in the health sector/COVID-19 hospitals or other occupations that require frequent interaction with the general public and being at risk for contracting the disease. COVID-19 diagnosis in the majority of the study participants was done through a confirmatory RT-PCR test (20,943, 32.4%) or Rapid Antigen Test (20,795, 32.2%). About one-third of the participants were enrolled based on the presence of symptoms suggestive of clinically compatible COVID-19 illness. Among the participants who underwent diagnostic testing (26,787, 64.2%), reported that testing was done due to the onset of symptoms, while 10,184 (24.4%) had reported a chance of exposure with positive cases. The majority of the participants (46,208, 71.5%), were having the symptomatic disease at baseline,

TABLE 1 | Baseline characteristics of the participants.

Characteristics (n = 64,642)		***n* (%)**
Age (in years): Mean ± SD		38.8 ± 11.72
Gender	Male	37,027 (57.3%)
Substance abuse	Present	6,560 (10.1%)
Vaccination status	Single dose/fully vaccinated	9,067 (14.1%)
Participants at higher risk of contracting the disease	General health worker/Occupation requiring frequent social/public interaction/ COVID frontline worker	15,408 (23.8%)
Co-morbidities	Present	3,644 (5.6%)
Method for diagnosis of COVID-19 disease	Positive RT-PCR/Rapid antigen assay for COVID-19	41,738 (64.6%)
	On the basis of COVID-19 like symptoms	22,904 (35.4%)
Reason for testing, (n = 41,738)	Chance of exposure	10,184 (24.4%)
	Onset of symptoms	26,787 (64.2%)
	Random testing (testing done in health camps, offices, stations, airports)	4767 (11.5%)
Symptomatic participants		46,208 (71.5%)
Disease severity (n = 46,208)	Mild	39,667 (85.9%)
	Moderate	6,541 (14.1%)
Participants taking conventional Standard Care along with AYUSH-64		37,674 (58.3%)
	Methylprednisolone	606 (0.9%)
	Dexamethasone	1,138 (1.8%)
	Inhalational Budesonide	830 (1.3%)
	Tab. Ivermectin	6,516 (10.1%)
	Tab. Paracetamol	28,052 (43.4%)
	Tab. Azithromycin	17,197 (26.6%)
	Tab. Vitamin C	28,505 (44.1%)
	Tab. Zinc	20,402 (31.6%)

among which, 39,667 (85.9%), were categorized as having mild COVID-19. Overall, 5,433 (8.4%) participants reported having co-morbidities, among which diabetes mellitus and hypertension were the most common. More than half of the participants (37,674, 58.3%) used AYUSH-64 as an add-on to the standard care and 41.7% preferred to use AYUSH-64 as a stand-alone intervention for the management of COVID-19. Vitamin C (44.1%) and zinc (31.6%) were the most common supplements used, while paracetamol (43.4%) and azithromycin (26.6%) were the most common therapeutic interventions utilized.

Geographical Coverage

The community study was executed in 27 States and 5 Union Territories across India through the identified 87 nodal points across the country, which indicates that the community approach was implemented as envisaged by the MoA. About one-third of the participants were enrolled from Kerala (20,419, 31.6%) and Andhra Pradesh (4,856, 7.5%) in the southern zone, followed by Maharashtra (3,704, 5.7%) in the western zone, Odisha (3,567, 5.5%) in the eastern zone, and Uttar Pradesh (3,489, 5.4%) in the central zone (**Supplementary File 1**).

Clinical Recovery and Disease Severity

Among the symptomatic participants who could be contacted for follow-ups till day 21, 35,587 (96.0%) recovered completely and only 1,474 (4.0%) participants remained symptomatic. Among those who used AYUSH-64 as a standalone care, 11,846 (95.2%) reported having attained clinical recovery, while 23,741 (96.5%) underwent complete recovery among the AYUSH-64 add-on users. Among the 25.5% of the asymptomatic participants, only 1,321(10.4%) developed symptoms in the course of the study (**Table 2**). Cough (63.1%), fever (54.7%), fatigue/tiredness (53.9%), headache (47.8%), body ache (47.7%), and sore throat (43.1%) were the most common symptoms reported by the study participants, as depicted in **Supplementary Table 1**. A good proportion of participants also reported symptoms such as (24.4%), loss of taste (22.7%), rhinitis (14.5%), and loss of appetite (13.4%). Psychological symptoms such as anxiety (5.6%) and insomnia (6.7%) were reported as symptoms at baseline in a few participants. In the participants who did not undergo complete clinical recovery, the residual symptoms reported were fatigue (2.4%) and cough (1.2%).

Clinical Outcomes in Terms of SARS-CoV-2 Clearance

It was observed that only 8,232 participants (16.54%) (among 49,770 utilized for analysis) had undergone a second RT-PCR/

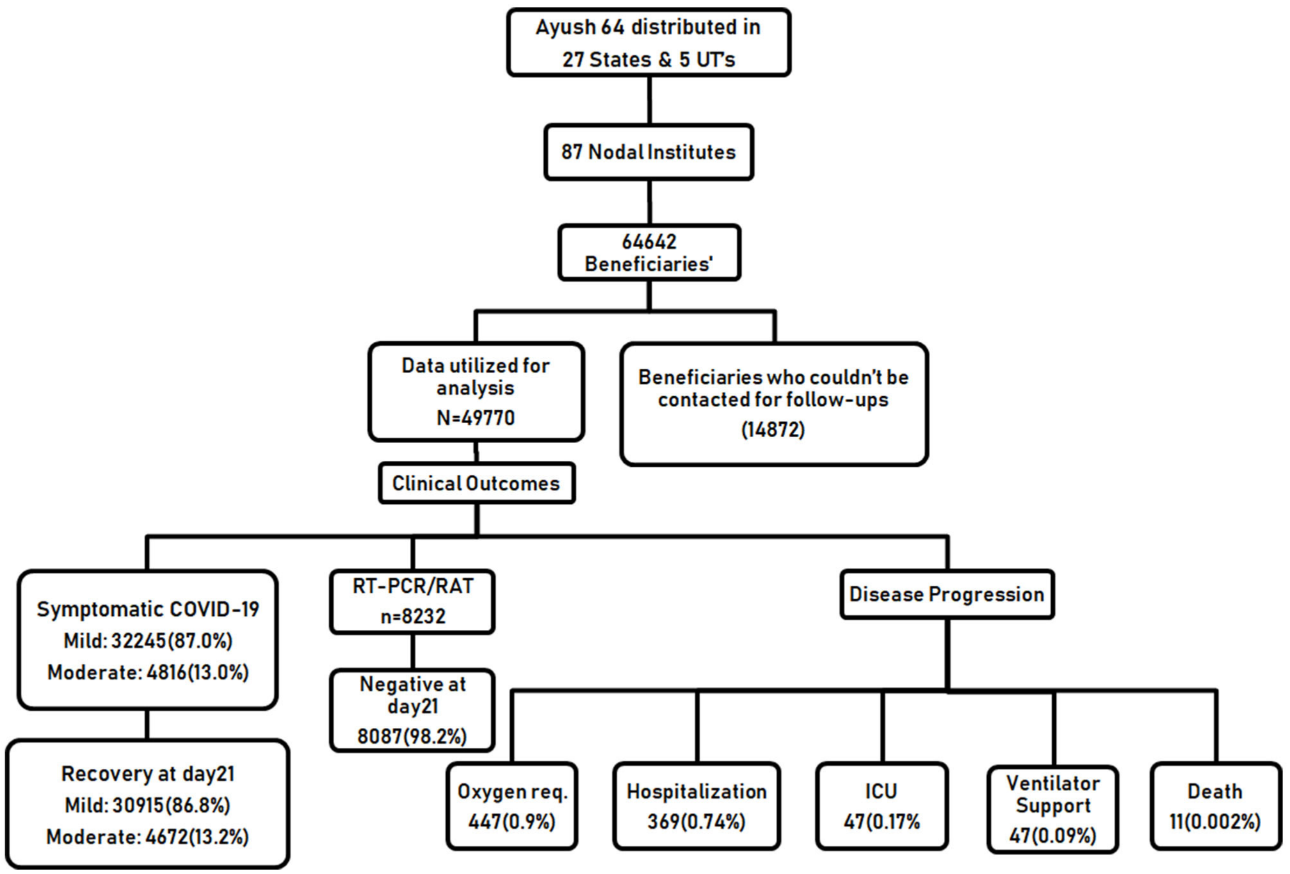

FIGURE 1 | Flow diagram of the study.

Rapid antigen assay for COVID-19 to confirm a negative COVID-19 status. It was observed that both AYUSH-64 standalone users and add-on to standard care users demonstrate comparable outcomes (98.3 and 98.2%, respectively) in terms of attaining SARS-CoV-2 clearance (**Table 2**).

Disease Progression

Only 0.90% (44) of the participants required oxygen supplementation and 0.74% (369) required hospitalization, among which 0.17% (84) required ICU admission and 0.09% (47) required invasive mechanical ventilator support. All the study participants who reported progression of disease depicting a possible poor outcome were followed till clinical recovery to report their disease outcomes. Among the total participants analyzed, 11 deaths (0.0002%) were reported (**Supplementary Table 2**).

Incidence of Adverse Events

A total of 204 adverse events (AE) were recorded in the participants during the entire study duration, among which 171 were reported in the AYUSH-64 add-on users and 33 in the AYUSH-64 standalone users. Diarrhea was the most common AE observed (61/204), followed by gastritis (39/204), acidity (22/204), and abdominal discomfort (22/204). The AE reported in AYUSH-64 standalone users was significantly lesser than that of the add-on users. However, due to the nature of the study and the large study size, causality and relatedness could not be established. Participants on AYUSH-64 as an add-on were also on other interventions, which hindered causality evaluation.

Hypoglycemia (5/204), vertigo (4/204), and vomiting (3/204) were the AE that were reported only in the AYUSH-64 add-on users. The causality and severity of AE with AYUSH-64 use could not be established (**Supplementary Table 3**).

Association of Demographic and Other Clinical Variables With Clinical Recovery

Multivariate logistic regression analysis of risk factors for patients with COVID-19 to attain clinical recovery within 21 days was done using selected five variables, *viz*., age, gender, co-morbidity, substance abuse, and vaccination history, that were predictive of a possible association with the clinical outcome, which is clinical recovery within the study duration of 21 days (**Table 3**). In the multivariate analysis, the factors independently associated with clinical recovery in 21 days were age (OR 0.82, 95%CI 0.73–0.91), gender (OR 0.94, 95% CI, 0.85–1.05), co-morbidities (OR 1.55, 95% CI, 1.33–1.82), substance abuse (OR 1.21 95% CI 1.03–1.42), and having

TABLE 2 | Status of RT-PCR/RAT assay and clinical recovery of participants during the study.

Status of the participants at baseline (n = 49,770)	Status during the study duration of 20 days	AYUSH-64 as stand alone	AYUSH-64 with standard care	Total
Symptomatic (n = 37061, 74.5%)	Turned asymptomatic (recovered from illness)	11,846 (95.2)	23,741 (96.5)	35,587 (96.0)
	Remain symptomatic	602 (4.8)	872 (3.5)	1,474 (4.0)
Total		12,448	24,613	37,061
Asymptomatic (n = 12709, 25.5%)	Turned symptomatic (disease progression)	686 (9.7%)	635 (11.2%)	1,321 (10.4%)
	Remain asymptomatic	6,367 (90.3%)	5,021 (88.8%)	11,388 (89.6%)
Total		7,053	5,660	12,709
Participants with negative RT-PCR assay		2,655 (98.3%)	5,432 (98.2%)	8,087 (98.2%)
Participants with positive RT-PCR assay		46 (1.7%)	99 (1.8%)	145 (1.8%)
Total[#]		2,701	5,531	8,232

[#]Participants who underwent RAT / RT-PCR assay for COVID-19 again during the study period.

TABLE 3 | Association between demographic and clinical variables with clinical recovery.

Variable	Clinically recovered	Remained symptomatic	COR (95% CI)	p-value	AOR (95% CI)	p-value
Age						
18–45 years	24,603 (69.1)	954 (64.7)	0.82 (0.73–0.91)	<0.001	0.82 (0.73–0.92)	0.001
46–70 years	10,984 (30.9)	520 (35.3)	1 (Ref)		1 (Ref)	
Gender						
Male	20,206 (56.8)	816 (55.4)	0.94 (0.85–1.05)	0.281	0.92 (0.83–1.03)	0.133
Female	15,381 (43.2)	658 (44.6)	1 (Ref)		1 (Ref)	
Vaccination status						
Vaccinated	5,211(14.6)	153 (10.4)	0.68 (0.57–0.80)	<0.001	0.60 (0.51–0.72)	<0.001
Not vaccinated	30,376 (85.4)	1,321(89.6)	1 (Ref)		1 (Ref)	
Substance abuse						
Yes	3,529 (9.9)	173 (11.7)	1.21(1.03–1.42)	0.023	1.21 (1.02–1.43)	0.028
No	32,058 (90.1)	1,301 (88.3)	1 (Ref)		1 (Ref)	
Co-morbidities						
Present	3,146 (8.8)	193 (13.1)	1.55 (1.33–1.82)	<0.001	1.54 (1.31–1.81)	<0.001
Absent	32,441 (91.2)	1,281 (86.9)	1 (Ref)		1 (Ref)	

COR, Crude Odds-ratio; AOR, adjusted odds-ratio; 95% CI, 95% confidence interval; Ref, reference category.

undergone vaccination (OR 0.68 95% CI 0.57–0.80). Younger age, being vaccinated, and having no co-morbidities or substance abuse were predictors of clinical recovery within 21 days (**Figure 2**).

Factors Associated With Participant Preference for AYUSH-64 as an Adjunct or Standalone

Multivariate logistic regression of variables that have an association with participant's care-seeking behavior, i.e., AYUSH-64 use as standalone or as an adjunct to standard care, was done using selected six variables *viz*., age, gender, co-morbidity, vaccination history, the risk of getting infected with COVID-19, and symptomatic disease at baseline (**Supplementary Table 4**). In the multivariate analysis, the factors independently associated with participant preference for the use of AYUSH-64 as standalone or as an adjunct to standard care were the presence of co-morbidities such as the existence of diseases such as DM, HTN, asthma, etc. (OR 2.96, 95% CI 2.75–3.17); having undergone vaccination (OR 1.62, 95% CI 1.55–1.70); being at risk for COVID-19 (OR 1.23, 95% CI, 1.18–1.28); and symptomatic disease at baseline (OR 2.40 95% CI 2.32–2.49). Those with co-morbidities had almost three times more odds of choosing AYUSH-64 as add-on care. Likewise, those with symptomatic disease (2.40 times) and who had completed vaccination (1.62 times) were more at odds for using AYUSH-64 as an adjunct. After adjustment of confounding variables such as age, vaccination status, etc., it was that participants in the younger age group (18–45 years) were more at odds for preferring the use of AYUSH-64 as an add-on treatment.

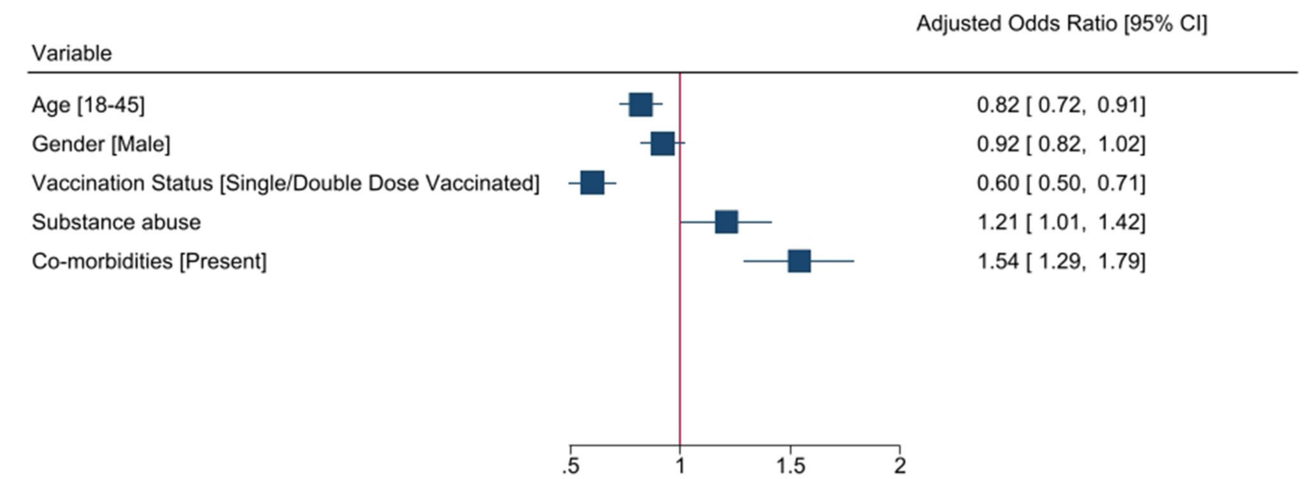

FIGURE 2 | Association of baseline characteristics with clinical recovery at day 21.

DISCUSSION

In this national level community-based study, it was observed that the majority of the participants were diagnosed based on a confirmatory laboratory test (RT-PCR/RAT assay for COVID-19) and only one-third were diagnosed based on symptoms suggestive of COVID-19 compatible illness. More than half the study population was not vaccinated, and maximum participants were not among the risk groups such as the professionals, health care, and frontline workers who were in contact with the public or involved in disease surveillance or management. The care-seeking behavior observed in the study reveals that the majority of the study participants, which may depict a representative sample of the Indian population with COVID-19 in home isolation, sought AYUSH-64 as an add-on to standard care for COVID-19. Vitamin C, paracetamol, and azithromycin were the most common interventions utilized by the participants under standard care. Through this community program, Ayurveda therapeutic care was made available as a standalone therapy for 41.7% of the study population, who did not make use of standard care for the management of COVID-19 across 27 states and 5 Union Territories. A good proportion (96.0%) of the study population demonstrated clinical recovery within 21 days during the peak of the second outbreak of COVID-19, which devastated the country and overtaxed the health care facilities. Participants who used AYUSH-64 alone for COVID-19 also demonstrated comparable clinical outcomes as that of the population that utilized it as an adjunct, such as clinical recovery within 21 days, the minimal incidence of adverse events, and minimizing the chance for disease progression. A comparable response was observed in terms of the proportion of participants with SARS-CoV-2 clearance (assessed by negative RAT/ RT-PCR assay for COVID-19), irrespective of whether AYUSH-64 was used as standalone or adjunct. Based on this evidence, AYUSH-64 use is associated with good clinical outcomes in asymptomatic, mild, or moderate COVID-19.

Though the Government of India initiated the vaccination drive for eligible beneficiaries on 16 January 2021, the caseload surged during March 2021, and a gradual rise in the death rate was observed (21). Despite the extensive efforts by the government to set up COVID care centers, COVID hospitals, deploy human resources, and arrange necessary resources to contain the second outbreak of COVID-19 that officially began in April 2021 in India, 50% of COVID-19 related deaths were reported during the peak of the second outbreak between April and June 2021 (22). The risk of severity increased the rate of hospitalization and unfavorable outcomes, unavailability of hospital beds due to heavy caseload, and increased stress on health care and economic resources to cater to the needs of a sizeable ailing population prompted the MoA to distribute AYUSH-64 to patients with COVID-19 in home isolation based on the empirical evidence generated from multiple clinical studies. The timing of this initiative was critical as there were stringent restrictions such as lockdowns and curfews implemented during the study period across the country. It is worth noting that delivering door to door health care to more than 64,000 individuals in 4 months with 3 more scheduled follow-ups (day 7, day 14, and day 21) was the result of systematic end-to-end planning, implemented through effective and efficient participation of various Ayush research and academic institutes across 27 States and 5 UTs in a decentralized framework with effective collaboration with state-level local self-governance bodies, voluntary organizations, and public health care delivery systems. A large number of beneficiaries in this study also depicts the public preference for Ayurveda for therapeutic care, even in infectious diseases, which corresponds to a survey study conducted in India during the pandemic, wherein 59.6% of respondents utilized Ayurveda interventions for the management of COVID-19 and post-COVID care (23). The majority of the beneficiaries were from Kerala, Andhra Pradesh, Maharashtra, Odisha, Uttar Pradesh, and the Union Territory of Delhi, which might be attributed to the high incidence of COVID-19 and case positivity rate in these states during the study period (24).

The study findings portray that more than 98% of the participants who underwent the RT-PCR/RAT test for a second time attained SARS-CoV-2 clearance within 21 days, irrespective of their use of AYUSH-64 as standalone or with standard care. Among the symptomatic participants, cough, fever, headache, body ache, sore throat, fatigue, loss of smell, and loss of taste were the most common symptoms that developed during the symptomatic phase. However, fatigue, tiredness, cough, body ache, and headache were persistent as residual symptoms even after 21 days. The findings from a meta-analysis of 148 studies from nine countries regarding the clinical symptoms of COVID-19 also corroborate this observation (25). It has been observed that symptoms such as anosmia and ageusia require a prolonged recovery period in COVID-19 patients, which is also a finding in the Indian sub-continent (26). A survey study conducted in India during the COVID-19 pandemic has reported that the mean duration of clinical recovery in COVID-19 patients is 25 days, with no difference in the recovery time between males and females, and in patients older than 60 years and younger (27). The findings in this community study reveal that symptoms such as cough and fatigue persist for more than 21 days in a very small proportion of the participants despite the type of health care utilized.

Only a small proportion of participants reported worsening/progression of disease in terms of hospitalization (0.74%), oxygen supplementation (0.90%), the requirement for ICU care (0.17%), or mechanical ventilator (0.09%) support in this study, while 20–23% of the active cases needed hospital care during the second outbreak of COVID-19 in India (28). Death as a complication of COVID-19 was observed in a minimal number of participants in the study. This may be considered a good outcome, and coupled with the evidence from the previous clinical studies in which AYUSH-64 as an adjunct to conventional standard care demonstrated better clinical recovery with no disease progression compared to standard care alone in COVID-19 (11–16), it is possible to say that AYUSH-64 use in COVID-19 may correlate with better clinical outcomes even if used alone. Adverse events reported in this community study were very minimal, and none of the events required the need for medical consultation or hospitalization. The study findings suggest that using AYUSH-64 for the management of COVID-19 patients in home isolation is no cause for concern regarding safety and tolerability. Having been vaccinated or being younger was associated with better clinical outcomes in terms of clinical recovery within 21 days. The odds of those who did not undergo clinical recovery within 21 days were more among those with co-morbidities and substance abuse issues. The factors that guide a patient's preference for using Ayurveda interventions as an adjunct to standard care for the management of COVID-19 were as follows: being at risk for COVID-19, having undergone vaccination, symptomatic disease, and presence of co-morbidities. The outcomes of this study reveal that the Indian population adopts Ayush interventions for the management of infectious diseases, and the preference for using standalone Ayurveda care might be attributed to the fact that the faith and reliance on Ayush systems are firmly rooted in the Indian heritage, popularity, and previous experiences in terms of utility, accessibility, and flexibility. The utilization of complementary and alternative medicine *(*CAM*)* services around the globe are reported to be between 9% and 65%. The use of CAM in India amounts to 65%, while in Asia, it is observed to be around 80% (29). The results of an observational study conducted during COVID-19 convey that a considerably large number of the Indian population utilized Ayush-based measures for COVID-19 prevention, as is observed in the care-seeking behavior of the study participants (30).

The interim guidance published by the WHO on 7 March 2020, addressing the community spread of COVID-19, opined that the prevention of COVID-19 would be possible through the development of coordination mechanisms not just in health but also in other areas which encompass the entirety of society, and keeping this in view, community participatory mechanism of engaging volunteers and dispensing medicines was sought to help the government in reducing the health burden attributed to COVID-19 (31).

An inclusive integrative health approach, structured with an operational component to create and mobilize an operational workforce and expertise to serve societal and public health goals, is the best solution to tackle such illnesses of a pandemic nature. The Ayush knowledge, practices, and human resources functioning outside the mainstream health architecture can be well integrated through a participatory approach in collaboration with public health providers for better outcomes.

LIMITATIONS

Due to the stringent restrictions laid down during the pandemic, mobilization of human resources to conduct follow-ups through direct assessments was not possible, and follow-ups were done through telephonic communication. A good proportion of the study participants could not be contacted through telephone during all the four scheduled follow-ups, and so were not utilized for analysis. The clinical outcomes in terms of negative RT-PCR/RAT assay for COVID-19 could only be assessed in a small proportion of the total study participants, as a second test was not mandated as per the existing government guidelines.

CONCLUSIONS

The outcomes of this community-based interventional study highlight that a significant proportion of the public residing across diverse demographics opted to use Ayurveda intervention (AYUSH-64) as standalone or adjunct to standard conventional care in managing COVID-19. The use of AYUSH-64 is associated with good clinical outcomes in patients with asymptomatic, mild, or moderate COVID-19 in home isolation. A decentralized and participatory community approach can effectively use the existing public health machinery to deliver integrated care services, utilizing the beneficial effects of Ayurveda during the pandemic.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Central Ethics Committee, CCRAS. The patients/participants provided their written informed consent to participate in this study.

STATE LEVEL COLLABORATORS

AIIA Delhi: Tanuja Nesari, Mahesh Vyas, Umesh Tagade; ITRA Jamnagar: Anup Thakar; Nilesh Bhatt, Kalpesh Dattani, Sagar Bhinde; NIA Jaipur: Sanjeev Sharma; Pawan Kumar Godatwar, Nisha Ojha, H.M.L.Meena, Harish Bhakuni; NEIAH Shillong: Pradeep Kumar Goswami, Bishnu Choudhury; RARI Vijayawada: Nishanth K, AJV Sai Prasad, Sujata Dhoke, Midhuna Mohan K, Savita Gopod; RARI Itanagar: Arvind Kumar; CARI Guwahati: Ekta Dogra, G.K.Bora, Pravin K S, Pravin Masarom Radheshyam, P.L.Bharati, Jeuti Rani Das; RARI Patna: Vimal Tewari, Deepika Tewari, Ritika Mishra, Kuldeep, D.S.Rotwar; RARI Ahmedabad: Anil Ahvad, Sumed Paikrao; CARI Delhi: Amit Madan, Nandini Jadhav; RARI Mandi: Vikas Nariyal, Kavita Vyas, Anubha Chandla, Vineeta Negi, Chris Antony; RARI Jammu: Vipin Sharma, Poonam Mohod, Subhash Sharma, Meenakshi Suri, Aaditya Shah; CARI Bengaluru: G.V.Ramana, Tejaswini C, Raghavendra, S.K.Giri, Shashidhar Doddamani, Shubhashree M.N, Srinibash Sahoo; NARIP Cheruthuruthy: K.M.Pratap Shankar, Parvathy.G.Nair, Devi R Nair, Krishna Kumar V., P.P. Pradeep Kumar, Remya E; RARI Thiruvananthapuram: Karthika A P, Sinimol. T.P, Meghna P P, Praveen Balakrishnan, Emy.S.Surendran, Varsha Sumedhan; RARI Gwalior: Amit Kumar, S.B.Singh, Neelam Singh, Anil Mangal, Deepa Sharma; CARI Mumbai: Laxman Bhurke, Dattatray Dighe, Kuldeep Choudhary, Saylee Deshmukh, Sneha Marlewar, Shyam Kale; RARI Nagpur: U.R.Shekhar Namboori, Savita Sharma, Priya Thakre, Prashant Shinde, Balaji Potbare; RARC Nagaland: Deepak Rahangdale, Gwachung Magh; CARI Bhubaneswar: G.C.Bhuyan, P.Panda, K.K.Ratha, Krishna Rao, Indu S, A.K.Panda, Banamali Das, Susmita Ota; CARI Patiala: Rinku Tomar, Harbans Singh, Sandeep Baheti, Sanjeev Kumar, Mahesh S, Sangeeta Sangvikar; RARI Jaipur: S.K.Vedi, Swati Sharma, V.B.Kumawat, Suhash Choudhary, Monika Kumari, Indu P P; RARI Gangtok: Rahul D.Ghuse, Shriprakash, Shrawan Kumar Sahu, Ashok Kumar Sinha; RARI Chennai: P.Srinivas, K.Prameela Devi, Asha S; RARC Tripura: Sojeetra Niral; RARI Lucknow: Karisma Singh, Kamble Pallavi, Ravi Ranjan Singh, Anjali B Prasad, Mayur Surana, Sanjay Kumar Singh, Harit Kumari, A.K.Srivastava; RARI Ranikhet: Tarun Kumar, Deepshikha Arya; CARI Kolkata: D.S.Sahu, Tushar Kanti Mondal, L.D.Barik, Suparna Saha, Ranjita Ekka, Shakti Bhushan, Achintya Mitra, Saroj Kumar Debnath, Debajyoti Das; RARI Port blair: Akashlal M, Abhayadev A; RARCMMMR Goa: Hemant Gupta, Ajay P Yadav; CCRUM: Asim Ali Khan, NRIUMSD Hyderabad: Munawar H Kazmi, Minhaj; RRIUM Delhi: Rahat Raza; CRIUM Lucknow: Md.Nafees Khan; RRIUM Patna: Md. Ishtiyaq Alam; RRIUM Mumbai: Haseeb Alam Lari; RRIUM Chennai: N. Zaheer Ahmed; RRIUM Bhadrak: Hakimuddin Khan; RRIUM Kolkata: Younis Iftikhar; RRIUM Srinagar: Seema Akbar; RRIUM Aligarh: Sheeren Afza; HAKILHRUM Delhi: Mohammad Fazil; RRC Allahabad: Ashok Kumar; CRU Meerut: Mohd Tarique; CRU Burhanpur: Amir Faisal Khan; CRU Bhopal: Amir Faisal Khan; CRU Kerala- Aijaz Ahmed; CCRH: Anil Khurana; NHRIMH Kottayam (Kerala): S. Karunakara Moorthi; CRI Noida: Subhash Kaushik; CRI Jaipur- Nitin Kumar Saklani; RRI Mumbai: B. S. Rawat; RRI Gudivada: Brunda Bezawada; RRI Shimla: Sunil Ramteke; RRI Puri: A.K. Prusty; RRI Guwahati: Liyi Karso; RRI Manipur: Amit Srivastav; RRI Tripura: Ratan Chandra Shil; RRI Kolkata: Partha Pratim Pal; HDRI Lucknow: Lipipushpa Debata; CRU Tirupati: G. Ravi Chandra Reddy; CRU Ranchi: Sunil Prasad; CRU Port blair: Uttam Singh; CRU Darjeeling: Baidurjya Bhattacharjee; CRU Gangtok: Santosh Kumar Tamang; CRU Puducherry: Ravi kumar Sadarla; CRU Mizoram: Pawan Sharma; Homeopathic Medical College Bhubaneswar: Amulya Ratna Sahoo; CVU Patna: Vibha; DSU Hyderabad: P Prasad; HRID Chennai: D. Karthikeyan; CCRYN: Raghvendra Rao; PGIYNER Harayana: Surender Sandhu; CCRYN Rohini (Delhi): Mohan Rao; PGIYNER Karnataka: Vadiraj HS; MDNIY Delhi: Ishwar V. Basavaraddi, Ishwar N Achary; NIN Pune: K Satyalakshmi, Shivkesh, P.Yuvaraj Paul; NIH Kolkata: Subhas Singh, Austin Jose; NEIFM Arunachal Pradesh: Robindra Teron, Imlikumba; NIUM Bangalore: Addul Wadud, Abdul Nasir Ansari, Tariq Nadeem Khan, Abdul Moheen; NISR Leh: Tsewang Dolma, Tenzin Tenba; RAV Delhi: Anupam Srivastav, N. Ramakrishnan; Directorate of Ayush, Gujarat: Surendra Soni, Ram Shukla, Rohini Salve, M.N. Shaikh, Daxen Trivedi, Shital Bhagiya, Asha Patel, Anup Indoriya, Rachna Gandhi, Naresh Jain, Nirmal Chavada, Rahul Shingadiya, Nilesh Bhadraka, Nrupesh Gupta, Dilip Italiya, Piyush Shah, Maya Chaudhari, Sumit Patel, Bhavin Chaudhari, Mehul Parmar.

AUTHOR CONTRIBUTIONS

NS: conceptualization, methodology, questionnaire development, project administration, resources, and validation. AK: methodology, project administration, co-ordination, and validation. BC, BY, and SK: methodology, questionnaire development, and writing—review and editing. RS: questionnaire development, data curation, formal analysis, and writing—review and editing. SJ: methodology, questionnaire development, visualization, and writing—review and editing. AR: visualization and writing—original draft. AT: data curation and formal analysis. RR: questionnaire development, data curation, and formal analysis. AA: visualization and writing—review and editing. BS: resources and writing—review and editing. AJ: data curation. RK: conceptualization, project administration, resources, and supervision. State Level Collaborators:

investigation. All authors read, provided feedback, and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Health Professionals' Knowledge, Attitude and Practices Regarding COVID-19 in Dessie City, Northeast Ethiopia: A Facility-Based Cross-Sectional Study

Tefera Alemu[1]*, *Seid Legesse*[2], *Abtew Abera*[2], *Semagn Amare*[2], *Minwuyelet Maru*[2†], *Birtukan Shiferaw*[2], *Assefa Missaye*[2] *and Getaneh Derseh*[1†]

[1] ICAP Ethiopia, Amhara Regional Office, Bahir Dar, Ethiopia, [2] Research and Technology Transfer Directorate, Amhara Public Health Institute Dessie Branch, Dessie, Ethiopia

Edited by:
Wondwossen Amogne Degu,
Addis Ababa University, Ethiopia

Reviewed by:
Neftali Eduardo Antonio-Villa,
Universidad Nacional Autónoma de México, Mexico
Zixin Wang,
The Chinese University of Hong Kong, China
Okon Okwong Kenneth,
Federal Medical Centre Makurdi, Nigeria

***Correspondence:**
Tefera Alemu
teferaalemu2@gmail.com

† These authors share senior authorship

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Background: Knowledge and attitudes are among the key drivers of social behavioral change. We assessed employed health professionals' (HPs) knowledge, attitude, and practice regarding COVID-19 in Dessie city, northeast Ethiopia.

Methods: A facility-based cross-sectional study was conducted among 419 HPs working at Dessie city from 17 to 21 May 2020. The data were collected using a self-administered structured questionnaire. Knowledge, attitude, and practice are measured using 19, 16, and 8 questions, respectively. Knowledge and attitude scores are dichotomized at the 3rd quartile, while practice is using the mean value. Data entry and analysis were conducted using EpiData Manager 4.2 and SPSS 25, respectively. Three independent logistic regression analyses were carried out to determine the associated factors. We defined significant association at a p-value of <0.05.

Results: Out of 419 participants, 369 (88.1%) have sufficient knowledge regarding COVID-19 (95% CI: 85–91). The mean knowledge score is 16.8 with a ± 2.1 SD. Similarly, 355 (84.7%) of the HPs have a favorable attitude toward COVID-19 (95% CI: 81–87.9). The mean attitude score is 14 with ± 2.1 SD. However, practice regarding COVID-19 is adequate only in 69.7% (292) of the HPs (95% CI: 65.2–94). The mean practice score is 5.1 with a ± 1.3 SD. Sufficient knowledge is significantly associated with the type of health facility (AOR: 4.4, 95% CI: 1.4–13.3), degree and above education (AOR: 2.6, 95% CI: 1.4–4.9), radio availability (AOR: 2.4, 95% CI: 1.3–4.7), and social media utilization (AOR: 2.3, 95% CI: 1.1–5.1). The predictors of favorable attitude are training (AOR: 3.1, 95% CI: 1.6–6.1), sufficient knowledge (AOR: 5.2, 95% CI: 2.6–10.4), and type of health facility (AOR: 2.3, 95% CI: 1.1–5.2).

Conclusion: Most HPs have sufficient knowledge and a favorable attitude regarding COVID-19. However, practice is relatively low and there remains plenty to build assertive preventive behaviors. The gap between knowledge and practice should be narrowed through an appropriate social and behavioral change communication strategy.

Keywords: COVID-19, KAP, Dessie, health professionals, Ethiopia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly discovered coronavirus, that was first recognized in Wuhan, China, in December 2019. Its mode of transmission is through respiratory droplets, direct contact, and feco-orally (1). At the moment, there is no cure for infection with the coronavirus[1,2]. However, the WHO has listed nine COVID-19 vaccines for emergency use to increase access to vaccination[3].

Thus, in case of such emergencies, health professionals (HPs) are the first to encounter patients, thereby exposing themselves to a greater risk of infection. For instance, during the SARS outbreak in 2002, one-fifth of all cases were in health professionals[4]. Moreover, recently, dozens of health professionals have fallen ill with COVID-19 in Italy, China, and the United States, and many more are in quarantine after exposure to the virus, an expected but worrisome (2, 3). This is alarming, as HPs are considered frontline fighters against the disease. Also, this will fasten the spread of the disease to the community as HPs are not only at risk of acquiring infections but also of being a source of infection to patients and their families (4). On the contrary, if large numbers of HPs get infected, it will deteriorate the healthcare system's capacity to respond to a healthy contingency (2).

Many of the diseased HPs have a positive contact family indicating that they might have acquired it in the community and not in their health facility. As stated in earlier studies, HP's adherence to disease control measures can be affected by their knowledge, attitudes, and practices (KAP) toward the disease (5, 6). Therefore, the best way to reduce the risk of infection to HPs is by educating them about the COVID-19 virus, the disease it causes, how it spreads, and the way how they can use personal protective equipment (PPE) appropriately (7). Subsequently, since its first detection in China and Ethiopia, an extraordinary effort has been made by the government of Ethiopia to raise public awareness of coronavirus transmission and prevention strategies. Moreover, capacity-building training and orientations on COVID-19 have been given to the HPs working at health facilities. Yet, researchers assessing KAP toward COVID-19 among HPs across the world observed a substantial amount of deficit in the knowledge, attitude, and practice among health professionals (5, 6, 8). For instance, in one study conducted through a web-based system, 61 and 63.6% of the HPs were having poor knowledge of COVID-19 transmissions and its symptom onset, respectively (5).

Nonetheless, to the best knowledge of the investigators, there was no published evidence that assessed the knowledge, attitude, and practices of HPs regarding COVID-19 in the Ethiopian setting, particularly in the study area. Therefore, we assessed employed HP's knowledge, attitude, and practice regarding COVID-19 to identify where the gap is, which enables public health authorities to redirect their anti-corona efforts toward the gap.

[1]https://www.britannica.com/story/is-there-a-cure-for-coronavirus

[2]https://www.who.int/docs/default-source/coronaviruse/key-messages-and-actions-for-covid-19-prevention-and-control-in-schools-march-2020.pdf?sfvrsn=baf81d52_4

[3]https://www.who.int/news/item/17-12-2021-who-lists-9th-covid-19-vaccine-for-emergency-use-with-aim-to-increase-access-to-vaccination-in-lower-income-countries

[4]https://www.theverge.com/2020/3/5/21166088/coronavirus-covid-19-protection-doctors-nurses-health-workers-risk

METHODS

Study Design and Period

A facility-based cross-sectional study was conducted from 17 to 21 May 2020 to assess employed health professionals' knowledge, attitude, and practice regarding COVID-19 in Dessie city.

Study Setting and Population

The study was conducted in Dessie city administration health facilities (both government and private). It is 401 km to the northeast of Addis Ababa, the capital city of Ethiopia. Dessie had 5 sub-cities divided into 18 urban and 8 rural kebeles. According to the 2007 Central Statistical Agency report, Dessie has 285,530 population in 2021/2022, of which 49.5% are men. In 2019/2020, there were 8 health centers, 8 health posts, 2 government hospitals, 3 private hospitals, 38 private clinics, 55 private drug stores, and 4 private diagnostic laboratories. Besides, there were two governmental COVID-19 testing laboratories in the city, namely, the Amhara Public Health Institute Dessie Branch and Wollo University laboratory center (9). All health professionals working in Dessie city health facilities were the source populations. Health professionals were randomly selected and included in the study.

Sample Size and Sampling Technique

The sample size was determined using a single population proportion formula by considering the following assumptions: 5% margin of error, 95% confidence level, and a prevalence of 50% since there was no study before. After adding a 10% nonresponse rate we obtained a minimum sample size of 424 health professionals. Using the list of health professionals as a frame, a random sampling technique was employed to select the required number of health professionals. The number of study participants in each health facility is determined based on the proportion to size allocation methods. All government health facilities are purposively included in the study, and 20 out of 38 private health facilities are selected randomly. The study is conducted in all government health centers (7), one hospital (1), all private hospitals (3), and 20 private clinics. At the time of data collection, Dessie health center and Boru Meda Specialized hospital were COVID-19 treatment centers, and HPs were not available for inclusion in the study.

Data Collection

Data were collected through a pretested, self-administered, structured, and paper-based questionnaire, which was prepared in the Amharic language (**Supplementary Material 1**). The questionnaire was first prepared in English language and then translated to the Amharic version, which is the participant's mother tongue. We developed the questionnaire from different works of literature and the World Health Organization resources. The questionnaire addressed information on sociodemographic characteristics, knowledge, attitude, and practice toward COVID-19.

Data Quality Assurance

Before the actual data collection period, pretesting of the questionnaire was conducted on 5% of the study population, and necessary modifications have been made. Training was given to data collectors/supervisors. Daily supervision was made by the investigators. At the time of data collection, respondents are briefed on the questionnaire, and the answers were given to each question raised by participants. Tool validation has been conducted, and Cronbach's alpha is found to be in the good range ($\alpha = 0.84$).

Data Analysis

Data entry and analysis were made using the EpiData Manager 4.2 and SPSS 25 software, respectively. Reverse coding of some questions was made for negatively worded questions. Logistic regression analyses have been conducted to identify factors associated with KAP regarding COVID-19. We entered a variable with a p-value of ≤ 0.2 in the bivariate analysis into the multivariate logistic analysis. Adjusted odds ratios with a 95% confidence interval were computed to observe the strength of association between the dependent and independent variables. A p-value of <0.05 was considered statistically significant. Before the regression analysis, the model fitness was checked by the Hosmer and Lemeshow goodness-of-fit test.

Operational Definition

Sufficient Knowledge

A total of 19 items are used to measure HP's knowledge regarding COVID-19. The mean knowledge score is 16.8, and those participants who scored 15 and more (3rd quartile) are classified as having sufficient knowledge. Those "Yes" responses are coded as 1 and those "No" and "I do not know" responses are taken as incorrect responses and coded as 0.

Favorable Attitude

A total of 16 items are used to measure participants' attitudes, and the mean attitude score is 14; those participants who scored 13 and more (3rd quartile) are classified as having favorable knowledge. Participants who answered "Agree/Yes" were considered correct responses, while those who answered "Disagree/No" and "I do not know" were taken as incorrect responses.

Adequate Practice

The overall practice regarding COVID-19 is measured using eight questions. The mean practice score is found to be 5.1 and scores above the mean value are taken as adequate.

Ethics Approval and Consent to Participate

Ethical approval was obtained from Amhara Public Health Institute Ethical review committee (Protocol No: H/R/T/T/D/3/791). Permission was also obtained from concerned bodies in Dessie city. Informed oral consent is also obtained from each participant. All possible COVID-19 measures are taken to prevent cross-contamination during data collection.

RESULTS

Sociodemographic Characteristics of Participants

A total of 419 participants aged >20 years were included in the study with a response rate of 98.8%. The mean age of participants was 32 years with ± 8.9 standard deviation. Half of the participants are male and about 61.3% were married. More than half (54.9%) of the participants are at least first-degree holders, while the rest 45.1% had a diploma in health science fields. The majority (88.8%) of the participants had a television in their houses, and 86.6% of them are currently social media users. Notably, 40% of the participants are working at health centers, while the rest 37.7% and 21.7% are working in hospitals and private clinics, respectively (**Table 1**).

Knowledge Regarding COVID-19

A total of 19 items are used to measure HP's knowledge regarding COVID-19. The mean knowledge score is 16.8 with ± 2.1 standard deviations, ranging from 6 up to 19 scores. Regarding specific knowledge items, more than 90% of the health professionals know the major COVID-19 symptoms like fever (95%), dry cough (90.7%), and shortness of breathing (92.6%). Similarly, most of the respondents know the major COVID-19 transmission routes like respiratory droplets (94.7%), direct (97.1%), and indirect contacts (92.4%). Furthermore, most HPs know all the COVID-19 prevention methods like frequent hand washing with soap (98.8%), physical distancing (97.1%), staying at home (95.9%), sanitizer utilization (95.7%), and facemask utilization (90.5%). Besides, 84% of the participants mentioned that the elderly and people with chronic illness are at higher risk of severe illness and bad outcomes. Also, 91.4% of the HPs mentioned that asymptomatic carriers can transfer the virus and 97.6% of them believe that more than one prevention method is important for COVID-19 prevention. In general, 88.1% (369) of health professionals have sufficient knowledge regarding COVID-19 (95% CI: 85–91) (**Table 2**).

Attitude Toward COVID-19

A total of 16 items are used to measure participants' attitudes toward COVID-19. The mean attitude score is 14 with ± 2.1 standard deviations, ranging from 1 up to 16 scores. Approximately 3.6% of the HPs agree that COVID-19 will not infect/kill Ethiopian/African origins; whereas the overwhelming majority (96.9%) disagree with the idea that COVID-19 only infects elders. Likewise, 96.7% of the HPs disagree with the idea that COVID-19 will not kill children and youths, and 89.5% of them believe that COVID-19 precaution measures are important to children. Besides, eight percent of the HPs believe that only N95 face mask utilization is adequate to prevent COVID-19 infection (**Table 3**).

Most of the HPs agree that avoiding mass gatherings (81.6%), frequent hand washing (88.1%), staying at home (89%), and maintaining a social distance (92.8%) will prevent COVID-19

TABLE 1 | Sociodemographic characteristics of health professionals in Dessie city, northeast Ethiopia ($N = 419$).

			Knowledge		Attitude		Practice	
Variables	**Category**	**Frequency (%)**	**Sufficient**	**Insufficient**	**Favorable**	**Unfavorable**	**Adequate**	**Inadequate**
Age	20–30 Years	254 (60.6)	220 (86.6)	34 (13.4)	216 (85)	38 (15)	170 (66.9)	84 (33.1)
	31–40 Years	104 (24.8)	92 (88.5)	12 (11.5)	86 (82.7)	18 (17.3)	77 (74)	27 (26)
	41 and above	61 (14.6)	57 (93.4)	4 (6.6)	53 (86.9)	8 (13.1)	45 (73.8)	16 (26.2)
Sex	Male	212 (50.6)	194 (91.5)	18 (8.5)	181 (85.4)	31 (14.6)	146 (68.9)	66 (31.1)
	Female	207 (49.4)	175 (84.5)	32 (15.5)	174 (84.1)	33 (15.9)	146 (70.5)	61 (29.5)
Religion	Orthodox	246 (58.7)	212 (86.2)	34 (13.8)	214 (87)	32 (13)	174 (70.7)	72 (29.3)
	Muslim	164 (39.1)	148 (90.2)	16 (9.8)	133 (81.1)	31 (18.9)	113 (68.9)	51 (31.1)
	Protestant	9 (2.1)	9 (100)	0	8 (88.9)	1 (11.1)	5 (55.6)	4 (44.4)
Marital status	Married	257 (61.3)	227 (88.3)	30 (11.7)	218 (84.8)	39 (15.2)	183 (71.2)	74 (28.8)
	Single	145 (34.6)	130 (89.7)	15 (10.3)	121 (83.4)	24 (16.6)	96 (66.2)	49 (33.8)
	Divorced/windowed	17 (4.1)	12 (70.6)	5 (29.4)	16 (94.1)	1 (5.9)	13 (76.5)	4 (23.5)
Level of education	Diploma	189 (45.1)	156 (82.5)	33 (17.5)	153 (81)	36 (19)	134 (70.9)	55 (29.1)
	Degree & above	230 (54.9)	213 (92.6)	17 (7.4)	202 (87.8)	28 (12.2)	158 (68.7)	72 (31.3)
Experience	0–5 Years	152 (36.3)	134 (88.2)	18 (11.8)	130 (85.5)	22 (14.5)	101 (66.4)	51 (33.6)
	6–10 Years	148 (35.3)	125 (84.5)	23 (15.5)	122 (82.4)	26 (17.6)	102 (68.9)	46 (31.1)
	≥11 Years	119 (28.4)	110 (92.4)	9 (7.6)	103 (86.6)	16 (13.4)	89 (74.8)	30 (25.2)
Owner of HF	Non-governmental HFs	154 (36.8)	138 (89.6)	16 (10.4)	136 (88.3)	18 (11.7)	116 (75.3)	38 (24.7)
	Governmental HFs	265 (63.2)	231 (87.2)	34 (12.8)	219 (82.6)	46 (17.4)	176 (66.4)	89 (33.6)
Type of HF	Health Center	170 (40.6)	144 (84.7)	26 (15.3)	133 (78.2)	37 (21.8)	112 (65.9)	58 (34.1)
	Clinic	91 (21.7)	87 (95.6)	4 (4.4)	79 (86.8)	12 (13.2)	63 (69.2)	28 (30.8)
	Hospital	158 (37.7)	138 (87.3)	20 (12.7)	143 (90.5)	15 (9.5)	117 (74.1)	41 (25.9)
Television availability	No	47 (11.2)	43 (91.5)	4 (8.5)	37 (78.7)	10 (21.3)	29 (61.7)	18 (38.3)
	Yes	372 (88.8)	326 (87.6)	46 (12.4)	318 (85.5)	54 (14.5)	263 (70.7)	109 (29.3)
Radio availability	No	236 (56.3)	154 (84.2)	29 (15.8)	153 (83.6)	30 (16.4)	118 (64.5)	65 (35.5)
	Yes	183 (43.7)	215 (91.1)	21 (8.9)	202 (85.6)	34 (14.4)	174 (73.7)	62 (26.3)
Social media utilization	No	56 (13.4)	44 (78.6)	12 (21.4)	48 (85.7)	8 (14.3)	41 (73.2)	15 (26.8)
	Yes	363 (86.6)	325 (89.5)	38 (10.5)	307 (84.6)	56 (15.4)	251 (69.1)	112 (30.9)

infection. About 86.9% of the HPs disagree with the idea of cultural medications to prevent and/or cure COVID-19 infection (**Table 3**). Nearly all (98.3%) health professionals agree to advise their friends and families about COVID-19-related issues. Besides, 97.6% of them are committed to reporting a suspected COVID-19 case to a health authority for quarantine. Also, 70.6% of the HPs are ready to procure COVID-19 prevention commodities and supplies even at a high cost (**Table 3**). Overall, 355 (84.7%) of the HPs have a favorable attitude toward COVID-19 (95% CI: 81–87.9).

Practice Regarding COVID-19

This study revealed that health professionals are uniformly implementing the major COVID-19 preventive measure in their day-to-day life. As reported by HPs, 94% of them are frequently washing their hands with soap, but only 87.8% utilize soap at each handwashing event. Similarly, even though 94.7% of the HPs reported sanitizer utilization, only 83.3% have sanitizer at data collection time. Despite the report to use facemasks by 86.4% of the participants, we found a regular utilization of facemasks in 51.8% of the HPs. Also, 95.5% of the HPs mentioned that they avoided handshaking, 85.7% are keeping their physical distance, and 61.3% have avoided visiting crowded places. Unprecedently, almost 5% of the study participants reported that they are not implementing any of the recommended COVID-19 precautionary methods. In general, the overall practice regarding COVID-19 is measured using eight questions, and the mean practice score is 5.1 with $\pm$ 1.3 standard deviation, which ranges from 2 up to 8 scores. Overall, 69.7% (292) of health professionals have adequate practice regarding COVID-19 (95% CI: 65.2–94) (**Table 4**).

Factors Associated With COVID-19 Knowledge and Attitude

In simple binary logistic regression, we recruited (p-value $<$ 0.2) the variables age, sex, marital status, type of health facility, level of education, presence of radio, and social media utilization for the final model. In multivariable logistic regression analysis, knowledge regarding COVID-19 is significantly associated with the level of education, type of health facility, the presence of radio, and social media utilization.

The type of health facility is significantly associated with sufficient knowledge regarding COVID-19. Hence, health professionals working in private clinics are four times more likely

TABLE 2 | Health professionals' knowledge regarding COVID-19 in Dessie city, northeast Ethiopia ($N = 419$).

Knowledge Items	Category	Frequency	Percent
Received COVID-19 training/orientation	Yes	174	41.5
	No	245	58.5
COVID-19 distribution	Pandemic	337	80.4
	Epidemic	81	19.6
Know toll-free line	Yes	298	71.1
	No	120	28.6
COVID-19 Symptoms			
Fever	Yes	398	95
	No	21	5
Dry cough	Yes	380	90.7
	No	39	9.3
Shortness of breathing	Yes	388	92.6
	No	31	7.4
Common cold-like symptoms	Yes	331	79
	No	88	21
Fatigue and myalgia	Yes	291	69.5
	No	128	30.5
Loss of appetite	Yes	250	59.7
	No	169	40.3
Mode of transmission			
Respiratory droplets	Yes	397	94.7
	No	22	5.3
Direct contact	Yes	407	97.1
	No	12	2.9
Indirect contact	Yes	387	92.4
	No	31	7.6
Eating vegetables and uncooked meats	Yes	358	85.4
	No	61	14.6
Air born	Yes	332	79.2
	No	87	20.7
COVID-19 prevention methods			
Handwashing with soap	Yes	414	98.8
	No	5	1.2
Physical distancing	Yes	407	97.1
	No	12	2.9
Staying home	Yes	402	95.9
	No	17	4.1
Facemask utilization	Yes	379	90.5
	No	40	9.5
Sanitizer utilization	Yes	401	95.7
	No	18	4.3
Avoiding crowded places	Yes	394	94
	No	25	6
Good respiratory hygiene	Yes	388	92.6
	No	31	7.4
Isolation and treatment	Yes	386	92.1
	No	33	7.9
Avoid touching openings	Yes	392	93.6
	No	27	6.4

(Continued)

TABLE 2 | Continued

Knowledge Items	Category	Frequency	Percent
The population at risk of getting infected			
All ages and both sex	Yes	402	95.9
	No	17	4.1
Vulnerable to becoming severely ill or die			
Older age group	Yes	353	84.2
	No	66	15.8
People with chronic illness	Yes	349	83.3
	No	70	16.7
Suspected case definition			
Symptoms plus travel history	Yes	382	91.2
	No	37	8.8
Symptoms plus contact history	Yes	389	92.8
	No	30	7.2
Symptoms plus occupational risk	Yes	334	79.7
	No	85	20.3
Symptoms only	Yes	238	56.8
	No	181	43.2
Activities following a single case detection			
Isolation and treatments	Yes	409	97.6
	No	10	2.4
Contact tracing and quarantine	Yes	395	94.3
	No	24	5.7
Laboratory test for contacts	Yes	390	93.1
	No	29	6.9
Disinfection of houses	Yes	366	87.4
	No	53	12.6
Other knowledge variables			
Are asymptomatic cases cannot transmit the virus?	No	383	91.4
	I do not know	4	1
	Yes	32	7.6
Is a single prevention method adequate?	No	409	97.6
	Yes	10	2.4
Children and young adults shouldn't take preventive measures	No	354	84.5
	I do not know	12	2.9
	Yes	53	12.6
Know the duration of quarantines	Yes	393	93.8
	No	26	6.2
Currently, a drug to cure COVID-19 is available.	No	377	90
	I do not know	36	8.6
	Yes	6	1.4
Currently, COVID-19 vaccination is available	No	372	88.8
	I do not know	43	10.3
	Yes	4	1

(Continued)

TABLE 2 | Continued

Knowledge Items	Category	Frequency	Percent
COVID-19 case fatality rate is 100%	No	389	92.8
	I do not know	22	5.3
	Yes	8	1.9
Supportive treatment can help patients to recover	Yes	377	90
	No	24	5.7
	I do not know	18	4.3
Is their COVID-19 death in Ethiopia?	Yes	410	97.9
	No	5	1.2
	I do not know	4	1
Knowledge classification	Sufficient	369	88.1
	Insufficient	50	11.9

to have sufficient knowledge than those working in government health centers (AOR: 4.4, 95% CI: 1.4–13.3). Health professionals who have a first degree and above education are 2.6 times more likely to have sufficient knowledge as compared to diploma holders (AOR: 2.6, 95% Cl: 1.4–4.9). The odd of sufficient knowledge is also increased over 2-fold among respondents having a radio in their house (AOR: 2.4, 95% CI: 1.3–4.7). In addition, health professionals who are utilizing social media are 2.3 times more likely to have sufficient knowledge as compared to their counterparts (AOR: 2.3, 95% CI: 1.1–5.1; **Table 5**).

In the second binary logistic regression, knowledge, religion, type of health facility, level of education, and training on COVID-19 are selected for the final model. However, in multivariable logistic regression analysis, the only variables independently associated with attitude are knowledge, type of working facility, and training on COVID-19.

As a result, the odd of a favorable attitude regarding COVID-19 is 3.1 times higher among health professionals who took COVID-19 training/orientation than their counterparts (AOR:3.1, 95% CI: 1.6–6.1). The presence of sufficient knowledge was another factor significantly associated with a favorable attitude regarding COVID-19. Consequently, health professionals who have sufficient knowledge about COVID-19 are five times more likely to have a favorable attitude regarding COVID-19 (AOR: 5.2, 95% Cl: 2.6–10.4). Besides, health professionals who are employed in private clinics are 2.3 times more likely to have a favorable attitude regarding COVID-19 than health professionals employed in government health centers (AOR: 2.3, 95% CI: 1.1–5.2). This also extends to health professionals working at hospitals that have higher odds of favorable attitudes than their counterparts working at health centers (AOR: 3.6, 95% CI: 1.8–7.2; **Table 5**).

DISCUSSION

Our study revealed a high level of knowledge and a favorable attitude in the study area. However, in our study, practice

TABLE 3 | Health professionals' attitude toward COVID-19 in Dessie city, northeast Ethiopia (*N* = 419).

Attitude Items	Category	Frequency	Percent
COVID-19 will not infect/kill Ethiopian/African origins	Disagree	404	96.4
	Agree	15	3.6
Do you agree that COVID-19 only infects elders?	Disagree	406	96.9
	Agree	13	3.1
Do you believe that COVID-19 will not kill children and youths?	Disagree	405	96.7
	Agree	14	3.3
No need to bother about COVID-19 precaution measures, leave it for God/Allah	Disagree	375	89.5
	Agree	44	10.5
Do you think that only N95 face mask utilization is adequate to prevent COVID-19 infection?	Disagree	385	91.9
	Agree	34	8.1
Do you think those cultural medications can prevent and/or cure COVID-19?	Disagree	364	86.9
	Agree	24	5.7
	I don't know	31	7.4
Do you think that avoiding mass gatherings will prevent coronavirus infection?	Agree	342	81.6
	Disagree	77	18.4
Do you believe that frequent hand washing and using sanitizers can prevent coronavirus infection?	Agree	369	88.1
	Disagree	50	11.9
Do you believe that staying at home can prevent coronavirus infection?	Agree	373	89
	Disagree	46	11
Do you believe that maintaining social distancing can prevent coronavirus infection?	Agree	389	92.8
	Disagree	30	7.2
Do you advise coronavirus prevention strategies for your friends and families?	Yes	412	98.3
	No	7	1.7
Do you report a suspected case of your intimate friend to a health authority for quarantine?	Yes	409	97.6
	No	10	2.4
Are you committed to supporting the government in fighting against COVID-19?	Yes	401	95.7
	No	18	4.3
Are you ready to procure COVID-19 prevention commodities even at a high cost?	Yes	296	70.6
	No	72	17.2
	I do not know	51	12.2
Do you agree that COVID-19 is a preventable disease?	Agree	306	73

(Continued)

TABLE 3 | Continued

Attitude Items	Category	Frequency	Percent
	Disagree	82	19.6
	I don't know	31	7.4
Do you agree that Ethiopia can win the battle against the COVID-19 virus?	Agree	250	59.7
	Disagree	80	19.1
	I don't know	89	21.2
Attitude classification	Favorable	355	84.7
	Unfavorable	64	15.3

is found to be inadequate in 30% of the participants, which shows that good knowledge and a favorable attitude do not necessarily lead to social behavioral change. A similar gap between knowledge and practice is also observed in a study conducted in the northeast part of Ethiopia (10, 11). Further study and evaluation are warranted to investigate the reason behind low infection prevention practice despite the high level of knowledge and favorable attitude in the area. However, the applications of an appropriate social and behavioral change communication strategy with an increased access to personal protective equipment and mandatory regulations can narrow the gap between knowledge and practice. Still, a high number of health professionals are practicing the major COVID-19 precautions like handwashing, sanitizer utilization, face mask, and avoiding handshaking.

Surprisingly, this study revealed that approximately 5% of the participants are not practicing any of the prevention methods. Also, nearly 4% of the HPs believe that COVID-19 will not infect/kill Ethiopian/African origins. Besides, 10.5% of them believe that people should not bother about COVID-19 precaution measures. That is why around 20–30% of the HPs are currently hesitant/delayed to take the COVID-19 vaccine once it became available (12, 13). The reason might be low perceived susceptibility to getting infected and/or severe COVID-19 outcomes, or it might show desperation to combat the virus, but it is largely undiscovered and similar findings are rare in literature. Overall, 15% of the HPs have an unfavorable attitude regarding COVID-19, which is alarming from the pandemic point of view as well as the overcrowded healthcare setups and living conditions in Dessie city. Such negative attitudes by HPs will further accelerate the spread of disease in the community, especially the omicron variant of the virus. In this regard, health facility governing bodies should seriously examine and take responsibility to execute COVID-19 preventive methods in the entire healthcare system. At present, special emphasis should be given to COVID-19 vaccination uptakes by all HPs, as the course of the disease has drastically changed with vaccines and failure to do so will lead to devastating effects on public health and hinder the healthcare system's ability to accommodate the challenges of the pandemic (14). Nonetheless, the 85% favorable attitude in our

TABLE 4 | Health professionals' practice on COVID-19 preventive measures in Dessie city, northeast Ethiopia (*N* = 419).

Practice Items	Category	Frequency	Percent
Which preventive measure are you mostly practicing?			
Frequent hand washing	Yes	394	94
	No	25	6
Alcohol-based hand rub	Yes	397	94.7
	No	22	5.3
Facemask	Yes	362	86.4
	No	57	13.6
Avoided handshaking	Yes	400	95.5
	No	19	4.5
Keeping physical distance	Yes	359	85.7
	No	60	14.3
Staying at home	Yes	187	44.6
	No	232	55.4
Good respiratory hygiene's	Yes	372	88.8
	No	47	11.2
Avoided touching eyes, nose and mouth	Yes	380	90.7
	No	39	9.3
Avoided taking public transportations	Yes	199	47.5
	No	220	52.5
I am not practicing any method	Yes	20	4.8
	No	399	95.2
In recent days, have you visited any crowded places?	No	257	61.3
	Yes	162	38.7
Are you keeping your physical distancing?	Always	115	27.4
	Sometimes	258	61.6
	No	46	11
Are you using a facemask outside the home?	Always	217	51.8
	Sometimes	165	39.4
	No	37	8.8
Hand washing increment as compared to the pre-corona area	The same	17	4.1
	Two times	43	10.3
	Three times	86	20.5
	Four times	84	20
	Five times	125	29.8
	Six and above	64	15.3
Frequency of soap utilization	Always	368	87.8
	Sometimes	44	10.5
	Never	7	1.7
Do you have sanitizer now?	Yes	349	83.3
	No	70	16.7
Is their patient triage in your facility?	Always	187	44.6
	Sometimes	123	29.4
	No	109	26

TABLE 5 | Factors associated with sufficient knowledge and favorable attitude regarding COVID-19 in Dessie city, northeast Ethiopia ($N = 419$).

Variables	Category	Knowledge				Attitude			
		Sufficient knowledge	Insufficient knowledge	COR (95%CI)	AOR (95%CI)	Favorable attitude	Unfavorable attitude	COR (95%CI)	AOR (95%CI)
Age	20–30 Years	220 (86.6)	34 (13.4)	1	1	216 (85)	38 (15)	1	
	31–40 Years	92 (88.5)	12 (11.5)	1.2 (0.6–2.4)	1.4 (0.6–3.2)	86 (82.7)	18 (17.3)	0.8 (0.5–1.6)	
	41 and above	57 (93.4)	4 (6.6)	2.2 (0.8–6.5)	3.7 (1.1–12.9)	53 (86.9)	8 (13.1)	1.2 (0.5–2.6)	
Sex	Male	194 (91.5)	18 (8.5)	1	1	181 (85.4)	31 (14.6)	1	
	Female	175 (84.5)	32 (15.5)	0.5 (0.3–0.9)	0.8 (0.4–1.6)	174 (84.1)	33 (15.9)	0.9 (0.5–1.5)	
Religion	Orthodox	212 (86.2)	34 (13.8)	1		214 (87)	32 (13)	1	1
	Muslim	148 (90.2)	16 (9.8)	1.5 (0.8–2.8)		133 (81.1)	31 (18.9)	0.6 (0.4–1.1)	0.6 (0.3–1.1)
	Protestant	9 (100)	0			8 (88.9)	1 (11.1)	1.2 (0.1–9.9)	1.1 (0.1–10)
Marital status	Married	227 (88.3)	30 (11.7)	1	1	218 (84.8)	39 (15.2)	1	
	Single	130 (89.7)	15 (10.3)	1.2 (0.6–2.2)	1.4 (0.7–3.0)	121 (83.4)	24 (16.6)	0.9 (0.5–1.6)	
	Divorced/windowed	12 (70.6)	5 (29.4)	0.3 (0.1–1.0)	0.4 (0.1–1.6)	16 (94.1)	1 (5.9)	2.9 (0.4–22.2)	
Level of education	Diploma	156 (82.5)	33 (17.5)	1	1	153 (81)	36 (19)	1	1
	Degree and above	213 (92.6)	17 (7.4)	2.7 (1.4–4.9)	2.6 (1.4–4.9)**	202 (87.8)	28 (12.2)	1.7 (1.0–2.9)	1.3 (0.7–2.4)
Experience	0–5 Years	134 (88.2)	18 (11.8)	1		130 (85.5)	22 (14.5)	1	
	6–10 Years	125 (84.5)	23 (15.5)	0.7 (0.4–1.4)		122 (82.4)	26 (17.6)	0.8 (0.4–1.5)	
	≥11 Years	110 (92.4)	9 (7.6)	1.6 (0.7–3.8)		103 (86.6)	16 (13.4)	1.1 (0.5–2.2)	
Owner of HF	Non-governmental HFs	138 (89.6)	16 (10.4)	1		136 (88.3)	18 (11.7)	1	
	Governmental HFs	231 (87.2)	34 (12.8)	0.8 (0.4–1.5)		219 (82.6)	46 (17.4)	1.6 (0.9–2.9)	
Type of HF	Health Center	144 (84.7)	26 (15.3)	1	1	133 (78.2)	37 (21.8)	1	1
	Clinic	87 (95.6)	4 (4.4)	3.9 (1.3–11.6)	4.4 (1.4–13.3)**	79 (86.8)	12 (13.2)	1.8 (0.9–3.7)	2.3 (1.1–5.2)*
	Hospital	138 (87.3)	20 (12.7)	1.2 (0.7–2.3)	1.1 (0.6–2.1)	143 (90.5)	15 (9.5)	2.7 (1.4–5.1)	3.6 (1.8–7.2)**
Television availability	No	43 (91.5)	4 (8.5)	1		37 (78.7)	10 (21.3)	1	
	Yes	326 (87.6)	46 (12.4)	0.7 (0.2–1.9)		318 (85.5)	54 (14.5)	1.6 (0.8–3.4)	
Radio availability	No	154 (84.2)	29 (15.8)	1	1	153 (83.6)	30 (16.4)	1	
	Yes	215 (91.1)	21 (8.9)	1.9 (1.1–3.5)	2.4 (1.3–4.7)**	202 (85.6)	34 (14.4)	1.2 (0.7–2.0)	
Social media utilization	No	44 (78.6)	12 (21.4)	1	1	48 (85.7)	8 (14.3)	1	
	Yes	325 (89.5)	38 (10.5)	2.3 (1.1–4.8)	2.3 (1.1–5.1)*	307 (84.6)	56 (15.4)	0.9 (0.4–2.0)	
Training/orientation	No	214 (87.3)	31 (12.7)	1		198 (80.8)	47 (19.4)	1	1
	Yes	155 (89.1)	19 (10.9)	1.2 (0.6–2.2)		157 (90.2)	17 (9.8)	2.2 (1.2–4.0)	3.1 (1.6–6.1)**
Knowledge	Insufficient					29 (58)	21 (42)	1	1
	Sufficient					326 (88.3)	43 (11.7)	5.5 (2.9–10.5)	5.2 (2.6–10.4)**

***P-value <0.01.*
**P-value < 0.05.*

study is higher than the 70.7% pooled estimate report in Ethiopia (15) and the 64% report from the northeast Ethiopia (10).

We also identified the predictors of knowledge and attitudes regarding COVID-19. The first variable is degree and above level of education that influences COVID-19 knowledge with more than 2-fold. A similar finding was also noted in southern Ethiopia (16). The other variable is working in private clinics, which increases the odds of sufficient knowledge by more than 4-fold as compared to participants working in government health centers. There might be more frequent staff orientations and emphasis on preventive measures at private clinics than at government health facilities, which can contribute to the current knowledge difference. Besides, social media utilization like Facebook is found to be a significant factor that influences participants' knowledge regarding COVID-19. The same finding is also reported from a multicentered study conducted in Ethiopia (17). This implies that the internet and social media can play a pivotal role in timely public health risk communication like COVID-19, which hinders mass classroom discussions and meetings. During similar emergencies, virtual means of communication like training through zoom meetings should be adopted, even for health workers' continuous professional growth in development situations. In this study, participating in COVID-19-related training is found to be a predictor of favorable attitude, which is like other studies conducted in southern Ethiopia (16) and Venezuelan HPs (18). Similarly, working in hospitals and clinics becomes significantly associated with a favorable attitude than working in health centers. This might be related to the easy accessibility of COVID-19 information through bedsides, patient rounds, case presentations, and discussions in hospitals and private clinics than in government health centers. As a limitation, our findings might be overreported by participants as it is a self-administered way of data collection.

CONCLUSION

Most health professionals have a high level of knowledge and a favorable attitude regarding COVID-19. However, practice is relatively low and there remains plenty to build assertive preventive behaviors. Factors associated with having sufficient knowledge are the type of health facility, degree and above educational status, social media utilization, and radio availability, while favorable attitude is significantly associated with COVID-19-related training, type of health facility, and having sufficient knowledge. The gap between knowledge and practice among HPs can be narrowed through the application of an appropriate social and behavioral change communication strategy and mandatory regulations.

DATA AVAILABILITY STATEMENT

Original datasets are available in a publicly accessible repository: This data can be found here: https://datadryad.org/stash/share/g9_e95UE7T-YHHA50pxSBkBnHyB7Y3h-ZHcm9Smv03I.

AUTHOR CONTRIBUTIONS

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

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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.2022.899808/full#supplementary-material

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Zisis Kozlakidis,
International Agency For Research on Cancer (IARC), France

REVIEWED BY
Hussein Kadhem Al-Hakeim,
University of Kufa, Iraq
Ramezan Jafari,
Baqiyatallah University of Medical Sciences, Iran

*CORRESPONDENCE
Zoltán Szekanecz
szekanecz@gmail.com

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Severity and prognostic factors of SARS-CoV-2-induced pneumonia: The value of clinical and laboratory biomarkers and the A-DROP score

Miklós Szabó[1], Zsófia Kardos[2,3], Csaba Oláh[4], Péter Tamáska[5], Katalin Hodosi[6], Eszter Csánky[1] and Zoltán Szekanecz[6]*

[1]Department of Pulmonology, Borsod Academic County Hospital, Miskolc, Hungary, [2]Department of Rheumatology, Borsod Academic County Hospital, Miskolc, Hungary, [3]Faculty of Health Sciences, University of Miskolc, Miskolc, Hungary, [4]Department of Neurosurgery, Borsod Academic County Hospital, Miskolc, Hungary, [5]Department of Radiology, Borsod Academic County Hospital, Miskolc, Hungary, [6]Department of Rheumatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Introduction: Numerous clinical and laboratory scores that include C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH), interleukin 6 (IL-6), procalcitonin (PCT), blood urea nitrogen (BUN), creatinine levels and oxygenation (PaO_2 and SaO_2) have been used for the prognosis of COVID-19. In addition, composite scores have been developed for the assessment of general state and risk in community-acquired pneumonia (CAP) that may be applied for COVID-19 as well. In this study, we assessed severity and potential prognostic risk factors for unfavorable outcome among hospitalized COVID-19 patients. We also applied the A-DROP general scoring system used in CAP to COVID-19.

Patients and methods: Altogether 233 patients admitted to our center with COVID-19 were included in the study. Clinical status, several laboratory biomarkers described above, indicators of oxygenation were determined at hospital admission. We also applied the A-DROP composite scoring system that includes Age ($\geq$ 70 years in males and $\geq$ 75 years in females), Dehydration (BUN $\geq$ 7.5 mmol/l), Respiratory failure ($SaO_2 \leq 90\%$ or $PaO_2 \leq 60$ mmHg), Orientation disturbance (confusion) and low blood Pressure (systolic BP $\leq$ 90 mmHg) to COVID-19.

Results: At the time of admission, most patients had elevated CRP, LDH, ferritin, D-dimer, and IL-6 levels indicating multisystemic inflammatory syndrome (MIS). Altogether 49 patients (21.2%) required admission to ICU, 46 (19.7%) needed ventilation and 40 patients (17.2%) died. In the binary analysis, admission to ICU, the need for ventilation and death were all significantly associated with the duration of hospitalization, history of hypertension or obesity, confusion/dizziness, as well as higher absolute leukocyte and neutrophil and lower lymphocyte counts, elevated CRP, PCT, LDH, ferritin, IL-6, BUN, and creatinine levels, low PaO_2 and SaO_2 and higher A-DROP score at the time of admission ($p < 0.05$).

Conclusion: Numerous laboratory biomarkers in addition to obesity, dizziness at the time of admission and the history of hypertension may predict the need for ICU admission and ventilation, as well as mortality in COVID-19. Moreover, A-DROP may be a suitable scoring system for the assessment of general health and disease outcome in COVID-19.

KEYWORDS

COVID-19, tocilizumab (IL-6 inhibitor), prognosis, pneumonia, outcome, A-DROP score

Introduction

In late 2019, a new strain of β coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, which caused a worldwide epidemic due to its rapid spread (1, 2). The COVID-19 pandemic puts an extreme load on healthcare systems including intensive care units (ICU) all over the world (1, 3–5). In the first waves of the epidemic, the hospitalization rate was 5–10 percent, while global mortality was 2–3 percent. In the majority of patients, the disease is asymptomatic or mild, but in some patient groups it may be severe with potentially fatal outcome (6). SARS-CoV-2 virus-induced pneumonia is a part of multisystemic inflammatory syndrome (MIS) associated with the advanced stages of COVID-19. MIS often leads to the damage of multiple organs and death (3, 4, 7).

The initial assessment of the severity of community-acquired pneumonia (CAP) is important for patient management (8). In addition the number of patients diagnosed with COVID-19 pneumonia in this epidemic is high, while health resources are finite. Identification of high risk patients are of paramount importance for the optimal use of hospital capacity and patient safety. There have been attempts to identify prognostic factors that might predict the outcome of early SARS-CoV-2 infection and COVID-19-associated pneumonia (4, 9–11). Comorbidities, such as hypertension, hyperlipidemia, ischemic heart disease, congestive heart failure, chronic pulmonary disease, diabetes mellitus, cerebrovascular disease, dementia, liver disease, chronic kidney disease, malignancies, sickle cell disease, organ transplantation, and other immunocompromising conditions have been associated with a higher risk of severe disease and death (12–15). Symptoms including dyspnea, coughs, expectoration, hemoptysis, abdominal pain, anorexia, diarrhea, fatigue, myalgia, arthralgia, and fever have been reported more common in severe than in mild COVID-19 patients (16). Physical examination provides valuable information about a patient's severity and prognosis. Tachypnea, tachycardia, hypotension, hypoxemia, confusion observed on physical examination are poor prognostic signs in COVID-19 patients (17, 18).

Laboratory tests are essential to determine hospitalization and therapy in patients with symptoms of infection. Several laboratory parameters monitoring hematological status or biochemical, inflammatory, immunological, and coagulation processes have been identified as prognostic factors for COVID-19 disease. Severe and fatal cases tended to show higher white blood cell, lower lymphocyte and platelet count, lower percentages of monocytes, eosinophils, and basophils, higher leukocyte and neutrophil-counts and a higher neutrophil lymphocyte ratio compared to mild cases (19, 20).

Some laboratory biomarkers including C-reactive protein (CRP), interleukin 6 (IL-6), ferritin, D-dimer, lactate dehydrogenase (LDH), leukopenia and cardiac troponin (cTn), in addition to clinical symptoms, such as fever have been identified as markers of MIS and cytokine storm associated with COVID-19 (21–23). For example, both CRP and D-dimer levels were elevated in patients in need for transfer to ICU compared to non-ICU patients (22). D-dimer > 3,500 ng/ml was associated with poor survival (24). Procalcitonin is a reliable indicator of bacterial co- or superinfection, the latter being a characteristic factor in the mortality of respirated patients (15).

Several composite scores have been developed for the assessment of general state and risk in CAP that may be applied for COVID-19 as well (25). These include APACHE, qSOFA, PSI, CURB65, and A-DROP (25). Among these scoring systems, CURB65 [confusion, blood urea nitrogen (BUN) > 7 mmol/l, respiratory rate ≥ 30/min, low blood pressure (BP; diastolic BP ≤ 60 mmHg or systolic BP < 90 mmHg) and age ≥ 65 years] has been introduced by the British Thoracic Society (8, 25, 26). More recently, A-DROP, a modified version of CURB65 has been validated by the Japanese Respiratory Society (8, 25). The A-DROP scoring system includes Age (≥70 years in males and ≥ 75 years in females), Dehydration (BUN ≥ 7.5 mmol/l), Respiratory failure ($SaO_2 \leq 90\%$ or $PaO_2 \leq 60$ mmHg), Orientation disturbance (confusion) and low blood Pressure (systolic BP $\leq$ 90 mmHg (8, 25). It has been confirmed that A-DROP and CURB65 are equivalent for predicting CAP severity (8, 25). The prognostic value of A-DROP has been studied in only very few cohorts (25, 27, 28).

In this study, we assessed severity and potential prognostic risk factors for unfavorable outcome among hospitalized COVID-19 patients admitted to our center. We also applied the A-DROP general scoring system used in CAP to COVID-19.

Patients and methods

Study design and patients

This single-center, retrospective cohort study was conducted at the dedicated COVID-19 department of the Borsod Academic County Hospital, Miskolc, Hungary. Data from patients hospitalized for COVID-19 pneumonia between October 1, 2020, and March 31, 2021 were retrospectively analyzed. Confirmation of SARS-CoV-2 infection was performed by RT-PCR method from throat-swab specimens. Pneumonia was confirmed by radiological imaging performing chest CT in 227 and plain X-ray in 6 cases. Most patients received favipiravir, corticosteroid (dexamethasone or methylprednisolone), enoxaparine treatment, as well as oxygen supplementation. In selected cases, remdesivir or tocilizumab was also introduced. The clinical criteria for hospital discharge included absence of fever for at least 3 days, cessation or significant improvement of respiratory symptoms, as well as clear improvement of the radiological picture.

The Ethics Committee of the Borsod Academic County Hospital approved this study (BORS 04/2021). We conducted this study according to the Declaration of Helsinki.

Clinical, laboratory and imaging data collection

We reviewed all clinical electronic medical records and laboratory reports, as well as chest CT and X-ray images. We collected data on age, sex, as well as history of smoking, chronic comorbidities including hypertension, coronary arterial disease (CAD), chronic obstructive pulmonary disease (COPD) or bronchial asthma, previous stroke, diabetes mellitus, current malignancy, chronic kidney disease (CKD), obesity, as well as the use of systemic immunosuppressive therapy within 1 month prior to the analysis. We also recorded the duration and type of symptoms (fever: axillary temperature $\geq$ 38°C, cough, dyspnea, confusion), vital signs (blood pressure, oxygen saturation [SaO_2] by pulse oximetry), laboratory values [white blood cell, absolute lymphocyte and platelet counts, serum CRP, ferritin, IL-6, LDH, D-dimer, procalcitonin (PCT), BUN, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer], partial arterial oxygen pressure (PaO_2) as determined by blood gas analysis, as well as treatment (corticosteroids, antiviral, and antibacterial agents, targeted therapies) at hospital admission and during the time of hospitalization. We also recorded the occurrence of pulmonary embolism and Clostridium difficile infection during hospitalization. A-DROP scores were calculated from the data obtained at the time of hospital admission (8).

All data were evaluated by two physicians (MS, ZK) and a third researcher (ZS) adjudicated any difference in interpretation between the two primary reviewers.

Outcome parameters

The primary outcome parameters were the need for intensive care, need for invasive (IV) vs. Non-invasive ventilation (NIV) and mortality. Mortality was calculated from mortality observed during hospitalization, and the disease-related mortality 30 days after discharge. The time of hospitalization was also recorded.

Statistical analysis

Statistical analysis was performed using the SPSS software v.26.0 (IBM, Armonk, NY, United States). Data are expressed as mean ± *SD* for continuous and case number plus percentages (*n*, %) for categorical variables. The distribution of continuous variables was determined by Kolmogorov-Smirnov test. Continuous variables were assessed by Mann-Whitney *U*-tests. Nominal variables were compared by χ^2 or Fisher's exact test. Spearman's analysis was used to test for correlations. Receiver Operating Characteristic (ROC) curves show the sensitivity and specificity for every possible cut-off for a test. Area under the ROC curve is measure of the usefulness of a characteristic, where a greater area means a more useful test. P-values < 0.05 were considered significant in all tests mentioned above.

Results

Characterization of patients

Altogether 233 patients were included in this study. Their main characteristics are included in **Table 1**. The patient cohort included 148 men and 85 women with a mean age of 56.8 ± 8.7 years (range: 40–76 years). Disease duration (time from the first symptom to hospital admission) was 8.5 ± 5.3 days (range: 1–35 days). Altogether 7.3% received

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TABLE 1 Patient characteristics.

Parameters at baseline	Total N	Mean ± *SD* or *N* (%)	Normal range
Age (years)	233	56.8 ± 8.7	–
Female: male ratio	233	85:148	–
Disease duration (days from first symptom)	233	8.5 ± 5.3	–
CRP (mg/l)	233	***123.0* ± *98.6***	0.2–10
Absolute WBC count (G/l)	233	8.9 ± 6.1	4.4–11.3
Absolute neutrophil count (G/l)	233	7.2 ± 7.7	2–8
Absolute lymphocyte count (G/l)	233	1.5 ± 4.3	0.8–4
Platelet count (G/l)	233	258.7 ± 108.3	150–400
PCT (ng/ml)	166	0.87 ± 7.40	0–0.5
LDH (U/l)	233	***744.7* ± *515.1***	230–460
D-dimer (ng/ml)	137	***2413.8* ± *4313.0***	0–500
ferritin (ng/ml)	124	***1207.4* ± *1927.4***	20–300
IL-6 (pg/ml)	67	***130.2* ± *138.4***	0–7
BUN (mmol/l)	233	6.6 ± 4.5	2.9–8.5
creatinine (μmol/l)	233	97.6 ± 89.9	64–104
Fever	233	146 (62.9)	–
Dyspnea	233	158 (68.1)	–
Coughs	233	162 (70.4)	–
Confusion/dizziness	233	10 (4.3)	–
PaO_2 (mmHg)	199	58.4 ± 16.2	80–100*
SaO_2 (%)	233	89.7 ± 7.8	95–99*
systolic BP (mmHg)	233	139.9 ± 23.5	90–140*
A-DROP	233	0.94 ± 0.79	0–1*
Immunosuppressive therapy (current)	233	17 (7.3)	–
Smoking (current)	68	13 (19.1)	–
Medical history	**Total *N***	***N* (%)**	
Hypertension (history)	233	151 (65.1)	–
CAD (history)	233	51 (22.0)	–
Stroke (history)	233	14 (6.0)	–
CKD (history)	233	13 (5.6)	–
Diabetes mellitus (history)	233	63 (27.2)	–
Obesity (history)	233	71 (30.6)	–
Malignancy (history)	233	10 (4.3)	–
COPD/asthma (history)	233	51 (22.0)	–
Outcome measures	**Total *N***	**Mean ± *SD* or *N* (%)**	
Time of hospitalization (days)	233	12.1 ± 6.8	–
ICU admission	233	49 (21.2)	–
Need for ventilation	233	46 (19.7)	–
Need for NIV	233	9 (3.9)	–
Need for IV	233	37 (15.9)	–
Deaths	233	40 (17.2)	–

*Age-dependent. Significantly elevated mean values are in bold italics. A-DROP, Age, Dehydration, Respiratory failure, Orientation disturbance (confusion) and low blood Pressure; BP, blood pressure; BUN, blood urea nitrogen; CAD, coronary artery disease; CTSS, CT chest Severity Score; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; IV, invasive ventilation; LDH, lactate dehydrogenase; NIV, non-invasive ventilation; PaO_2, partial oxygen pressure; PCT, procalcitonin; SaO_2, oxygen saturation; WBC, white blood cell.

immunosuppression, 19.1% were current smokers. The medical history of the patients included hypertension (65.1%), CAD (22%), stroke (6%), CKD (5.6%), diabetes mellitus (27.2%), obesity (30.6%), malignancies (4.3%), and COPD/asthma (22%). At the time of admission, about two-third of patients had fever,

TABLE 2 Determinants of ICU admission, need for ventilation and survival.

Parameter	*p*-value		
	ICU vs. non-ICU	Vent vs. no vent	Death vs. survival
Age	0.121	0.078	***0.003***
Disease duration at admission	0.304	0.720	0.134
Duration of hospitalization	***<0.001***	***<0.001***	0.190
Male sex	0.050	***0.018***	0.097
Immunosuppressive therapy	0.261	0.588	0.589
Current smoker	0.154	0.221	0.326
Hypertension (history)	***0.002***	***0.010***	***0.011***
CAD (history)	0.929	0.691	***0.029***
Stroke (history)	0.599	0.649	0.206
CKD (history)	0.197	0.503	0.395
Diabetes mellitus (history)	0.182	0.239	***0.045***
Obesity (BMI)	***0.014***	***0.031***	***0.043***
Malignancy (history)	0.135	***0.021***	0.236
COPD/asthma (history)	0.929	0.931	0.354
Fever	0.292	0.560	0.309
Dyspnea	0.422	0.174	0.868
Coughs	0.885	0.120	0.846
Confusion/dizziness	***0.034***	***0.044***	***0.014***
Absolute WBC count	***0.045***	***0.012***	***0.007***
Absolute neutrophil count	***0.034***	***0.031***	***<0.001***
Absolute lymphocyte count	***0.007***	***0.011***	***0.003***
Absolute platelet count	0.276	0.141	0.891
CRP	***<0.001***	***<0.001***	***<0.001***
PCT	***<0.001***	***<0.001***	***<0.001***
LDH	***<0.001***	***<0.001***	***<0.001***
D-dimer	0.124	0.087	***0.009***
Ferritin	***0.042***	0.102	***0.041***
IL-6	***0.026***	***0.024***	***0.014***
BUN	***0.015***	***0.001***	***<0.001***
Creatinine	***0.001***	***0.001***	***<0.001***
PaO_2	***0.001***	***0.001***	***0.004***
SaO_2	***0.001***	***<0.001***	***0.002***
Systolic BP	0.777	0.513	0.505
A-DROP	***0.002***	***<0.001***	***<0.001***

Mann-Whitney test was used. Significant differences are in bold italics. A-DROP, Age, Dehydration, Respiratory failure, Orientation disturbance (confusion) and low blood Pressure; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; LDH, lactate dehydrogenase; PaO_2, partial oxygen pressure; PCT, procalcitonin; SaO_2, oxygen saturation; Vent, ventilation; WBC, white blood cell.

dyspnea and/or coughs, while 4.3% had confusion/dizziness (Table 1). According to the mean laboratory values, most of these patients had elevated CRP, LDH, ferritin, D-dimer and IL-6 levels indicating systemic inflammation (MIS) (Table 1). Out of the 233 hospitalized patients, 49 (21.2%) required admission to ICU. Altogether 46 patients (19.7%) needed ventilation, out of which 9 (3.9%) required NIV and 37 (15.9%) invasive ventilation (IV). Forty patients (17.2%) died. The mean (± *SD*) duration of hospitalization was 12.1 ± 6.8 days (range: 2–48 days) (Table 1).

Determinants of intensive care units admission, need for ventilation and death

In the binary analysis, admission to ICU was significantly more often associated with the duration of hospitalization ($p < 0.001$), hypertension ($p = 0.002$) or obesity ($p = 0.014$) in the medical history, as well as with confusion/dizziness at hospital admission ($p = 0.034$). Among the laboratory parameters, ICU admission was associated with higher absolute leukocyte ($p = 0.045$), higher neutrophil ($p = 0.034$) and lower lymphocyte counts ($p = 0.007$), CRP ($p < 0.001$), PCT ($p < 0.001$), LDH ($p < 0.001$), ferritin ($p = 0.042$), IL-6 ($p = 0.026$), BUN ($p = 0.015$), creatinine ($p = 0.001$), PaO_2 ($p = 0.001$) and SaO_2 ($p = 0.001$) (Table 2).

The need for ventilation was significantly associated with days of hospitalization ($p < 0.001$), male sex ($p = 0.018$), history of hypertension ($p = 0.010$), obesity ($p = 0.031$) or malignancy ($p = 0.021$), as well as with confusion/dizziness upon admission ($p = 0.044$). Among the laboratory parameters, the need for ventilation was associated with leukocytosis ($p = 0.012$), neutrophilia ($p = 0.031$) and lymphopenia ($p = 0.011$), as well as CRP ($p < 0.001$), PCT ($p < 0.001$), LDH ($p < 0.001$), IL-6

TABLE 3 Determinants of ICU admission and death.

Parameter	ICU admission (Y/N)					Death (Y/N)				
	Cutoff	Sens.	1-Spec.	ROC area	*p*-value	Cutoff	Sens.	1-Spec.	ROC area	*p*-value
A-DROP	1.5	0.35	0.17	0.61 ± 0.05	***0.026***	1.5	0.47	0.16	0.71 ± 0.05	***<0.001***
Age (year)	64.5	0.35	0.21	0.57 ± 0.05	0.121	61.5	0.58	0.32	0.65 ± 0.05	***0.003***
PaO_2 (mmHg)	53.7	0.41	0.71	0.33 ± 0.05	***0.002***	55.3	0.32	0.63	0.34 ± 0.06	***0.004***
SaO_2 (%)	90.2	0.41	0.68	0.36 ± 0.05	***0.010***	87.6	0.52	0.80	0.36 ± 0.06	***0.012***

ROC analysis was performed. Significant differences are in bold italics. A-DROP, Age, Dehydration, Respiratory failure, Orientation disturbance (confusion) and low blood Pressure; N, no; PaO_2, partial arterial oxygen pressure; SaO_2, oxygen saturation; Sens., sensitivity; Spec., specificity; Y, yes.

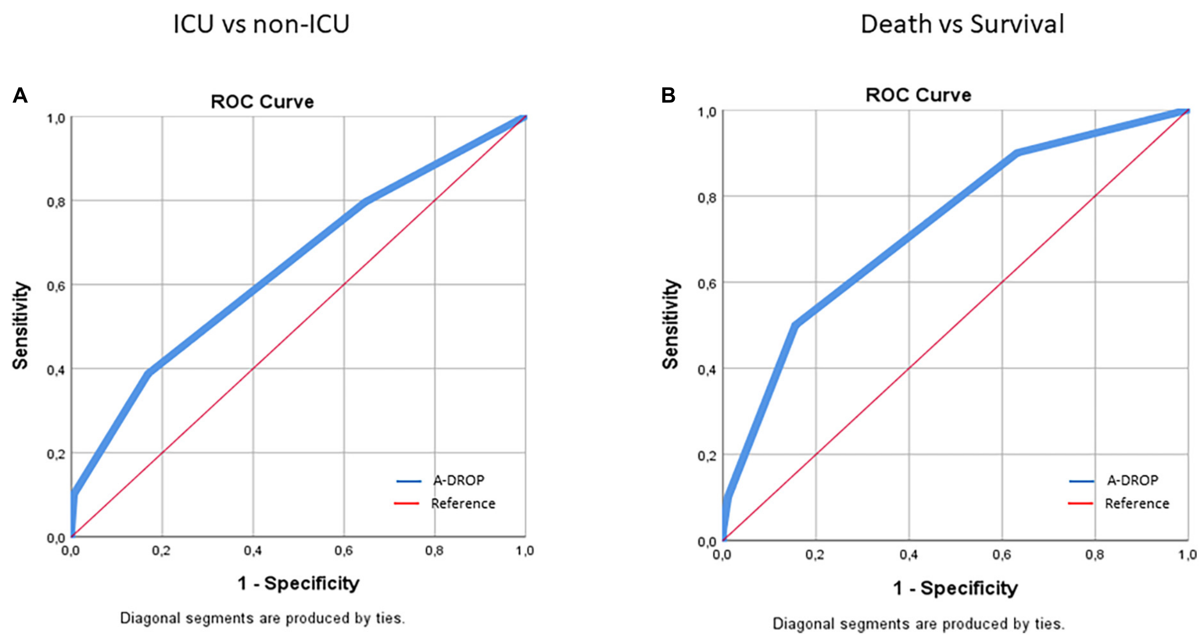

FIGURE 1
ROC curve analysis of the association of A-DROP values with the need for ICU admission **(A)** and death **(B)** in COVID-19 patients.

(p = 0.024), BUN (p = 0.001), creatinine (p = 0.001), PaO_2 (p = 0.001), and SaO_2 ($p < 0.001$) (Table 2).

Finally, death was associated with age (p = 0.003), hypertension (p = 0.011), CAD (p = 0.029), diabetes mellitus (p = 0.045) or obesity (p = 0.043) in the medical history, as well as with confusion/dizziness at hospital admission (p = 0.014). Poor survival was associated with higher absolute leukocyte (p = 0.007) and neutrophil ($p < 0.001$) but lower lymphocyte counts (p = 0.003), as well as CRP ($p < 0.001$), PCT ($p < 0.001$), LDH ($p < 0.001$), D-dimer (p = 0.009), ferritin (p = 0.041), IL-6 (p = 0.014), BUN ($p < 0.001$), creatinine ($p < 0.001$), PaO_2 (p = 0.004) and SaO_2 (p = 0.002) (Table 2).

We also assessed possible predictors of ICU admission and survival by ROC curve analysis. Again, higher age was significantly associated with mortality (p = 0.003), but not with the need for ICU admission (p = 0.121) (Table 3). Both lower arterial PaO_2 and SaO_2 were associated with increased need for ICU admission (p = 0.002 and p = 0.010, respectively) and death (p = 0.004 and p = 0.012, respectively) (Table 3).

A-DROP is a suitable method to assess general state and risk in COVID-19-associated pneumonia

In the binary analysis, admission to ICU (p = 0.002), the need for ventilation ($p < 0.001$) and death ($p < 0.001$) were significantly associated with higher A-DROP (Table 2). In the ROC analysis, A-DROP > 1.5 significantly predicted admission to ICU (p = 0.026) and mortality ($p < 0.001$) (Table 3 and Figure 1). In the simple Spearman's correlation analysis, A-DROP significantly and positively correlated with absolute WBC and neutrophil counts, CRP, PCT, LDH, D-dimer, ferritin, IL-6, and creatinine (Table 4).

TABLE 4 Correlations of A-DROP with clinical and laboratory parameters.

Parameter	A-DROP	
	***R*-value**	***p*-value**
Hospitalization days	0.097	0.159
Disease duration	0.129	0.057
Absolute WBC count	0.341	***<0.001***
Absolute neutrophil count	0.339	***<0.001***
Absolute lymphocyte count	−0.081	0.221
Absolute platelet count	0.043	0.514
CRP	0.270	***<0.001***
PCT	0.599	***<0.001***
LDH	0.299	***<0.001***
D-dimer	0.354	***<0.001***
Ferritin	0.421	***<0.001***
IL-6	0.365	***0.002***
BUN	0.575	***<0.001***
Creatinine	0.317	***<0.001***
Systolic BP	0.065	0.331

Spearman's correlation analysis was performed. Significant differences are in bold italics. A-DROP, Age, Dehydration, Respiratory failure, Orientation disturbance (confusion) and low blood Pressure; BP, blood pressure; BUN, blood urea nitrogen; CRP, C-reactive protein; IL, interleukin; LDH, lactate dehydrogenase; procalcitonin; WBC, white blood cell.

Discussion

In this single-center study of 233 COVID-19 patients admitted to hospital, we assessed elements of medical history, as well as numerous clinical and laboratory parameters in association with the need for admission to ICU, need for ventilation and death. We also focused on the value of the A-DROP scoring system in the assessment of general health and prediction of outcome in hospitalized COVID-19 patients.

At the time of admission, among laboratory biomarkers, patients had elevated CRP, LDH, D-dimer, ferritin, and IL-6 levels. All these parameters, as well as higher absolute WBC and neutrophil and lower absolute lymphocyte counts, PCT, BUN, creatinine, PaO_2, and SaO_2 were associated with ICU admission, need for ventilation and death. Among clinical and other factor, age was associated with death only, male sex with the need for ventilation only and the duration of hospitalization with the need for ICU admission and ventilation. CRP, IL-6, ferritin, D-dimer, LDH and high neutrophil/lymphocyte, as well as BUN/creatinine ratios have been identified as markers of MIS/cytokine storm associated with SARS-CoV-2 infection (21–23). Both CRP and D-dimer levels were elevated in patients in need for transfer to ICU compared to non-ICU patients (22). D-dimer > 3,500 ng/ml was associated with poor survival (24). Obesity and confusion (dizziness) at the time admission, as well as the history of hypertension were associated with all three outcome measures. Obesity may be associated with increased mortality in COVID-19 (29). Dizziness has also been reported as an indicator of critical outcome in COVID-19 (30).

In addition to other known scoring systems, A-DROP has recently been validated for the assessment of health status in CAP (8, 25). In other studies, A-DROP has proven to be of great value in predicting CAP severity (8, 25). In the present cohort, the mean value of A-DROP at the time of admission was 0.94 on a 0–5 scale. A-DROP value of two or above were significantly associated with the need for ICU admission and ventilation, as well as with death. A-DROP also significantly correlated with absolute WBC and neutrophil counts, CRP, PCT, LDH, D-dimer, ferritin, IL-6, BUN, and creatinine. As discussed above, most of these parameters have been associated with severe COVID-19 including MIS and cytokine storm (21–23).

In other studies, various cardio-pulmonary, renal, hepatic, hematologic, and immunologic comorbidities have been associated with poor COVID-19 outcome (12–15). In addition, similarly to our findings, CRP, IL-6, ferritin, D-dimer, LDH, and troponin have been identified as severity and prognostic markers of COVID-19-associated MIS (21–23).

This study has certain strengths and limitations. The major strength of this study is that this is the first relatively large study assessing the prognostic value of A-DROP in a complex way, in association with numerous clinical and laboratory markers of outcome including ICU admission, ventilation and death in COVID-19. Possible limitations may include the single-center nature of the study. In addition, we have not included chest CT scans in this analysis, we have not validated our findings against other cohorts and we have not considered for population-specific biases.

Conclusion

In conclusion, A-DROP may be a suitable scoring system for predicting the need for ICU admission and ventilation, as well as mortality in COVID-19. In our study, we identified several clinical and laboratory parameters that, when combined with the A-DROP scoring system, could further increase its sensitivity and specificity, providing clinicians with an appropriate risk assessment tool to identify high-risk patients in need of advanced health care. Further studies are planned to develop a scoring system with sufficient sensitivity and specificity.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Borsod Academic County Hospital (BORS 04/2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS: study design, patient recruitment, data collection, manuscript drafting, and finalization. ZK, PT, CO, and EC: patient recruitment and data collection. KH: statistical analysis and data interpretation. ZS: supervisor, study design, manuscript drafting, and finalization. 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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EDITED BY
Chantal M. Morel,
Université de Genève, Switzerland

REVIEWED BY
Charles J. Vukotich Jr.,
University of Pittsburgh, United States
Hanjia Lyu,
University of Rochester, United States

*CORRESPONDENCE
Feng Qi
fqi@kean.edu

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Evaluating spatial accessibility to COVID-19 vaccine resources in diversely populated counties in the United States

Feng Qi[1]*, Daniela Barragan[1], Maverick Garcia Rodriguez[1] and Jiongcheng Lu[2]

[1]School of Environmental and Sustainability Sciences, Kean University, Union, NJ, United States, [2]Gobal Business School for Health, University College London, London, United Kingdom

This study examines the accessibility to COVID-19 vaccination resources in two counties surrounding Newark, NJ in the New York Metropolitan Area, United States. The study area represents diverse population makeups. COVID-19 vaccines were made available by different types of vaccination sites including county mass vaccination sites, medical facilities and pharmacies, and a FEMA community vaccination center in spring 2021. We used the two-step floating catchment area method to measure accessibility and calculated the average accessibility scores of different population groups. We examined the patterns and tested the significance of the differences in accessibility across population groups. The results showed clear spatial heterogeneity in the accessibility to vaccine resources with the existing infrastructure (medical/pharmacy vaccine sites). Accessibility patterns changed with the introduction of county mass sites and the FEMA community site. The county mass vaccination sites in one county greatly increased accessibilities for populations of minority and poverty. The FEMA community site in the other county accomplished the same. Both the local health department and the federal government played an important role in mitigating pre-existing inequalities during the vaccination campaign. Our study shows that social determinants of health need to be addressed and taken into explicit consideration when planning resource distribution during the pandemic.

KEYWORDS

COVID-19, vaccine, accessibility, equity, disparity

Introduction

The COVID-19 pandemic not only caused profound damage to human health, livelihood of humans and economy worldwide (1), but posed an unprecedented challenge to our healthcare system as well as public health planning and response systems (2). During the early stage of the pandemic, containing the spread and reducing healthcare demand had mostly relied on public health measures known as non-pharmaceutical interventions (NPIs) such as social distancing, contact tracing, travel-related restrictions, and personal protective measures (3). The effectiveness of these interventions, however, has not been consistent across different countries (4, 5) and different states in the US (6) due to a variety of policy and social factors. The fast development and roll-out of COVID-19 vaccines brought a substantial impact on mitigating outbreaks (7) when combined with the NPIs. Mass vaccination offers a crucial pharmaceutical strategy for exiting the pandemic while preventing excessive demands on the health-care system (8).

The United States started its COVID-19 vaccination campaign in December 2020. By spring 2021, vaccine production and supply had increased for vaccination to open up to all adult populations. Counties established community vaccination sites in addition to medical facilities and pharmacies to push for mass vaccinations. The Federal Emergency and Management Agency (FEMA) also established community vaccination centers in dense urban areas (9). Production, accessibility, and acceptance are all essential factors that ensure a majority of the population gets vaccinated at this stage (10). In particular, accessibility to vaccination resources is an important determinant of efficient and equitable vaccine distribution (11).

The existence of disparities in COVID-19 infections and mortality between racial groups in the US has been widely documented (11–14). It calls for actions in various aspects of public health response from data collection to resource allocation in order to avoid further propagating the inequities (12). Examples include establishing testing sites in underserved communities to increase accessibility during the testing and containment stages (14) and incorporating health equity into reopening plans (15). During the current vaccination campaign, health equity should also be addressed through incorporating social factors in the distribution of vaccine resources. Accessibility to vaccine resources by different population groups should be evaluated in a systematic manner across multiple sectors (13) to mitigate disparities and prioritize accessibility of the disproportionately affected racial and ethnic minority groups.

Access to vaccination sites can be evaluated using proximity-based measures such as distance from census tract centroids to vaccination sites (16). Additionally, vaccination capacity of the individual sites affects accessibility as supply varies greatly among sites. Geospatial measures of accessibility take into consideration the spatially varying supply and distribution of the supply to population demands based on travel distance. Previous research measured accessibility to influenza A/H1N1p vaccination sites as vaccination capacity divided by travel distance (17). For each site, accessibility was adjusted by dividing the sum of accessibilities to all nearby sites. It considered other sites as competing factors and the accessibility measure was about one's tendency to get vaccinated at a particular site and not others. We aim to measure one's accessibility to the general vaccine resource. Multiple vaccine sites thus supplement each other and not compete with each other. The study (17) also did not consider the sharing of the vaccine supply among the population. Another study quantified accessibility to H1N1 vaccines by incorporating not only the distance and capacity factors, but also population demand in the service area (18). An optimization approach made it possible to also capture system constraints such as individuals' choices. The optimization model, however, relied on a number of assumptions regarding user choices as well as users' full knowledge of all vaccine sites within 50 miles and their capacities when making their choices. Some of these assumptions could not be met during the COVID-19 vaccination campaign. The model was also computationally intensive and thus best used for retrospective studies and did not fit our goal for rapid assessment of vaccine access among disproportionally affected populations during an ongoing vaccination campaign.

During early stages of the COVID-19 pandemic, studies evaluated accessibilities to testing sites using rapid measures by taking into consideration of testing capacities, population demands, and travel distances (19–21)). We adopted a similar approach to examine the vaccine accessibility landscape in NJ counties surrounding Newark in the NY Metropolitan area. The study area has diverse population makeups and vaccination resources were distributed by a layered system consisting of county mass vaccination sites, medical facilities and pharmacies, as well as a FEMA community vaccination center during the vaccination campaign.

The objectives are to (1) examine the spatial heterogeneity of accessibility in diversely populated communities, (2) investigate the relationship between accessibility and socioeconomic factors, and (3) compare the effect of different types of vaccination sites during the mass vaccination campaign. The goal is to provide insight into any mismatch of resources and population, inform public health planners to guide efforts in establishing sites, and allocate resources in an equitable manner. The method provides rapid assessments with readily available data and is applicable for prospective analysis by public health decision makers during an ongoing vaccination campaign to evaluate scenarios for resource distribution and adjust the setup of vaccination sites. Thus it adds to the toolset for future vaccination planning of other emerging/re-emerging infectious disease outbreaks or if COVID-19 co-exists with the human population for a long time and yearly re-vaccination becomes necessary.

Methods

This study was performed in Essex County and Union County, New Jersey. New Jersey is one of the most affected US states in the COVID-19 pandemic (40) and the impact has been disproportionately concentrated among Black and Hispanic populations (22, 23). The two counties selected for analysis of vaccine accessibility are located within close proximity to New York City and Newark International Airport, making them a major transmission hub during each wave of the pandemic. Both counties have diverse populations. The largest Essex County racial/ethnic groups are Black (37.5%) followed by White (27.2%) and Hispanic (24.3%). The largest Union County racial/ethnic groups are White (36.7%) followed by Hispanic (33.9%) and Black (19.5%). Both counties started to distribute COVID-19 vaccines through medical facilities and pharmacies and established community vaccination sites in early 2021. One of FEMA's community mass vaccination centers was also located in Newark of Essex County.

Data

Vaccination site locations as of May 23rd 2021 were obtained through the NJ Department of Health's COVID-19 information hub (24) and geocoded with the ArcGIS World Geocoding Service (25). Daily available appointments at each site were used to represent the vaccination capacity of the individual sites. Socioeconomic data at the census tract level was compiled as Geographic Information System (GIS) maps and associated attribute tables containing variables from the US Census 2019 American Community Survey (ACS), including age and sex, race and ethnicity, income and poverty, housing characteristics, technology and internet availability, among others.

Accessibility calculation and mapping

We used the two-step floating catchment area (2SFCA) method (26) to calculate accessibility to vaccine resources for each of the 318 census tracts in the two counties. The method computes a supply-to-population ratio to measure accessibility to facilities or resources such as healthcare facilities (27), food resources (28), and most recently COVID-19 testing sites (19) and hospital beds (21). To measure accessibility to vaccines, the first step is to assess the availability of supply at each vaccination site as the ratio of supply to the demand population located within a catchment area of each site (j). Delineation of catchment areas is based on a threshold travel distance (d_0) along road networks. A supply-to-demand ratio R_j is then computed for each site using Equation 1.

$$R_j = \frac{S_j}{\sum_{k\in\{d_{kj}\le d_0\}} P_k} \quad (1)$$

S_j is the available vaccination appointments of site j, P_k is the population of census tract k, whose centroid falls within the catchment of site j. The travel distance d_{kj} from k to j is no greater than a preset threshold driving distance d_0. In our study, we tested different thresholds in the delineation of catchments from 1–5 miles. It was observed that with 5-mile catchments, almost all areas in the two counties are covered. As vaccines can be readily administered at many pharmacies, accessibility to vaccination sites should be evaluated differently from accessibility to primary care doctors, for which the commonly used threshold is a 30 min travel time (19). With nearly 9 in 10 Americans living within 5 miles of a community pharmacy (29), we adopted the 5-mile threshold for calculating accessibility scores. One other note in the calculation of accessibility in our study is that the county mass vaccination sites are only open to the county's own residents. Thus we adjusted catchment delineation for county-operated mass sites using county boundaries.

One census tract may fall within the catchments of multiple vaccination sites. The second step of 2SFCA is to calculate the accessibility score A_i for each census tract i by summing up the supply of all nearby vaccination sites whose catchment areas contain the census tract i using Equation 2, where A_i is the accessibility score calculated for census tract i.

$$A_i = \sum_{j\in\{d_{ij}\le d_0\}} R_j \quad (2)$$

The accessibility scores of the census tracts were mapped with GIS. Cluster and outlier analysis was conducted using the Anselin Local Moran's I (30) to measure the concentration of high and low accessibilities in the study area with ArcGIS Pro (31).

Accessibility analysis

In order to examine how accessibility varies among different populations, we selected a set of variables from the census attribute table. These include the percentage of population under poverty, percentage of 65 years and older, and percentage of different racial/ethnic groups. We calculated the average accessibility scores of each population group, following Lu et al. (19), using Equation 3. A^g is the average accessibility score of population group g, P_i^g is the percentage of population of group g in census tract i, and n is the total number of census tracts.

$$A^g = \frac{\sum_{i=1}^{n} P_i^g A_i}{\sum_{i=1}^{n} P_i^g} \quad (3)$$

In order to test the significance of the differences in accessibility across population groups, we conducted spatial lag regressions with accessibility scores as the dependent variable and the socioeconomic variables as independent variables. A spatial lag of accessibility was added to the linear regression model as an independent variable to account for spatial autocorrelation between neighboring tracts because spatial accessibility measures are usually strongly spatially auto-correlated (19, 26). Specifically, let y_i be the accessibility score of

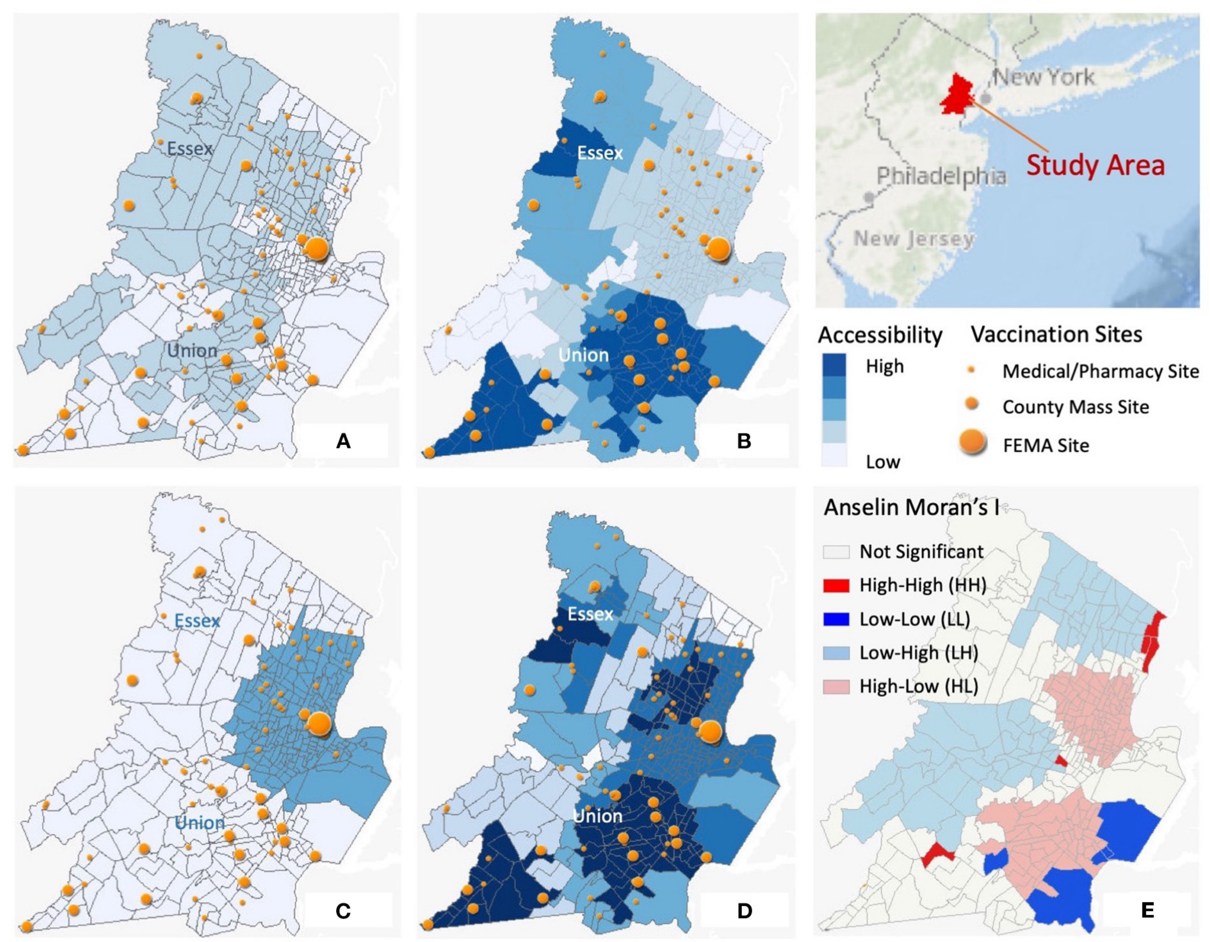

FIGURE 1
Spatial distributions of accessibility scores. **(A)** Accessibility with medical/pharmacy sites only; **(B)** Accessibility with county mass sites only; **(C)** Accessibility with FEMA sites only; **(D)** Accessibility with all sites combine; **(E)** Cluster analysis with Anselin Moran's I.

a census tract i and the vector of covariates for tract i is x_i. The model is expressed as:

$$y_i = \rho w_i y + x_i \beta + \varepsilon_i \quad (4)$$

ε_i is a random error term. $w_i y$ is the spatial lag, a weighted average of the spatial neighbors of census tract i, defined by a spatial contiguity matrix W. ρ represents the relationship between accessibility at a location with accessibilities of its neighbors and $\beta$is the vector of local regression coefficients associated with x_i. We adopted the first order Queen contiguity to define the spatial contiguity matrix (19, 32) and conducted the analyses using GeoDa 1.18 (33).

In order to examine how a certain socioeconomic factor is correlated with accessibility and how the correlation varies geographically in the two counties, we conducted local bivariate relationship analysis using local entropy maps (34). It allows for the quantification of spatial heterogeneity of the correlation between two variables. It uses a local entropy statistic to measure the amount of shared information between the two involved variables. Entropy can capture complex relationships including exponential, quadratic, and not just linear relationships like other statistics. The results will help us answer specific questions such as: if poverty has a significant correlation with accessibility to vaccination resources, how does the strength of the relationship vary across the different neighborhoods in the two NJ counties? The spatial variation of relationship types and strengths could give insights to resource disparity and guide future public health planning and responses.

Results

Spatial heterogeneity of accessibilities

Figure 1 shows the distribution of accessibility scores with different types of vaccination sites: medical/pharmacy sites (Figure 1A), county mass vaccination sites (Figure 1B),

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TABLE 1 Average accessibilities of different population groups.

	All population	White	Black	Native	Asian	Hispanic	Poverty	Elderly
Essex county								
County mass sites	3.15	3.93	2.35	2.12	4.69	3.70	2.33	3.62
Medical/Pharmacy sites	1.11	1.26	1.01	0.88	1.22	1.17	0.95	1.22
County + Medical	4.26	5.19	3.36	3.00	5.92	4.87	3.28	4.84
County + Medical +FEMA	11.6448	9.93	13.29	13.10	10.10	12.41	13.16	11.10
Union county								
County mass sites	14.81	12.93	17.53	18.40	11.78	13.16	17.89	13.91
Medical/Pharmacy sites	1.03	1.08	0.97	0.92	1.18	1.06	0.88	1.06
County + Medical	15.84	14.01	18.50	19.31	12.96	14.22	18.77	14.97
County + Medical +FEMA	16.10	14.13	19.22	19.31	13.03	14.71	19.05	15.19

and FEMA site (Figure 1C). There are notable variations of accessibility depending on the type of facilities. The county sites map visualizes a large cluster in Union county with high accessibility scores compared to the lower accessibilities with only medical/pharmacy sites. In Essex county, high accessibility clusters appear on the northwest side for both county mass sites and medical/pharmacy sites but not the southeast. It is the FEMA community site established in Newark that improved accessibility to the southeast portion of the county. By May 2021, all three types of vaccination sites were in operation. Spatial heterogeneity and local clustering are still notable on the accessibility map combining all vaccine resources (Figure 1D).

The significance of spatial clusters is also confirmed by Anselin Local Moran's I measures. Figure 1E shows significant local clusters include high value clusters (HH) and low value clusters (LL). Significant outliers are neighborhoods with high accessibility surrounded by those with low values (HL), and vice versa (LH). Two small high accessibility score clusters are identifiable in part of Essex (Newark) and Union (Union Township). Two large clusters of low accessibility are located near Montclair in Essex and Springfield in Union. Contrasting accessibility in neighboring communities can be found in many areas such as part of Belleville with high accessibility tracts surrounding low accessibility neighborhoods. These results indicate significant spatial heterogeneity of accessibility to vaccine resources.

Accessibilities of socioeconomic groups

Table 1 lists the computed average accessibilities of different socioeconomic population groups. In Essex County, Black and Native Americans' accessibilities are lower than average with county mass sites only. So is the accessibility of the population under poverty. Adding medical/pharmacy sites increased overall accessibilities just slightly and did not change the pattern. It was the FEMA site that increased accessibilities greatly and especially for Black, Native, Hispanic populations and the population under poverty. Union county has overall higher accessibilities than Essex. Black and Native Americans' accessibilities are always higher than average starting with county mass sites. So is the accessibility of the population under poverty. Asian and Hispanic populations' accessibilities are slightly lower than average. The FEMA site did not change the situation much as most Union residents live more than 5 miles away from Newark. With all vaccine resources combined, most minority population groups and populations under poverty have higher than average accessibilities in the two counties. Elderly population has slightly lower than average accessibility in both counties. These results indicate that the low accessibility clusters in Union County are not necessarily associated with unfavorable social vulnerability in the aspect of minority population and only corresponds slightly to elderly population.

Spatial lag regression

We fitted spatial lag regression models with two sets of variables to further explore the relationships between the socioeconomic variables and vaccine accessibility. The first set includes the percentage of the total minority population, percentage of population under poverty, percentage of people aged 65 years or older, percentage of the population with no computer and smartphone access, and population density. We conducted spatial lag regression with a second set of variables to break down the percentage of minority population into individual racial/ethnic groups. We performed analyses for accessibility in multiple scenarios: with all vaccination sites combined, with medical sites only, with county mass sites only, and with county mass sites plus medical sites combined. Complete results of this analysis can be found in the Supplementary Material.

The pseudo R^2 values for most spatial lag models range between 0.7 and 0.8 in the various scenarios for the two counties, indicating a moderately strong predictive power. The most significant explanatory variable, however, is the spatial

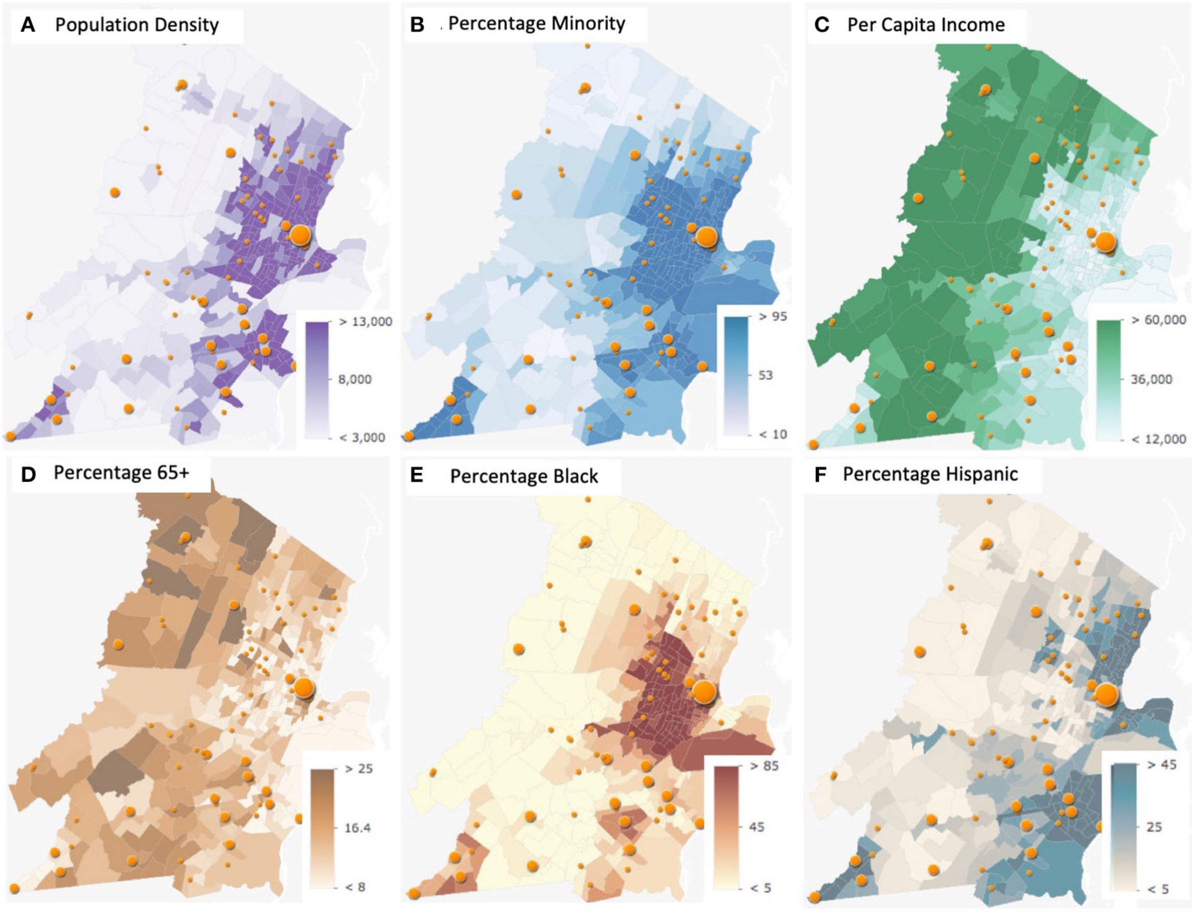

FIGURE 2
Spatial distributions of socioeconomic variables. **(A)** Population density; **(B)** Percentage minority; **(C)** Per capita income; **(D)** Percentage 65+; **(E)** Percentage black; **(F)** Percentage hispanic.

lag variable. This is expected as spatial accessibility measures are often strongly spatially autocorrelated, since neighboring tracts are generally located in close proximity to the same facilities (19). The results show that for Essex County with all vaccination sites combined, most variability of accessibility are explained by such spatial auto-correlation and not most of the other explanatory variables except for the percentage of minority. A positive coefficient, though, suggests a positive correlation, meaning that the higher the minority population, the higher accessibility. This positive relationship is not present with only medical sites, county mass sites, and when the two are combined. Results with the minority population broken down to individual groups show that the percentages of Black and Hispanic populations have significant correlations with accessibility. The correlations, once again, are both positive, indicating the higher these minority population percentages, the higher accessibility to vaccine resources.

In Union County, there is a significant correlation between minority and accessibility and it is also a positive relationship. This relationship starts to be present when we add county mass sites to medical sites. Breaking down to individual minority groups, the significant correlations are present with both Black and Hispanic populations. And similar to Essex county, the correlations are positive, indicating that these minority groups have higher accessibilities.

Discussion

The results from both Table 1 and spatial lag regressions suggest that minority populations in the two NJ counties do not have disadvantages in their spatial accessibility to vaccine resources, especially with all three types of vaccination sites combined. This can be attributed to the setup of the county mass vaccination sites in Union County and the FEMA community site in Essex County. Figure 2 shows the locations of the different types of vaccination sites overlaid on maps of socioeconomic variables. In Essex County, the county mass sites are more or less

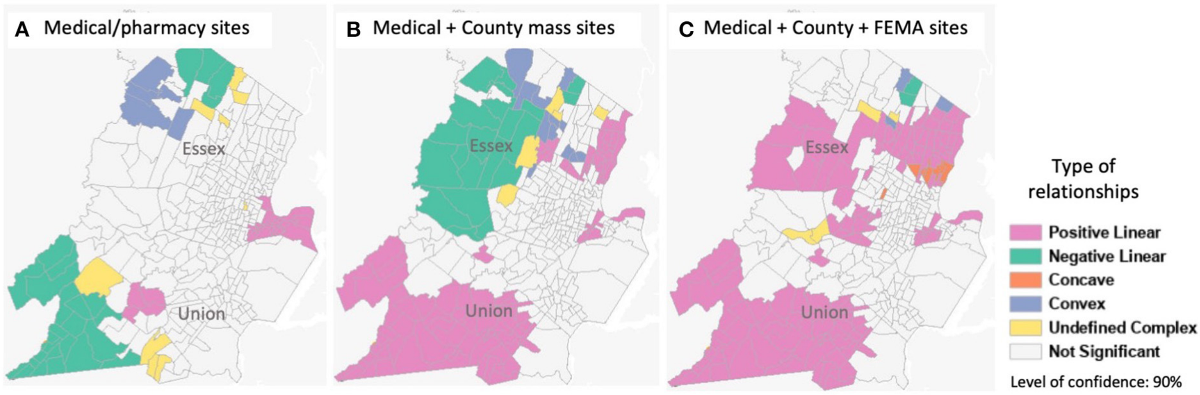

FIGURE 3
Bivariate relationship analysis between the percentage of minority population and accessibility. **(A)** Medical/pharmacy sites. **(B)** Medical + County mass sites. **(C)** Medical + County + FEMA sites.

evenly distributed over space. Vaccine resources are therefore shared by dense populations in the southeastern region (in and around Newark) with high percentages of poverty and minority populations, resulting in low accessibilities for these populations. The setup of the FEMA site in Newark, supplying 6,000 doses of vaccines every day, corrected this shortage. In Union County, the setup of the county mass sites largely observes the population density patterns, with a number of sites concentrated on the eastern site (Elizabeth) and a small cluster covering the southwestern corner (Plainfield). This setup targets the disproportionately affected populations with high infection and mortality rates, resulting in higher-than-average accessibilities to vaccine resources for such populations.

Results from the bivariate relationship analysis revealed local correlations between the socioeconomic variables and accessibilities that help us assess the effect of the different vaccination sites. Majority of Essex county did not show significant relationship between the percentage of minority and accessibility with medical sites only (Figure 3A). The introduction of the county mass sites resulted in a large area in the west side having a negative relationship (Figure 3B), that is, lower minority population with higher accessibility.

As shown in Figure 2 and discussed above, this is due to the spatially even distribution of the site locations. The distribution did not consider the greatly varying population density over space and the population distribution of minority groups. The introduction of the FEMA site on the east side corrected this (Figure 3C). In Union County, although a negative correlation was present in the west side of the county with the medical/pharmacy sites, the introduction of county mass sites corrected this, and even resulted in large areas of the county having a positive correlation. That means the higher the minority population, the better accessibility. With all vaccination sites combined (Figure 3C), both counties' minority populations have higher than average accessibilities, confirming the results from Table 1.

Conclusions

Based on our analyses, a few conclusions can be drawn. First, the COVID-19 pandemic exposed health and socioeconomic inequities in our communities that need to be addressed at the various stages from testing to vaccination. Public health decision making at different levels (county, state, and federal) are all critical in mitigating the disparities. In the case of the two diversely populated New Jersey counties, there was clear spatial heterogeneity in the accessibility to vaccine resources with the existing infrastructure (medical/pharmacy sites). Accessibility patterns changed with the introduction of county mass sites and the FEMA community site. In particular, county mass sites were set up in Union County targeting densely populated areas and minority populations, so was the FEMA community site in Essex County. These resulted in notable changes in the accessibility landscape. It shows how both the local health department and the federal government play an important role in mitigating pre-existing inequalities.

Second, social determinants of health need to be addressed (13) and taken into explicit consideration when distributing resources and evaluating resource accessibility. In our study, the county mass sites in Union County greatly increased accessibilities for populations of minority and poverty. The county mass sites in Essex County, on the other hand, were set up evenly across space, and did not show the same effect. This suggests that the setup of mass vaccination sites should not just cover the geographic space, but need to address the attribute space defined by variables including population density and socioeconomic factors, especially when some socioeconomic groups have been found to be disproportionately affected by the pandemic. Spatial distributions of such socioeconomic variables should direct the vaccine site selections.

Third, utilizing appropriate tools and technology can help improve public health response and decision making. The quick accessibility measure and geospatial analysis used in this study could be applied prospectively during an ongoing mass vaccination campaign to provide essential and timely evaluation of resource accessibility to guide decision making. County health departments can repeatedly run such analyses with various scenarios to guide site selection. Continued analyses could be done to monitor the change of accessibility landscape as vaccine shipments and daily operations of vaccination sites change from time to time.

Limitations

The accessibility measure used in this study can be quickly calculated with readily available data. Improvements can be made to increase the accuracy of accessibility evaluation, such as considering distance decay (21) or using dynamic catchments (27). Catchment areas could also be delineated based on travel time and transportation modes such as driving, public transportation, and walking could be separately considered. Ecological fallacy is another factor that may affect the accuracy of our accessibility analysis. As we use aggregated data at the census tract level, the inferences about the group may differ from the real experience of individuals (35). Additional analysis is needed to provide more in-depth investigations to individual's experience and perception of accessibility. Additionally, if detailed vaccination record is available, gravity models could be employed to study the flow of population to specific vaccine sites and examine other influencing factors of vaccination such as characteristics of vaccine site locations (17). Lastly, regardless of the setup of the county mass sites and FEMA site prioritizing accessibility for populations disproportionately affected by the pandemic, there is still disparity in vaccination rate among populations and communities. Our study only focused on accessibility to vaccine resources and did not consider one major factor that influences vaccination rates, which is vaccine acceptance/hesitancy (36–39). More in-depth studies on this front could provide valuable insights to innovative solutions in mass vaccination campaigns. The findings could also inform the constraints built in optimization-based methods (18) regarding individual choices.

Public health implications

This pandemic has shown how marginalized and minority groups have and will suffer disproportionately due to the inequities in society perpetuated by systematic practices. This study is timely to investigate one aspect of health equity, raise consciousness, and use tools and resources to confront inequities. Vaccine distribution system design can greatly influence equity and accessibility at the community level (18). As public health decision makers at different levels set up vaccination sites, evaluating accessibility helps to inform policy and improve coverage and accessibility for disproportionately affected populations. During a vaccination campaign, health equity should be addressed through incorporating social factors in the distribution of vaccine resources to mitigate disparities and prioritize accessibility of the disproportionately affected groups. The results from this study indicate that improving accessibility of these groups can be achieved when site selection considers explicitly the socioeconomic landscape of the population. The methodology employed in this study provides a tool for quick and timely assessment of resource accessibility to make necessary public health decision adjustments during the pandemic.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://covid19.nj.gov/pages/covid-19-vaccine-locations.

Author contributions

FQ conceived the study and wrote the manuscript. DB and MR implemented the analyses. JL assisted in the analyses and writing. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.895538/full#supplementary-material

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Estimation of Excess Deaths Associated With the COVID-19 Pandemic in Istanbul, Turkey

Abdullah Ucar[1]* and *Seyma Arslan*[2]

[1] Anafartalar Primary Healthcare Center, Ministry of Health, Istanbul, Turkey, [2] Arnavutköy District Health Directorate, Ministry of Health, Istanbul, Turkey

Background and Objectives: The official number of daily cases and deaths are the most prominent indicators used to plan actions against the COVID-19 pandemic but are insufficient to see the real impact. Official numbers vary due to testing policy, reporting methods, etc. Therefore, critical interventions are likely to lose their effectiveness and better-standardized indicators like excess deaths/mortality are needed. In this study, excess deaths in Istanbul were examined and a web-based monitor was developed.

Methods: Daily all-cause deaths data between January 1, 2015- November 11, 2021 in Istanbul is used to estimate the excess deaths. Compared to the pre-pandemic period, the % increase in the number of deaths was calculated as the ratio of excess deaths to expected deaths (*P*-Scores). The ratio of excess deaths to official figures (T) was also examined.

Results: The total number of official and excess deaths in Istanbul are 24.218 and 37.514, respectively. The ratio of excess deaths to official deaths is 1.55. During the first three death waves, maximum *P*-Scores were 71.8, 129.0, and 116.3% respectively.

Conclusion: Excess mortality in Istanbul is close to the peak scores in Europe. 38.47% of total excess deaths could be considered as underreported or indirect deaths. To re-optimize the non-pharmaceutical interventions there is a need to monitor the real impact beyond the official figures. In this study, such a monitoring tool was created for Istanbul. The excess deaths are more reliable than official figures and it can be used as a gold standard to estimate the impact more precisely.

Keywords: COVID-19, excess mortality, excess deaths, expected deaths, *P*-Score, Istanbul, Turkey, TURCOVID19

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Correspondence:
Abdullah Ucar
abdullah.ucar1@saglik.gov.tr

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INTRODUCTION

Since 31 December 2019, the number of confirmed cases and deaths due to COVID-19 around the world has reached 255 million and 5 million, respectively. The number of cases and deaths in Turkey has reached 8 million and 70.000, respectively (1). The WHO has published daily epidemiologic data between 21 January- 16 August 2020, and weekly thereafter. With a dashboard created by Johns Hopkins University on February 22, 2020, global data was visualized in real-time and a pandemic monitor was created (2, 3). In Turkey, the number of cases and deaths is announced on the official website of the Ministry of Health (MoH) daily.

To assess the impact of the pandemic, the numbers of daily cases and deaths are the main indicators that affect all others (4). Regular access to accurate information on these indicators from a reliable source is critical in pandemic governance. Planning and implementation of non-pharmaceutical interventions (NPIs) and interpretation of results are assessed *via* these reference indicators. In this context, the accurate detection of the number of cases and deaths is critical to a precision assessment of the real impact in the field and for the re-optimization of the NPIs.

Certain factors (testing policies, case definitions, reporting procedures, etc.,) may differ from country to country. This makes it difficult both to evaluate the number of cases and deaths and to make comparisons between countries (5). In this case, better-standardized indicators and criteria are required to assess the impact accurately and to minimize the difficulties on country comparisons. At this point, the epidemiological concept "excess mortality/death" is used as a better-standardized indicator than official COVID-19 death numbers (6).

Excess mortality refers to the total number of direct and indirect deaths during a public health crisis that occurs in greater numbers than expected in the pre-crisis period (4, 7). The number of deaths in public health crises is higher than in the pre-crisis period and deaths may result from both the causes directly related to the crisis or issues that are secondary to the crisis (8). Direct deaths during the COVID-19 pandemic are deaths directly related to the COVID-19 infections. Secondary deaths are caused by not being able to access health services due to the blocked health system, lockdown, fear of disease, etc., (9). Suicides due to stress caused by the pandemic may also constitute a part of indirect deaths (10). Excess mortality is recommended as the gold standard for a more accurate estimation of the number of deaths caused by COVID-19 and for the real impact of the pandemic (6, 11–13).

In the first months of the pandemic, the total number of monthly deaths in the United States was higher than expected based on the average number of deaths between 2014 to 2019 (14). The comparison of the number of deaths in 2020–2021 to the period 2016–2019 shows the first peak in excess mortality occurred in March-April 2020 in various European countries. After a few months of decline, a new increase started in August 2020, reaching a peak in November 2020 (14). These developments have shown the need for the creation of regularly updated dynamic datasets and digital platforms where these datasets are analyzed in real-time to monitor the trend of excess mortality over time, to compare countries, and to assess the impact of interventions. Several platforms have been collecting data on excess deaths from around the world, of which EuroMOMO, Eurostat, UNDATA, SMTF, mortality.org, and the World Mortality Dataset Project are the leading ones. Based on these datasets, excess mortality data has been visualized in real-time on interactive web-based platforms. Our World in Data, The Economist, the Financial Times, and the New York Times are prominent among these platforms (8).

Unfortunately, Turkey is not among the countries evaluated on these platforms and research (15, 16). The main reason is that there is no dynamic and open access dataset containing the daily number of deaths for Turkey. However, the daily numbers of all-cause deaths in Istanbul are presented as open data on the state's official website, turkiye.gov.tr. Istanbul includes 18.66% of Turkey's population and is one of the 12 NUTS-1 regions in Turkey. Istanbul is the most crowded city in Turkey and has a cosmopolitan population from all over the country, so the statistics for Istanbul should give a good idea of the general population.

Most of the excess mortality studies in Turkey were conducted in the early stages of the pandemic. These cross-sectional studies are static, as they do not offer a constantly updated dataset or a dynamic visualization. This study aims to examine the number of excess deaths, the ratio of excess deaths to official deaths, and the size of the death waves during the COVID-19 pandemic in Istanbul. A dynamic dataset generated by sarkac.org and TURCOVID19 Project in Turkey was used in this study and presented as open access data (**Supplementary Material 1**). Additionally, an interactive web-based dashboard was created that was updated in real-time depending on the dataset.

MATERIALS AND METHODS

Study Design

In this study, the number of excess deaths during the COVID-19 pandemic has been examined using the daily all-cause death statistics in Istanbul between January 1, 2015 and November 11, 2021. This study consists of 4 stages. In the first stage, the average number of daily deaths over the pre-pandemic 5 years (2015–2019) was taken as the baseline and the daily number of excess deaths in 2020 and 2021 was calculated. In the second stage, to enable comparisons with other countries and regions we calculated the measure (*P*-Score) suggested in the Aron and Muellbauer 2020 study (17). In the third stage, the size and duration of the death waves in the pandemic period were examined. In the fourth stage, the official COVID-19 deaths and the excess deaths in Istanbul were compared, and an examination of the extent to which the pandemic's true impact went beyond the official statistics was conducted. The calculations were made available to the public through a dynamic open dataset and an interactive web-based excess death monitor was formed.

Data Source, Scope, and Preparation

Daily all-cause death data from Istanbul Metropolitan Municipality was publicly available on the state's official website, turkiye.gov.tr. The daily all-cause death data include given names, surnames, and the total number. With the cooperation of sarkac.org and the TURCOVID19 project, daily all-cause death numbers of Istanbul since 2015 have been collected, and a dynamic dataset that is regularly updated has been created.

The dataset includes 365 days of the year as rows, and all-cause death numbers for the years 2015–2021 as columns. In the dynamic dataset, the minimum, maximum, average, and median values of the pre-pandemic years' data are calculated automatically for each day.

Inclusion and Exclusion Criteria

Data from February 29 are excluded due to the associated confounding effect in the calculations because the date February 29 only occurs once every 4 years in the Gregorian calendar.

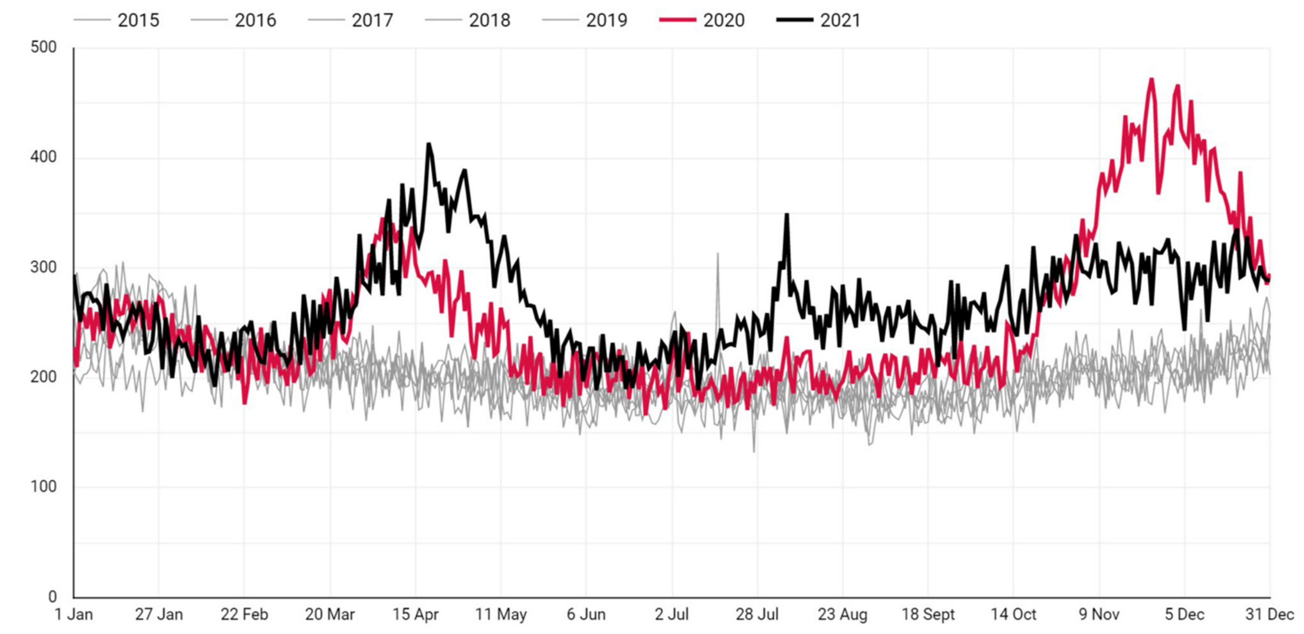

FIGURE 1 | The daily number of all cause deaths in Istanbul (2015–2021).

Data Analysis

First Stage: Calculating the Excess Deaths for Istanbul

The average values of the daily all-cause deaths in Istanbul for the pre-pandemic period (2015–2019) were calculated for each day. Although the simple average method has some limitations in estimating expected deaths based on pre-pandemic data, the simple mean method was preferred because comparative studies showing that estimations based on Poisson, Gamma or Binomial distributions are superior in this regard are still limited. number of average daily deaths in pre-pandemic and post pandemic years has been compared with the Mann-Whitney *U*-test.

For the day t, the average daily number of all-cause deaths in pre-pandemic period (expected) were subtracted from the number of daily all-cause deaths during the pandemic period (observed). In the calculation, the five-year average number of all-cause deaths for each day of the year expresses the expected death value for that day ($D_{expected}$), and the number of daily all-cause deaths during the pandemic period expresses the observed death value ($D_{observed}$). In this case, the equation for the number of excess deaths on a day t (Dt_{excess}) is:

$$Dt_{excess} = Dt_{observed} - Dt_{expected}$$

Second Stage: Establishing *P*-Score

The ratio of excess deaths to expected deaths presented as *P*-Scores. *P*-Score shows the percentage difference how much the number of excess deaths during the pandemic period deviated from the expected number of deaths. The equation for the *P*-Score on the day t (Dt) is given by:

$$P - Score_t = \frac{Dt\,(excess)}{Dt\,(expected)}$$

Third Stage: Analysis of Death Waves During the Pandemic Period

The parts of the daily death charts where the number of observed deaths increased and peaked over the pandemic period were considered as “death waves”. The total number of deaths during these waves and the maximum values in each wave were calculated and compared.

Fourth Stage: Official Death Numbers and Comparison With Excess Deaths

The estimated excess deaths were compared to the official number of COVID-19 deaths announced by the Turkish Ministry of Health (MoH). The daily official death numbers due to COVID-19 in Turkey have been announced as the total daily value for the country. Between 28 June 2020 and 25 October 2020, the number of official deaths at the NUTS-1 level was published as weekly reports by the MoH. Istanbul is one of Turkey’s twelve NUTS-1 regions on its own. For this reason, the official death numbers in Istanbul were recorded weekly between 28 June and 25 October 2020 and made available as open data on the TURCOVID19 website (**Supplementary Material 2**). According to the first official report (June 28, 2020) the ratio of the total official COVID-19 deaths registered in Istanbul to the official number of deaths registered in the whole country was %52,72. This ratio decreased over time and fell to 33.2%

TABLE 1 | The average number of daily deaths in Istanbul during pre-pandemic* and post-pandemic** years.

Years	*N*	Minimum	Maximum	Mean	Std. deviation
*2015	365	148	243	193.33	21.86
*2016	365	147	314	202.20	25.71
*2017	365	139	299	205.65	28.07
*2018	365	155	263	204.37	20.09
*2019	365	132	306	208.53	28.44
**2020	**365**	**166**	**473**	**253.65**	**68.63**
**2021	**365**	**189**	**414**	**266.97**	**43.09**

Bold values represent the numbers during the pandemic period.

in the latest published report (October 25, 2020). Namely, at the relevant date 33.2% of official deaths due to COVID-19 in Turkey occurred in Istanbul. After this date, the publication of the reports was stopped the death numbers continued to be announced for Turkey in general. This ratio was used as the reference parameter to estimate the number of daily official deaths in Istanbul. In this calculation, the official number of deaths in Istanbul ($Ot_{Istanbul}$) was estimated by multiplying the total number of deaths in Turkey on the day t (Ot_{Turkey}) by 0.332. In addition, calculations for the period (27 June—25 October 2020) of the official reports were made separately, with and without extrapolation.

$$Ot_{\text{istanbul}} = Ot_{\text{Turkey}} \times 0.332$$

In addition, total excess deaths in Istanbul ($\sum_{i=1}^{t} Dt_{excess}$) were compared to total official deaths ($\sum_{i=1}^{t} Ot_{istanbul}$) to determine the extent to which the pandemic's true impact exceeded the official figures. The ratio of these two parameters (T) has been calculated as follows:

$$T = \sum_{i=1}^{t} Dt_{excess} \div \sum_{i=1}^{t} Ot_{istanbul}$$

RESULTS

The daily number of deaths in 2020 and 2021 in Istanbul comparison to previous years are as illustrated in **Figure 1**. The total number of excess deaths in Istanbul up to the date November 11, 2021 is 37.514. Daily number of deaths during pre-pandemic and post-pandemic years are shown in **Table 1**. The daily average of excess deaths since the beginning of 2020 has been 55.17 (SD: 57.94 Max: 264.8). The number of daily average deaths in post-pandemic years is significantly greater than in the pre-pandemic years ($p < 0.001$).

P-Scores from the beginning of 2020 are shown in **Figure 2**. On a daily and monthly basis respectively, *P*-Scores have reached a peak of 71.8 and 49.5% during the first wave, 129.0 and 102.32% during the second wave, 116.3 and 77.61% during the third wave.

The first wave occurred between March and May 2020, the second wave occurred between October and January 2020, and the third wave occurred between February and June 2021. The excess deaths in these three waves are 4.604, 11.934, and 9.221, respectively. The largest number of excess deaths occurred in the second wave. The magnitude of the second wave was 2.59 times greater than that of the first wave and 1.29 times greater than that of the third wave. The third wave was the first wave of 2021. During this wave, the number of excess deaths between February and June 2021 ($n = 9.221$) was more than double that of the same period during the previous year ($n = 4.604$).

In the first wave of 2020, the number of excess deaths ($n = 4.604$) during March-May was 3.06 times that of the official number of deaths ($n = 1.507$). The daily maximum number of excess deaths and the official deaths were 144 and 42, respectively. In this period, one out of every three deaths was recorded in the official records. In the four-month period between June and September 2020, the first wave faded because of the measures taken, and the gap between official deaths and excess deaths decreased. During this period, the number of excess deaths ($n = 2.027$) was 1.67 times that of the official number of deaths ($n = 1.213$).

The second wave of 2020 lasted for 4 months, from October 2020 to January 2021. In this wave, the number of excess deaths ($n = 11.934$) was double that of the official death count ($n = 5.945$). The daily maximum number of excess deaths and the official deaths were 264 and 86, respectively. For the first time in this wave, on 31 December 2020, the number of excess deaths fell below the official number of deaths and decreased rapidly, in a trend that continued for 3 months.

The third wave lasted for 5 months, from February to June 2021. During this wave, the number of excess deaths ($n = 9.221$) was 1.16 times that of the official number of deaths ($n = 7.908$). The daily maximum number of excess deaths and the official deaths were 223 and 131, respectively. For the first time in this wave, on 12 March 2021, the number of excess deaths increased rapidly, exceeding the official number of deaths, and continuing in this way for 2 months. After official and excess death numbers had progressed at the same rate for 1 month following May 23, with the commencement of the normalization phase in Turkey the number of excess deaths began to rise again after 23 June. At the time of this study, the fourth death wave was on the rise.

The number of total estimated official deaths ($\sum_{i=1}^{t} Ot_{istanbul}$) and excess deaths ($\sum_{i=1}^{t} Dt_{excess}$) in Istanbul since the beginning of the pandemic have been 24.218 and 37.514, respectively. The total number of excess deaths is 1.55 (T) times that of the official number of deaths.

According to the calculations made for the period in which the official reports are published (27 June−25 October 2020), the extrapolated T parameter is 1.57, while it is 4.34 according to the non-extrapolated calculations. In this period, the ratio of the weekly official death toll in Istanbul to the overall death toll in Turkey was as in **Figure 3**. The official number of COVID 19 deaths in Istanbul during this period was 12.04% of the overall number in Turkey during this period.

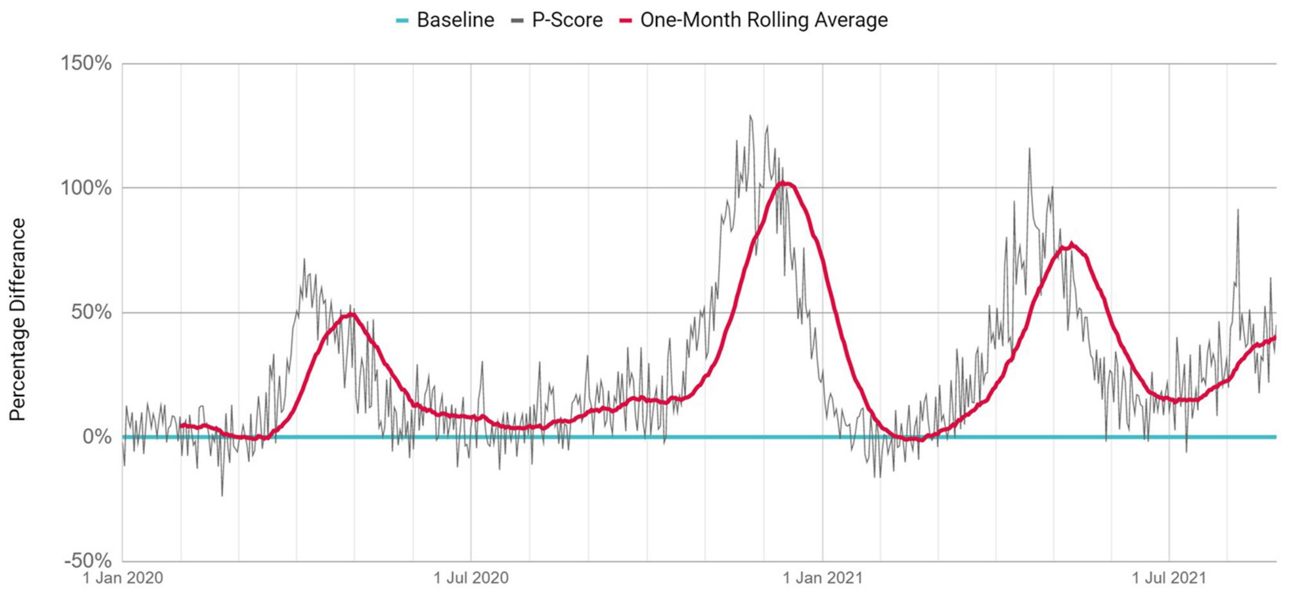

FIGURE 2 | The ratio of excess deaths to expected deaths (*P*-Scores).

DISCUSSION

The number of deaths in Istanbul during the COVID-19 pandemic was considerably higher than in the pre-pandemic period. While the number of daily deaths between 2015–2019 was within a certain range, it increased in 2020 and 2021, creating large waves of deaths. Death waves last between 3 and 5 months on average. These waves tend to fall when non-pharmaceutical interventions are applied and rise during periods of relaxation.

The first confirmed COVID-19 case and death in Turkey were announced on 11 and 17 March 2020, respectively. However, as shown in **Figure 4**, excess deaths in Istanbul started to increase earlier, in the first days of March 2020. This indicates that there were cases of COVID-19 in Istanbul long before the first case was announced.

The ratio of excess deaths to expected deaths (*P*-Score) and the ratio of excess deaths to official deaths (T) have been used as indicators throughout the pandemic. In Istanbul, the maximum values of monthly-based *P*-Scores were realized in the first wave as 49.5%, in the second wave as 102.3 and the third wave as 77.6%. In a study that included 94 countries around the world, the top three countries with the highest *P*-Scores between January and June 2020 were Peru (146%), Ecuador (77%), and Bolivia (61%) (8). In Europe during the first wave the highest excess deaths were observed in Spain (80.8%), Belgium (73.1%), and Netherland (53.8%); in the second wave, Poland (97.0%), Bulgaria (94.4%), and Slovenia (93.2%); and in the third wave, Bulgaria (76.9%), Poland (65.3%), and Czechia (62.0%). Compared to European countries, the total number of deaths per unit population in Turkey seems to be lower, but in terms of excess deaths, it is seen that the excess deaths in Istanbul are close to the peak values in Europe.

The ratio of the total number of excess deaths to official deaths (T) shows the underreporting level of the COVID-19 deaths and this value is 1.55 for Istanbul. Additionally, this ratio shows that official deaths can just explain 61.52% of the excess deaths in Istanbul. The remaining 38.47% include undetected COVID-19 deaths and indirect deaths. However, the T value also varies seasonally in the same country. T value was 3.06 in the first wave in Istanbul and decreased to 1.16 in the third wave. As well as the calculations without extrapolation using direct official figures over the time period of official reports show that the T value was 4.34. This high rate confirms that the excess deaths in the relevant time period far outnumber the official deaths. In Italy, Spain, the Netherlands, and the United Kingdom, the T value was at a maximum of ∼1.5 in the first wave but dropped to ∼1.0 in the second wave. The T value was below 3 for most countries in the world, but much higher values were observed in some countries. The highest values were 100 in Tajikistan, 51 in Nicaragua, 31 in Uzbekistan, 14 in Belarus, and 13 in Egypt (8).

The use of official death numbers to measure the effectiveness of responses to the pandemic or to make comparisons between countries raises several issues. Official numbers are affected by many factors. For example, the low number of cases and deaths related to COVID-19 in some countries may be due to the low number of tests (18, 19). In addition, definitions of COVID-19 cases and deaths may be different between countries. Some countries include only deaths of PCR-positive people in their COVID-19 deaths, while others also include suspected COVID-19 deaths (8). Another confounder is that

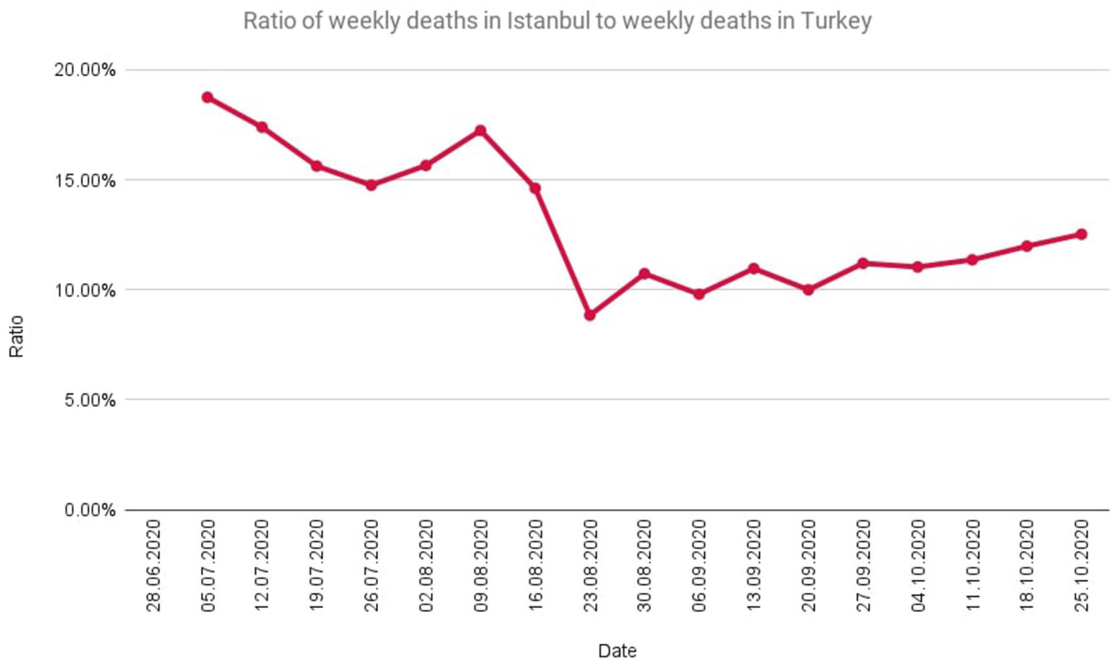

FIGURE 3 | The ratio of weekly deaths in Istanbul to weekly deaths in Turkey during the time period in which official reports are published.

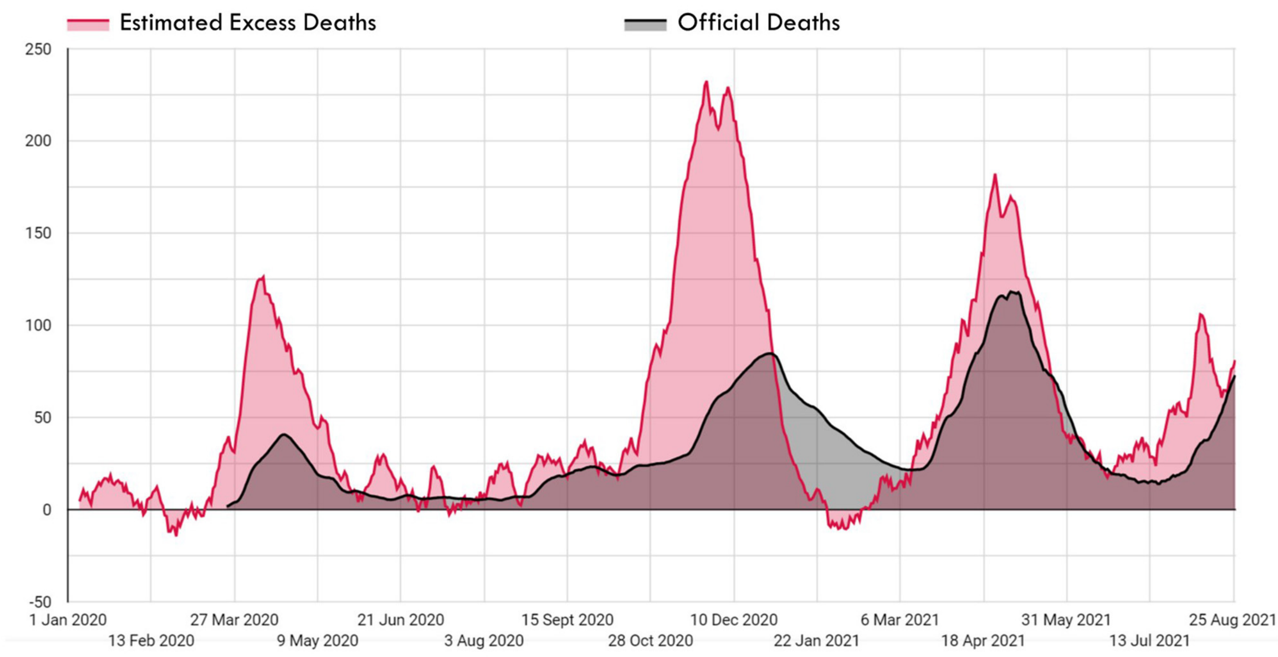

FIGURE 4 | Excess deaths and official deaths during the COVID-19 pandemic in Istanbul.

deaths that occurred in hospitals do not represent all COVID-19 deaths (6). In this context, the Statistics Netherlands's (CBS) study proposes that all excess deaths be considered COVID-19 deaths (20). And a study supports this proposal by expressing excess mortality offers a much more robust assessment opportunity compared to the official number of COVID-19 deaths (14).

Due to the measures taken against the pandemic, there may be indirect deaths that have been prevented. These prevented deaths can result in a shift in the number of deaths due to various causes. According to our findings, the daily death numbers in January and February in 2021 vary more and are distributed in a wider range than the other months of the year during 2015–2019. The number of excess deaths decreases to negative values in January-February. It is thought that this variability may be due to influenza-related deaths experienced in the winter season. In theory, unless there are other confounding factors, the number of excess deaths should not be less than the official COVID-19 deaths. The paradox here is thought to be caused by a confounder. The most likely reason for this is the decrease in influenza deaths in the winter period due to pandemic measures, which were replaced by COVID-19 deaths. According to the studies, there was a decrease in deaths from other infectious diseases, particularly seasonal flu, as a result of social interventions (8, 13, 14, 18–24). In the United States, the 99,3% decrease in influenza cases in the 2020–2021 winter season compared to 2019–2020 supports the shift argument presented above (19). Another confounder may be early deaths. According to Institute for Health Metrics and Evaluation (IHME), deaths from chronic diseases of the heart and respiratory system decreased by 2% in some European countries in the middle of the year 2020. Large numbers of elderly and chronically ill people are likely to have died early in the year as a result of COVID-19, and their early deaths may explain the negative additional deaths during the winter period (19). However, other effects reduce deaths in the pandemic. According to IHME, mobility restrictions reduced the number of traffic accident-related deaths by 5%, and 215.000 traffic accident-related deaths were prevented globally in 2020 (19). In this regard, during the pandemic, it is possible the effects that increase and decrease the number of excess deaths balance each other.

CONCLUSION

In this study, the number of excess deaths which is one of the most important indicators for monitoring the real impact of the pandemic has been estimated for Istanbul. These estimations give an idea about the excess deaths around Turkey. The outcomes of this study support that the progression of the pandemic should be monitored not just with official COVID-19 deaths, but also utilizing excess deaths. The number of excess deaths begins to rise earlier than the number of official deaths. Delays are inevitable in social intervention measures which are decided based on the official deaths. The excess deaths have predictive value for official death numbers. However, there are also periods when the number of excess deaths falls below the official numbers, or even becomes negative. In light of the literature, we also address the possible causes of this condition in our study.

Excess mortality is a key indicator for monitoring the true consequences of the pandemic, developing a more precise pandemic management strategy, ensuring that interventions are implemented without delay and on time, and, indeed, increasing the effectiveness of such interventions. To be faster than the spread of the pandemic is a key factor in governing it. At this point, the application of digital technology to this field opens up new frontiers for us.

Previous studies on excess death in Turkey are at the cross-sectional level, whereas evolving digital technologies make it possible to build up-to-date monitoring screens based on dynamic datasets, allowing decision-makers and scientists to monitor the pandemic situation in real-time (25, 26). In this regard, digital epidemiology applications have a significant role in monitoring the pandemic's consequences.

LIMITATIONS OF THE STUDY

In this study to estimate the expected deaths as a baseline in the pandemic period, the simple average method is used with 2015–2019 data. Although this method has some limitations it is used in the Eurostat study (14).

The use of the simple average method when calculating the expected number of deaths according to the pre-pandemic period may cause the baseline to be underestimated for countries where the number of deaths increased by years, or to be overestimated for those with decreased death numbers. This baseline method doesn't consider changes in the population's age structure and reduction in mortality rates over years.

The multiplier (0.332) used to estimate how many of the COVID-19 deaths in Turkey occurred in Istanbul includes the possibility of extrapolation in the calculation of future data after the latest report released by MoH. This multiplier is based on the latest report of MoH and there is no other official reference to use in Turkey.

Excess mortality estimates assume that daily deaths in the pre-pandemic years occurred under ordinary conditions. There was no extraordinary public health crisis in Turkey in the pre-pandemic years 2015–2019.

There is also the possibility of displacing deaths caused by the pandemic with deaths prevented due to preventive measures against the pandemic in excess mortality estimates. In this study, the subject is discussed based on the example of the displacement of influenza deaths and COVID-19 deaths during post-pandemic years.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

Conceived and designed the analysis, contributed data or analysis tools, and wrote the paper: AU and SA. Collected the data and performed the analysis: AU. All authors contributed to the article and approved the submitted version.

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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.2022.888123/full#supplementary-material

Supplementary Material 1 | Dynamic dataset of daily official and excess deaths in Istanbul.

Supplementary Material 2 | Weekly death numbers at NUTS-1 level in Turkey.

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Experience of rehabilitation management in public hospital after it was identified as designated rehabilitation hospital for COVID-19 patients: A qualitative study

Shuxiao Hu[1], Changfu Chen[1], Biwen Yang[1], Qing Liu[1,2]* and Han Hu[1]

[1]School of Public Policy and Administration, Xi'an Jiaotong University, Xi'an, China, [2]First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China

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EDITED BY
Sadia Ilyas,
Jeonbuk National University,
South Korea

REVIEWED BY
Anne-Sophie Jung,
University of Leeds, United Kingdom
Saidur Mashreky,
Centre for Injury Prevention and Research (CIPRB), Bangladesh

*CORRESPONDENCE
Qing Liu
emma1845@163.com

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Objective: It is essential to focus on the rehabilitation of COVID-19 patients after discharge to prevent their long-term sequelae, but there is less research on healthcare organizations enhancing rehabilitation services for patients discharged from COVID-19. Therefore, this study aimed to describe how a public hospital provides better rehabilitation services for patients after being identified as a designated rehabilitation hospital for patients with COVID-19 and attempted to combine the theory of organizational change to analyze how the hospital finally successfully transformed.

Methods: A tertiary public hospital located in the center of Xi'an was selected for the study. It was identified as a designated hospital for the rehabilitation of patients discharged from the hospital with COVID-19. Nine hospital leaders and group leaders closely related to the rehabilitation management work were invited to participate in interviews to explore the fact about the hospital's rehabilitation work. The semi-structured interview with the hospital director and the focus group interview with group leaders were used for data collection. Two researchers independently conducted a thematic analysis of these responses.

Results: One hundred and seventy-eight primary codes, 22 subcategories, six main categories, and one core theme were obtained from data analysis. The main categories include organization and coordination (overall deployment, transfer patient, and external coordination), hospital infection prevention and control (process transformation, ward disinfection, hospital infection training, inspection, and supervision), staff management (staff classification, closed-loop management, and staff health screening), individual services for patients (create an individual scheme, humanistic care, organize special activities, and strengthen communication and guidance), comprehensive supporting (basic medical guarantee, daily necessities guarantee, health and nutrition guarantee, and assistance fund guarantee) and positive transformation (strategic thinking, benchmarking, strengthen cohesion, and expand influence).

Conclusion: The hospital had to transform its operations in the face of a complex environment during the pandemic. After deciding to transform, the hospital effectively prevented nosocomial infections and provided rehabilitation services to 583 patients through systematic management measures such as organizational coordination, staff classification, and personalized services. In the end, it has been successfully transformed and has grown rapidly. To ensure that it can continue to grow sustainably, the hospital enhanced the new ways that have emerged from this transformation.

KEYWORDS

public hospital, rehabilitation, rehabilitation management, COVID-19, organizational change theory, qualitative study

Introduction

With the rapid increase in the number of confirmed and dead patients with the COVID-19 (1, 2), the COVID-19 outbreak was declared a pandemic by the WHO in March 2020. COVID-19 has brought huge shocks and changes to all aspects of the global society (3, 4), and all medical departments, including rehabilitation medicine, are no exception (5). For example, as part of efforts to ensure the health system is not overwhelmed, the usual pathway of care in Britain's National Health Service has been suspended (6, 7). Rehabilitation clinicians and programs have had to take on new challenges to provide safe, effective, and efficient rehabilitation for patients recovering from COVID-19 and other traditional rehabilitation diagnoses within the changing circumstances and constraints of this unprecedented epidemic (8).

Rehabilitation is an important part of healthcare and medical management (9). Many patients with COVID-19 have sequelae after being cured and discharged. An Italian study followed 143 individuals 7 weeks after discharge and found that 53% reported fatigue, 43% had difficulty breathing, and 27% had joint pain (10). The NHS England predicted that COVID-19 survivors have high physical, neuropsychological and social needs after discharge (11). Therefore, attention should be paid to the rehabilitation needs of discharged patients with COVID-19. Rehabilitation interventions for COVID-19 patients or those recovering from COVID-19 include aerobic conditioning, strength training, energy-saving training, dyspnea management, and activity-specific training (12, 13). These interventions can improve walking speed, endurance, and pulmonary function syndrome in patients recovering from the severe acute respiratory disease (14, 15). Rehabilitation care can shorten hospital stays at all stages of healthcare, optimize health outcomes and avoid readmissions. Rehabilitation care can also reduce health care and social costs, increase employment rates for COVID-19 survivors, and strengthen the healthcare workforce. Therefore, some recommendations need to be considered to achieve the highest level and quality of rehabilitation services during COVID-19 (and in the long term).

In response to the increasing number of COVID-19 patients worldwide, much of the literature in rehabilitation has focused on the early impact of COVID-19 on the rehabilitation system and on proposing rehabilitation protocols during COVID-19 recovery at the patient level. Many studies have examined changes in their physical symptoms and psychological conditions (16–18). Physical symptoms that COVID-19 patients may experience, such as fever, dyspnea, cough, adverse drug reactions (16), as well as psychiatric symptoms, such as fear of contracting a new virus, loneliness, anger associated with treatment in isolation, and post-traumatic stress (16–18). Comorbidities observed in COVID-19 patients requiring intensive care include muscle weakness, nerve damage, delirium, and more, which have the potential to significantly affect their physical and cognitive functions (19–21). As the pandemic continues to spread around the world, experience with post-discharge rehabilitation care for COVID-19 patients has slowly begun to mature (22).

However, the premise of high-level rehabilitation care for patients with COVID-19 or those who have recovered from COVID-19 is premised on the availability of vectors and adequate resources. The surge in intensive-care patients reduced post-acute facility use, and prolonged hospital stays have put pressure on health systems to consider alternative strategies to promote hospital throughput and maintain capacity (23). These factors have made it necessary to open field hospitals or designated rehabilitation hospitals to treat the increasing number of infected patients. COVID-19 designated rehabilitation hospital is established by the government to fully rehabilitate patients who have recovered from COVID-19. The local government selects a hospital and plans to transform it to receive patients cured of COVID-19 and discharged from the hospital. From the perspective of organizational reform, the public hospital has to make a series of adjustments to adapt to the changes in internal and external environments after being designated as a designated rehabilitation hospital (24). According to the organizational change theory put forward by Kurt Lewin, an organization may experience a variety of differences from change to success due to different factors. However, as a whole, successful organizational change has the common feature that it takes "unfreeze—change—refreeze" to get to success (25).

This study takes a public hospital in Shaanxi Province, China, as an example to describe its experience in carrying out systematic rehabilitation management after it was identified as a designated rehabilitation hospital for discharged patients with COVID-19 during the pandemic. This study also attempts to combine the theory of organizational change to analyze how it finally successfully transformed through its own series of efforts under the complex internal and external environment during that period.

Materials and methods

Participants

SXDS Hospital is a general tertiary hospital located in the center of Xi'an City, integrating medical treatment, teaching, scientific research, prevention, health care, and rehabilitation. It was designated as a rehabilitation hospital for discharged COVID-19 patients by Shaanxi Provincial Government on January 6, 2022. From the discovery of the first confirmed patient on December 9, 2021, to the entire city of Xi'an was declared a low-risk area on January 24, 2022, the epidemic in Xi'an lasted 47 days. The epidemic's sever gradually decreases from the city center to the suburbs (Figure 1). The patients with COVID-19 are discharged from the designated hospital after being cured and would be arranged in the designated rehabilitation hospital to receive rehabilitation services. In the late stages of the epidemic, more and more patients were cured and discharged from the hospital with COVID-19. The hospital was identified as a designated rehabilitation hospital for discharged patients with COVID-19 when the number of cured and discharged patients exceeded the number of confirmed patients (Figure 2). A total of 583 discharged patients with COVID-19 were accepted and treated by the hospital during this mission.

The main problem in rehabilitation is that most patients do not need medical treatment but only psychological support and health education. But some patients still need treatment. For this reason, after receiving the task, the hospital held a hospital-wide meeting and arranged for six working groups to complete the task. Each group leader has full authority to handle everything in the working group, accepting feedback from the primary medical staff and reporting the group's work to the director. Each group leader is very familiar with the work they are responsible for. We adopted the method of purposeful sampling to recruit nine hospital leaders and group leaders closely related to this rehabilitation management work (Table 1). The research team obtained the list of working group leaders who had expressed their willingness to participate in the study from the head of the Business Development Department through a formal process with the hospital. Participants were contacted by phone and their consent was reconfirmed before participating in the study.

Data collection

This study was conducted when the epidemic spread was serious in Xi'an city. The Xi'an municipal government advocates less going out and not gathering. Semi-structured telephone interviews and focus group interviews in the form of video conferences were used for data collection. The day after the SXDS hospital was identified as a designated rehabilitation hospital, the researchers conducted a semi-structured in-depth interview with the hospital director *via* telephone. The interview outline focused on collecting the participants' perspectives, including what preparations have been made in terms of wards, staff, facilities, and equipment after the hospital was identified as a designated rehabilitation hospital? What rehabilitation methods will be adopted for the discharged patients with COVID-19? How will the hospital provide social and psychological counseling for the patients? The whole interview lasted for 90 min. The interviews were recorded verbatim and analyzed as they were conducted to facilitate thematic development.

To saturate the data, the research team conducted online focus group interviews (Tencent conference) with other participants when the epidemic in Xi'an was less severe on January 18. The focus group was mainly composed of group leaders who were responsible for each task, excluding the director and the secretary. On the one hand, focus group interviews without the director and the secretary present allow other managers to speak freely. On the other hand, the focus group interviews can help us verify the credibility of the first telephone interview with the director. The questions of the focus group interview focused on what work did each medical team had done in this rehabilitation management? What effect has the work done on the hospital and patients? How to do an excellent job in the future transformation and sustainable development of hospitals?

When no new information was obtained from the participants, the data reached saturation and the research team canceled subsequent interviews. Data for this analysis was collected from Jan 7 to Jan 18, 2022. The Biomedical Ethics Committee of Xi'an Jiaotong University Health Science Center approved this program (approval number: 2020-1258). Before the interview, all participants were explained the purpose of the study and their roles in the study, and their consent to participate

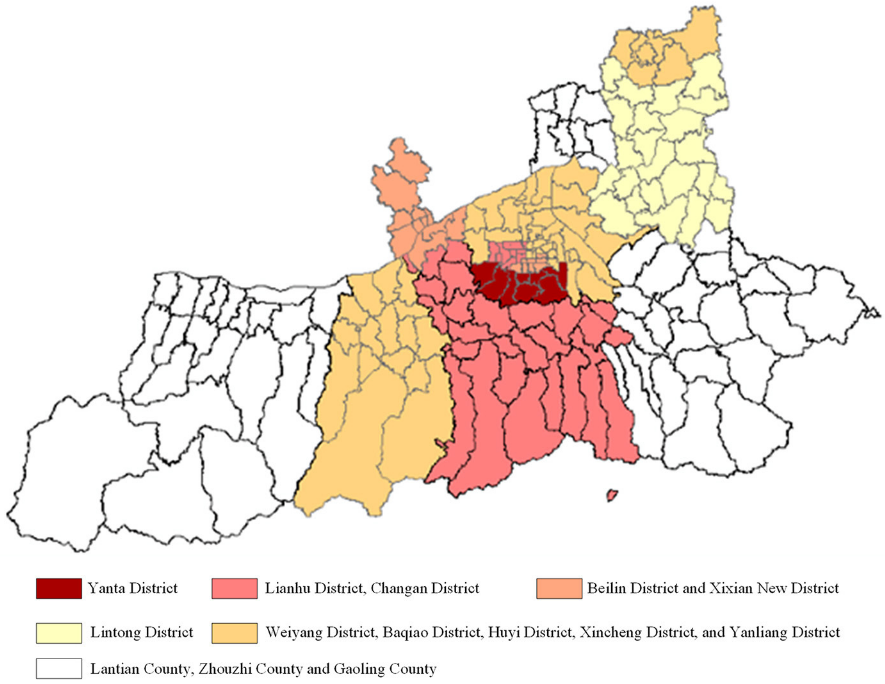

FIGURE 1
Real-time map of epidemic levels in Xi'an city.

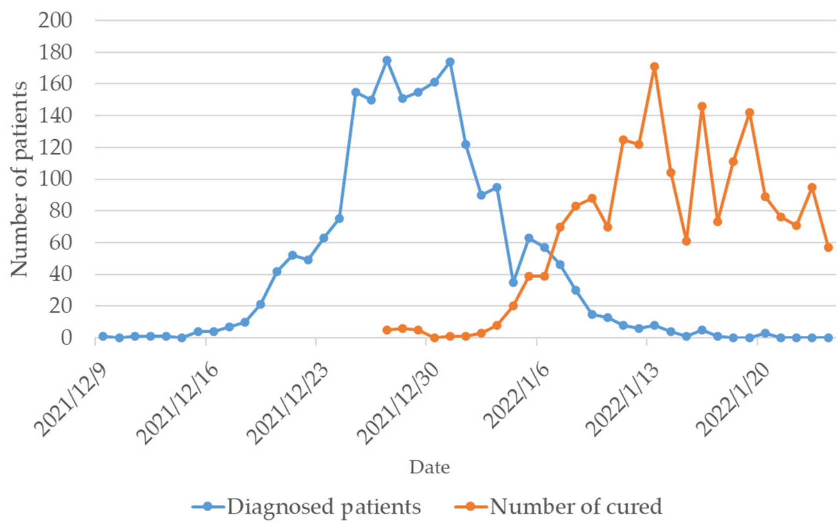

FIGURE 2
Changes in the number of diagnosed patients and the number of cured in Xi'an during this epidemic.

in the research and record their voices was obtained. Participants were assured that the recorded material would be used, but their names and details would not be disclosed. Participants had the right to withdraw at any study stage if they did not want to partake.

Analysis

The data generated in this study were coded using thematic analysis through a systematic categorization process, and then themes and patterns were identified (26). This approach

TABLE 1 Demographic characteristics of participants and data related to rehabilitation management.

Participant	Gender	Age	Working years	Post/department	Responsible for the content of this task
1	Male	62	23	Director of hospital	Mission commander
2	Male	55	20	Vice president of hospital	Patient management
3	Male	52	16	Discipline Inspection Commission	Management of hospital staff
4	Female	53	22	Internal Medicine Department	Nursing team management and hospital infection prevention and control
5	Male	56	18	Anesthesiology Department	Treatment guidelines for patients with disease
6	Female	43	12	Business Development Department	External coordination and Internet projects
7	Female	49	15	Finance Department	Expenditure management of all hospital expenses
8	Male	42	12	Assistant to the hospital director	Nucleic acid test outside the hospital and rehabilitation treatment in the hospital
9	Female	46	21	Health Services Section	Patient admission and discharge management

supports immersion in the data to enable new insights to emerge and inductively develop categories without imposing preconceived categories (27). After the data collection process was completed, all generated data (interviews) were converted to text. After the data was converted, we used Nvivo Chinese software (12.0) to encode important statements.

The general inductive approach was applied in this study (28, 29), allowing our findings to emerge from the most common and dominant themes in the original data without the constraints of more structured methods such as deductive experiments and hypothesis testing studies. The detailed data analysis process is as follows: First, we read the interview text repeatedly to familiarize ourselves with the data and extracted important statements directly related to the research phenomenon. We then formulated broader meanings from important messages while including our premises as closely as possible, similar meanings were clustered into themes, and similar themes were integrated into thematic clusters. In the end, we wrote a comprehensive description of the phenomenon, covering all the revealed themes, and summarized the detailed report into a condensed statement.

To ensure the study's trustworthiness, we applied the criteria of credibility, fit, auditability, and verifiability (30). The principal investigator collected and organized the coded statements followed by discussions with other researchers to derive and refine significant statements, themes, and thematic clusters. In order to establish credibility, two researchers recorded and transcribed the participants' statements verbatim, reviewed the transcripts against the recordings, and finally compared the encoded texts. The *kappa* value of all codes remained between 0.5 and 0.75, indicating a high fit and suitable for data analysis.

Results

In this study, 178 primary codes, 22 subcategories, and six main categories emerged from the data analysis (Table 2).

Based on the above coding conceptualization of the interview data, the distillation of the categories, and the summarization of the themes, we used the theoretical coding strategy of "cause, process, and effect" from Glaser's classical grounded theory to summarize them into the core theme of "Self-transformation of public hospital after it was designated as COVID-19 rehabilitation hospitals." This study also combines a planned organizational change model proposed by Lewin, which contains three steps of unfreezing, changing, and refreezing. A theoretical framework was built for the public hospital self-change process (Figure 3) to explain and guide how public hospitals launch, manage and stabilize the organizational change.

Organization and coordination

Overall deployment

After receiving the notification from the superior that it was determined to be the designated hospital for the rehabilitation and treatment of COVID-19 cured patients, SXDS Hospital quickly made various preparations and entered a state of "24-h standby preparation" that can welcome patients at any time. Hospital leaders systematically thought about and discussed this task that day, discussing how to take over the battle against the pandemic and how to fight this battle well. The next morning, the hospital mobilized all-party committee members and relevant functional departments by

TABLE 2 The rehabilitation works organized by the hospital.

Categories	Subcategories	Number of materials	Reference points	Examples of codes
Organization and coordination	Overall deployment	4	7	• Hold an enlarged meeting to inform the functional departments • Divide into 6 workgroups to work on tasks • Develop plans for infants and young children • The guarantee of funds is handed over to the Federation of Trade Unions for the overall planning
	Transfer patient	2	3	• Mobilize existing hospital patients to discharge • Transfer of inpatients from the hospital to brother hospitals • The process of receiving patients is relatively smooth
	External coordination	3	9	• Connect with the community • Connect with the government • Connect with hotel • Connect with other rehabilitation hospitals to exchange learning experience
Hospital infection prevention and control	Process transformation	3	4	• Divide the infection ward into three zones and two channels • Clear division of clean, semi-contaminated, and contaminated areas • Hard-isolate the patient's channel and the staff's channel • Put anti-epidemic materials on designated floors
	Ward disinfection	2	3	• Cleaned and sanitized the ward overnight • Every paramedic has a sanitization task • The sterilization of other areas in the hospital
	Hospital infection training	1	2	• Training for medical staff • Arrange special personnel to supervise and put on the isolation suit
	Inspection and supervision	1	2	• Daily monitoring of the environment • Nursing is not only to provide nursing services but also some people need to supervise the nosocomial infection
Staff management	Staff classification	2	3	• Divide staff into four categories • Staff classification management for each area • Divide work so that everyone has work to do
	Closed-loop management	4	6	• Don't drop around at work • Do not cross when handover • Closed-loop management of physicians and nurses entering inpatient buildings • Work in the hospital for 6 h, the rest of the time is closed-loop management in the hotel
	Staff health screening	2	5	• Investigate whether to get a COVID-19 vaccine • Health review of blood routine, antibody test, and CT test • Nucleic acid testing for all staff once a day • Rebate personnel at the hotel are double-managed and do a good job of health testing
Individualized services for patients	Create an individual scheme	3	3	• Arrange shifts for patient care needs • Symptomatic treatment of patients with complications or other diseases • Chinese medicine treatment according to the needs of patients
	Humanistic care	3	5	• Purchase daily necessities for patients • Communicate with the heating company to ensure a 24-h hot water supply • Celebrate birthdays for patients • Provide featured catering services

(Continued)

TABLE 2 Continued

Categories	Subcategories	Number of materials	Reference points	Examples of codes
	Organize special activities	3	3	• Encourage patients to get out of bed to exercise • Involve patients in a variety of activities • Create a schedule for patient
	Strengthen communication and guidance	8	10	• Communicate through online diagnosis and treatment on the Internet, • Psychologists are also members of the rehabilitation team to help patients do some counseling • Increase communication by phone or WeChat • Invite psychologists to enter the Internet Hospital
Comprehensive guarantee	Basic medical guarantee	5	10	• Establishment of a new inpatient building as a recovery ward • 7 intensive care units to accept critically ill patients • Clean the ward every day • The medical security team also participates in first aid for critically ill patients • Guarantee common medicines and COVID-19 special medicines • 24 h on duty to enter the ward for rescue • 2/3 of the staff devoted to the care and rehabilitation work
	Daily necessities guarantee	3	6	• Medical staff complete all services for patients • Provide essential household items to patients • Distribute masks to patients every day • Transport items to patients by docking with hypermarkets • Purchase items on third-party platforms
	Health and nutrition guarantee	3	3	• Three meals a day must be nutritious • Patients were guaranteed a bag of milk and a fruit every day • Make sure the patient's food is not cold
	Assistance fund guarantee	3	3	• All treatment funds for patients are paid in advance by the hospital • Including the patient's meal funds, patients do not need to spend a cent • The hospital received no special funds, the hospital pays all in advance
Positive transformation	Strategic thinking	3	5	• The whole hospital attaches great importance to this task • Take this opportunity to shorten the relationship with the government, • Take this opportunity to do a good job in the rectification and transformation of the hospital • The original 5G + Health Management project will be done well
	Benchmarking	2	2	• Learn from the industry's outstanding benchmarking units • Communication with Qinhuang Hospital on the patient management model
	Strengthen cohesion	4	6	• Strengthen confidence in video conferences for middle-level leaders • Employees actively participate in this task • Everyone's hearts are connected in special times • Hospital team cooperation and dedication are reflected
	Expand influence	2	6	• Services should also be provided after 14 days of discharge • Extend online services to patients through an internet hospital platform • Follow up with patients and carry out targeted interventions

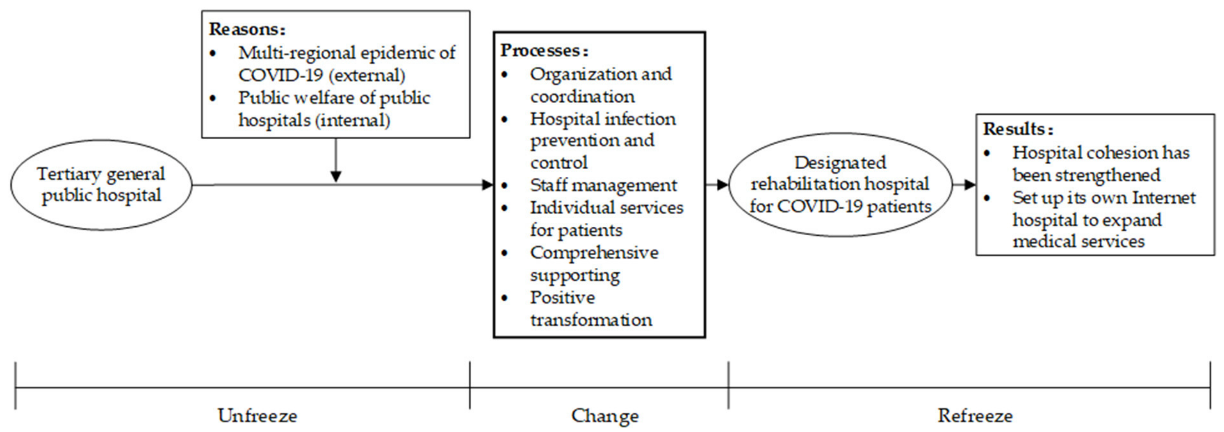

FIGURE 3
The theoretical framework of the organizational self-transformation process.

holding a party member meeting. After discussion, a preliminary action plan was determined, and a plan was prepared for some emergencies.

> *On the morning of the 7th, we held an enlarged meeting of the Party Committee of the Academy, and through the Party organization, we communicated this matter to our Party committee members and relevant functional departments.* (Participant 1)

In the process of playing the role of a rehabilitation hospital for patients cured of COVID-19, SXDS Hospital also divided corresponding task groups according to different business contents and arranged special personnel to be responsible for the leadership of sub-tasks, and achieved efficient operation in management.

> *Our hospital is divided into six task groups, of which I am in charge of the support group. My support group has five functional departments—Finance, General affairs, Information, Medical equipment, and Pharmacy.* (Participant 7)

Transfer patient

After SXDS hospital was identified as a designated rehabilitation hospital, it was necessary to transfer all of the original inpatients out of the hospital in order to prevent them from becoming infected. Therefore, the middle-level leaders of the hospital did their best to explain and comfort the patients as well as their families and took the initiative to push the patients to the ambulance, pack up the items for the patients, and assist the family members of the discharged patients from the hospital, etc. For the critically ill patients who were originally hospitalized, the hospital contacted other medical units on a humanitarian basis to request they accept these patients. After all these inpatients were transferred, the hospital could re-plan the ward. In addition, at the time of transferring the original inpatients, the hospital has also achieved a seamless connection in receiving COVID-19 inpatients based on the work plan formulated the previous day.

> *On January 7th, we have another important task, which is to transfer all the patients in our hospital. As of 10 p.m., we have successfully transferred all 250 patients out.* (Participant 1)

> *In the process of picking up patients, due to our adequate preparation and smooth communication, after the patient arrived at our hospital, there was not a single patient who stayed in the hospital and was not arranged.* (Participant 2)

External coordination

In the process of SXDS hospital serving the cured patients with COVID-19, the hospital was not coping alone but also connected with many stakeholder groups. For example, the hospital was identified as a designated rehabilitation hospital for COVID-19 patients by the government. Therefore, it must first coordinate with the government to successfully complete the task. Secondly, it is necessary to conduct learning exchanges with other designated rehabilitation hospitals and negotiate the statistics of patient information. In addition, when the cured patients reach the standard of recovery and discharge, the hospital also needs to communicate with the community to ensure that the cured patients can return home smoothly.

> *The task assigned to us by the Xi'an Epidemic Prevention and Control Headquarters, we have to communicate with it. After the communication, we have to complete how to communicate with the government.* (Participant 2)

> *In order to ensure that patients can be discharged from our hospital smoothly, we have set up a working group for this discharge and community connection.* (Participant 9)

Hospital infection prevention and control

Process transformation

During the epidemic outbreak in Xi'an, nosocomial infections occurred in three designated hospitals in Xi'an. Therefore, another critical task of SXDS hospital is to prevent nosocomial infection. In this regard, hospital managers have thought of a lot of ways, such as transforming the hospital from a large process so that the hospital's admitted patients and staff can walk in different areas, and the patients and staff are not in the same area, which can effectively prevent the spread of diseases.

> *Actually, one of our characteristics is that the infection ward built on the first floor in the past was divided into three areas and two passages. We made it three-dimensional and created a three-dimensional division of three regions and two passages.* (Participant 2)

> *Then on the evening of January 7th, we clarified the division of clean areas, semi-contaminated areas, and polluted areas, which is a very critical link in terms of nosocomial infection.* (Participant 1)

Ward disinfection

Sorting out and sterilizing the ward is the essential preparation for the hospital to carry out rehabilitation and treatment tasks. The hospital will focus on arranging for nursing staff to be responsible for implementing this work.

> *Every person who enters the building has a disinfection task, not only to take care of patients, to do basic nursing and nursing work but also to disinfect.* (Participant 2)

> *We cleaned and sanitized the ward overnight, which is the essential preparation for the ward.* (Participant 1)

Hospital infection training

In order to effectively control the occurrence of nosocomial cross-infection, the hospital has also continuously carried out special training on epidemic prevention and control for all medical staff in the hospital. The focus is on strengthening the learning of knowledge related to epidemic prevention and how to do personal protection at work. This effectively improved the medical staff's awareness of hospital infection prevention and control, standardized the daily work process, and ensured that the hospital's prevention and control work was carried out in an orderly manner.

> *And then there is our hospital infection training for medical staff. Especially the training on putting on and taking off isolation suits and protective suits.* (Participant 2)

> *If the method of taking off the isolation suit is wrong and incorrect, it is easy to cause one's own infection, so this procedure is very critical.* (Participant 2)

Inspection and supervision

In order to continuously strengthen infection management in hospitals, implement various infection control measures in each department, and ensure that all staff, the whole process, and the whole hospital strictly adhere to the bottom line of "zero infection," the hospital has also strengthened its inspection and supervision functions to prevent and control the occurrence of nosocomial infections to the greatest extent possible.

> *In addition, we have to monitor the environment every day. Judging from the operation for more than 10 days, our environmental monitoring is all negative. It should be said that we are still relatively stable at present.* (Participant 2)

> *We stimulated all the head nurses and infection controllers as our supervisors to strengthen our hospital sense supervision, and the purpose is also to prevent the occurrence of hospital sense.* (Participant 2)

Staff management

Staff classification

Although the main business of the SXDS hospital has changed after being identified as a designated rehabilitation hospital for COVID-19 patients, the work of the opened Internet hospital, or the service work for the isolation hotel, still requires people. Therefore, during this period, the hospital carried out a work diversion so that everyone could do an excellent job in the various tasks at hand.

> *We divided our staff into four categories. The first category is people who enter the COVID-19 ward and have direct contact with patients, and the second category is security service personnel, who do not have direct contact with patients but may also enter the vicinity of the rehabilitation ward. The third category is those who are not physically suitable to work in the hospital, such as those who are pregnant or breastfeeding, and a reasonable arrangement should be made for them. The fourth category is the work that needs to be managed while stationed in isolated hotel personnel.* (Participant 3)

Closed-loop management

After classifying the personnel, the hospital adopted closed-loop management for some personnel, especially the doctors, nurses, and service personnel who entered the inpatient building, and provided room and board for the closed-loop management personnel. The staff who are arranged to work in the hotel also adopt a closed-loop management method. In addition, the hospital sense department has specially formulated rules and regulations for closed-loop management.

> *The meeting the day before was the target of adjustment. Previously, we thought that the staff who entered the ward were the main targets of strict closed-loop management, but the municipal government required all hospital staff the night before yesterday to be regarded as the target of crucial supervision.* (Participant 3)

> *In addition to working in the hospital, the medical staff works 6 h a day, and the other time is closed-loop management in the hotel. In the hotel, it is also a single room, and they are not allowed to visit each other and are not allowed to gather.* (Participant 2)

> *We entered 585 people in these 12 wards, 300 medical staff, and 180 cleanings and security personnel outside the building. These personnel is also closed-loop, and they need the hospital to provide accommodation.* (Participant 7)

Staff health screening

A general goal at the hospital level is zero infection, so in addition to closed-loop management of classified personnel, another job the hospital does in personnel management is to monitor personnel health. Especially for this group of people who have direct contact with patients, before such personnel is stationed, in accordance with the requirements of the National Health and Health Commission and the Prevention and Control Headquarters, all personnel must undergo a physical examination and pass the physical test before they are allowed to work. If there is a problem with the inspection, the hospital will also make corresponding adjustments.

> *We first conducted an epidemiological investigation in the early stage. Whether the new crown vaccine has been vaccinated in the whole process is the most basic.* (Participant 3)

> *There is also the nucleic acid test of the staff in our hospital. The nucleic acid test of all staff is carried out once a day.* (Participant 2)

Individual services for patients

Create an individual scheme

After the clinical cure of COVID-19 patients, there are often residual problems in breathing, appetite, sleep, psychology, etc. It may also be because the illness aggravates or affects the original underlying diseases. Therefore, to better promote the recovery of patients after the cured patients enter the recovery period, the hospital makes a comprehensive evaluation based on the overall condition of each patient's disease process, such as symptoms at onset, treatment plan, length of recovery time, previous underlying diseases and the patient's ability to live in daily life, etc. Then determine an individual rehabilitation treatment plan.

> *Then we also formulated some nursing routines and nursing regulations for this patient in our hospital and arranged shifts.* (Participant 4)

> *If there is a need for some patients during the recovery period, we can treat them with traditional Chinese medicine according to the needs of the patients. If some patients have poor cardiopulmonary function, such as the elderly who need oxygen, we will also provide some oxygen therapy.* (Participant 1)

> *From waking up in the morning to resting in the evening, when to wash, eat, and exercise, we will formulate a model for the patient. Of course, the patient can do it without following the schedule when there are individual needs.* (Participant 9)

Humanistic care

In addition to physical health, the hospital also pays attention to the mental health of the recovered patients in a timely manner, allowing them to feel humanistic solid care during the recovery period. For example, the hospital tries its best to give more care to the patients in life and actively helps the patients to purchase daily necessities. When doing catering, the hospital also provided special services, including baby meals, children's meals, and diabetes meals.

> *We will ask all medical staff to give them some humanistic care. After all, the patient has to stay in the hospital for more than 10 days. From a closed area to a closed area, the patient may have some psychological pressure or other negative emotions.* (Participant 1)

> *We are now trying to make our doctors be more careful, be more careful than usual when treating patients, speak softer, have a better attitude, and soothe the patient's emotions.* (Participant 4)

Organize special activities

Recovered patients are most of the time under closed management during treatment in the hospital. To help them expand their interpersonal circle, the hospital has explored various forms of activities. For example, as the Chinese traditional Spring Festival was approaching, patients were given laba porridge and warm wishes on the laba Rice Porridge Festival. In addition, the hospital celebrated birthdays for some patients and invited others to participate. Through these activities, patients feel solid humanistic care. These activities also help them to recover quickly.

> *We have adopted various forms of activities so that everyone can participate in it, and it is more pleasant to enjoy the treatment process for more than 10 days.* (Participant 1)

> *Next, we will celebrate the patient's birthday with the nursing team and provide warm services.* (Participant 7)

Strengthen communication and guidance

The discharged patients with COVID-19 were transferred to the designated rehabilitation hospital for continued rehabilitation after regular treatment at the designated treatment hospital. The mindset of patients is different in these two hospitals. Patients infected with COVID-19 were more obedient to the hospital when they received service at the designated treatment hospital because they felt they were a patient. However, when patients were cured and discharged from the hospital to receive rehabilitation services at the designated rehabilitation hospital, they thought of themselves as no longer patients and were less obedient to the management. Facing the negative emotions of patients, the hospital first adopted various methods to strengthen communication and gain the understanding of patients.

> *We have also thought of a lot of ways. For example, we can set up a WeChat group of doctors, nurses, and patients, and patients can express their opinions in the WeChat group.* (Participant 4)

> *We are a medical institution, and we will not provide them with such good services as hotels do. We also communicate with patients in some ways, and after communicating well, we gain an understanding of the patients.* (Participant 2)

By medical standards, recovered patients are cured, but the way they behave, and the way they see others acting, is a reminder that the true cure has not yet been achieved. Therefore, for patients' physical and mental recovery, the hospital has also taken practical interventions to help COVID-19 patients regain their enthusiasm for life and work so that they fully realize that they have not been abandoned by society.

> *Our hospital launched an online psychological consultation, and if the patient had any psychological problem, our online chief physicians were also constantly explaining it.* (Participant 1)

> *We are still doing this online psychological counseling service, and we invite some psychologists from other hospitals to settle in our Internet Hospital to provide timely psychological counseling and intervention for recovered patients.* (Participant 5)

> *The psychologist is also a member of the rehabilitation team and conducts some communication, exchange, and mediation on the patient's psychological problems.* (Participant 6)

Comprehensive supporting

Basic medical guarantee

In order to ensure the smooth progress of medical treatment, rehabilitation treatment for COVID-19 patients, and first aid for critically ill patients, the hospital has given full play to the advantages of various human and material resources based on the innate conditions of the original general hospital. It provides the most basic medical security conditions for patients who have recovered from COVID-19, such as setting up a special medical security team to be responsible for this work, opening additional wards to accept critically ill patients, and ensuring the use of essential conventional and special drugs for patients.

> *In addition, our hospital is a general hospital, we have a relatively good condition, that is, we can still keep up with the treatment of patients' basic diseases.* (Participant 2)

> *In addition to supplies, we also have to ensure the medicines we give to patients. In terms of drugs, we must find ways to ensure regular drugs and special medicines for COVID-19.* (Participant 1)

> *So, two-thirds of our staff are involved in the treatment and recovery of the COVID-19 epidemic.* (Participant 7)

Daily necessities guarantee

In the case of comprehensive material support under the epidemic, it is necessary to establish a team that responds quickly. The team's ability to cooperate is essential. Among the six departments divided by SXDS hospital for this task, the comprehensive material support team is one of them. They created a special response team. In the material group for prevention and control, members in the group respond immediately, and they can perform tasks well. Through various efforts, group members have provided comprehensive living supplies to patients who have recovered from COVID-19.

> *Actually, we are also considering that we want to connect with a superstore and then transfer it directly to the patient.* (Participant 1)

> *These patients basically do not receive medical treatment. The primary need is daily necessities, from nail clippers to razors. We collect and purchase on behalf of them and use the fastest and most convenient way of shopping to meet their needs for daily items.* (Participant 7)

Health and nutrition guarantee

A good diet is essential for curing patients. Drug treatment blocks the replication of the virus, and immunity is the final line of defense to kill the virus and invade cells. In terms of catering services, the hospital has carried out nutrition matching for three meals to ensure patients' essential diet and nutrition during hospitalization and enhance immunity.

> *There is also the issue of food and beverages. Three meals a day must be nutritious and delicious.* (Participant 2)

> *For the quality standard of meals, we also ensure that patients can have a certain amount of nutrition here three times a day, such as a bag of milk every day and a fruit every day. We must guarantee these things to patients.* (Participant 1)

> *You know that for 585 patients' three meals a day, we must ensure that the meals are not cold, and we must ensure that 585 meals are delivered within 40 min. Everyone is under a lot of pressure, and we have to take the risk that we will not be infected. Therefore, our hospital director set up the delivery group and the transfer group in time.* (Participant 7)

Assistance fund guarantee

Since SXDS Hospital was identified by the government as a designated rehabilitation hospital for the recovery of COVID-19 patients this time, it was a process of "receiving orders in a critical situation," and the hospital did not receive special funds in advance. All the funds used for medical assistance this time were paid in advance by the hospital. The chief accountant has done a lot of work in this area to raise funds.

> *All the relief funds we give to the patient, including his catering funds, are all paid in advance, and the patient does not need to spend a penny.* (Participant 2)

> *We didn't get the special funds, and we didn't apply for it ourselves. All of them were paid by the hospital itself. It can be said that we were "instructed in times of crisis" and unconditionally accepted this task.* (Participant 1)

Positive transformation

Strategic thinking

Being identified as a designated rehabilitation hospital for COVID-19 patients this time has the triple attributes of politics, social welfare, and self-reform for the hospital. Hence, the whole hospital attaches great importance to this. Strategically, the hospital regards it not only as a high-quality political task delivered by superiors but also as a task of serving the masses and anti-contribution to society. At the same time, it also regards it as a way for the hospital to realize self-reform and transformation.

> *Our hospital has become a rehabilitation hospital through this transformation, it should be said that the relationship between the government and us will be stronger.* (Participant 2)

> *We hope that after completing the rehabilitation and treatment of COVID-19 patients with high quality and efficiency, we will continue to "strike while the iron is hot," gather the energy of all hospital staff, and do an excellent job in the follow-up transformation and development of the hospital.* (Participant 1)

Benchmarking

While taking on this task and making a series of decisions, the hospital conducted a systematic review, profound reflection, and experience summarization of the past management, and had the courage to face up to and admit the many deficiencies and mistakes in the past management, and learned the lessons of these past failures. At the same time, it also actively learned from the excellent benchmarking units in the industry.

> *Then before this patient was admitted, we also did a lot of work in nursing. For example, we communicated with Qinhuang Hospital, and we also asked about a model of managing these patients.* (Participant 4)

Strengthen cohesion

The development of the hospital is inseparable from the hard work of every employee. The hospital's task of accepting this task belongs to "being ordered to be in crisis." The time is very urgent. It is by no means that one person or a group can do all the preparatory work. It is the active support and decisive actions of all the staff to promote it. The rapid and effective implementation of various measures of the hospital.

> *We didn't actually do a lot of mobilization in the early stage, but the employees could actively participate in this task, which moved me very much.* (Participant 1)

> *It is the setting of our entire hospital to face the COVID-19 rehabilitation designated hospital this time. Under such opportunities and challenges, our hospital has grown, and our team cooperation ability and dedication have been reflected.* (Participant 6)

> *Because as a member of the party committee, I also constantly boost the morale of everyone in our group, including conveying the spirit of the superiors to everyone, complimenting their work, and fighting with everyone.* (Participant 7)

Expand influence

Coinciding with the new year when this task was undertaken, the hospital leadership team hopes to take this opportunity to do an excellent job in the rectification and transformation, and development of the hospital. For example, as a regional urban medical group, the hospital makes full use of the advantages of 5G Internet Hospital and Internet of Things technology to carry out the Internet + Health Management service for COVID-19 patients and discharged patients on the Internet platform. This makes the patient feel that although he has left the hospital, the service can still be extended to the patient through the Internet.

> *I plan to set up an online rehabilitation and health management class on the Internet. On the Internet Hospital platform, online health management services for patients with COVID-19 on the Internet will be launched.* (Participant 6)

> *After the patient is discharged from the hospital, how can we give him some health guidance in the next step? How can we make this patient in a radius of several kilometers recognize our hospital? For example, he will come to our hospital for the following review. So that's the things we're going to consider doing next.* (Participant 9)

Discussion

The rehabilitation of patients with COVID-19 represents a new clinical and organizational type of rehabilitation. From the clinical viewpoint, rehabilitation of COVID-19 patients requires special medical assistance, and these patients have higher diagnostic and therapeutic needs than non-COVID-19 rehabilitative patients (31–34). The planning of the COVID-19 recovery unit requires an organizational analysis of the specific needs of this new clinical entity, which has not been previously provided by healthcare organizations around the world (35). A comprehensive health organization is essential to respond to current and future epidemics. It must include strengthening and properly organizing rehabilitation as an integral part of the treatment process. Figure 3 is an action framework for transforming public hospitals constructed from the interview data combined with the theory of organizational change. It was used to analyze how a public hospital carried out systematic rehabilitation management after it was identified as a designated rehabilitation hospital for discharged patients with COVID-19 to successfully treat patients and realize its own transformation. This is of great significance for improving the operational efficiency of medical institutions and the allocation of medical and health resources, as well as improving the quality of patient rehabilitation services under the pandemic.

Changes in the internal and external environment drive the hospital to unfreeze

The delta virus in this epidemic in Xi'an has the characteristics of "fast spread," "high viral load," and "occult transmission" (36). It has formed a certain scale of community transmission and spillover cases. Yanta and Beilin districts, which are located in the city center, were the areas of high epidemic prevalence (Figure 1). Coincidentally, SXDS hospital is also located in the center of Xi'an and is a general tertiary hospital that integrates medical treatment, teaching, scientific research, preventive care, and rehabilitation. It is equipped to treat patients recovering from COVID-19. Changes in the external environment and internal conditions make it a designated rehabilitation hospital. Its original routine medical consultation services had to be suspended and turned into rehabilitation services for patients discharged from the COVID-19. That is, the organization began to unfreeze.

The focus of this step of organizational unfreezing is to create motivation for change. Employees are encouraged to change their old behavior patterns and work attitudes and adopt new behaviors and attitudes that are adapted to the organization's strategic development (37, 38). In order to do this, the hospital strategically treats it as both a political task that must be accomplished and a social task that serves the public, as well as an internal task to achieve self-reform. In other words, this task has the triple attributes of politics, social welfare, and self-reform for the hospital, so the whole hospital attaches great importance to it. After the hospital received the government's notice to become a designated rehabilitation hospital, a hospital-wide staff representative meeting was held to inform all-party committee members and relevant functional departments. This made the leaders and staff realize the urgency of the change. The most important thing is that the hospital had developed a preliminary action plan through this congress.

The hospital carries out systematic rehabilitation management to actively transform

The complex internal and external environment changes have brought opportunities and challenges to this hospital. Timely adjustment, improvement, and innovation of elements in the organization, such as its management philosophy, working methods, organizational structure, staff management, organizational culture and technology, largely determine the success of a change (39). Through semi-structured in-depth interviews and focus groups with senior executives of the public hospital, this study provides essential information about the successful transformation of a public hospital after being identified as designated rehabilitation hospital. This study confirmed the effectiveness of a series of transformation efforts, such as renovating wards to meet the treatment standards of COVID-19 rehabilitation hospitals and providing special rehabilitation services for patients, in the face of multiple challenges such as lack of funds, prevention of nosocomial infections, and psychological panic among the population.

First, SXDS hospital adopted an internal and external organizational coordination after becoming the designated rehabilitation hospital for the COVID-19. In China's national conditions, public hospitals are subordinate to government administrative agencies. They are subject to administrative mechanisms and their governance means have administrative characteristics (40). Therefore, being identified as a designated rehabilitation hospital for COVID-19 also has administrative tasks for public hospitals. This study shows that organizational coordination inside and outside the hospital can help organizations quickly complete basic deployments after unfreezing. After SXDS Hospital was identified as a COVID-19 rehabilitation hospital during the epidemic, the hospital managers strengthened external contacts at the first time, and they quickly established a task group. This is the primary element of China's modern emergency management system with "three cases and one system" as the core for public health emergencies since the SARS (41). In extraordinary times, the hospital implements a significant leadership responsibility and accountability system by setting up a working leadership group or task force to avoid confusion of authority and responsibility and multiple leadership.

In addition to ensuring medical treatment, another significant challenge of becoming a rehabilitation hospital for COVID-19 patients is to prevent nosocomial infection. From the national incidence rate, approximately a quarter of medical staff are direct victims of infectious diseases (42). These results appear to be that participants in the study contracted the virus early in the outbreak before disinfection systems were firmly established. In addition, this suggests that the problems that emerged in past outbreaks, such as inadequate public health crisis response systems, limited understanding of the outbreak, and poor communication about disease risks, remain (43, 44). The study reveals that a "three districts and two channels" process transformation of the existing hospital infrastructure is necessary to prevent nosocomial infections. The "three districts" refer to clean, contaminated and semi-contaminated areas. The "two channels" refer to the medical staff channel and the patient channel. The coronavirus spreads from person to person through a droplet and aerosol transmission and indirect transmission by touching pollutants or contaminated surfaces (45). The process transformation of three districts and two channels separates patients from susceptible groups. It reduces the risk of infection by physically achieving not being in the same area, not meeting, and not crossing. In addition, ward disinfection, hospital training and inspection and supervision are also essential. In fact, the hospital had not experienced a single nosocomial infection during the period when it was designated a rehabilitation hospital for patients with COVID-19.

Personnel management in public hospitals is the crucial and difficult point of becoming a designated rehabilitation hospital. The risk of coronavirus infection among medical staff, especially primary care doctors and nurses, is very high (46). Personnel management should not allow mistakes. Otherwise it will cause large-scale nosocomial infections and increase the pressure of COVID-19 treatment. Considering the different aspects of the task content during an epidemic, the hospital has categorized and managed its personnel. Personnel involved in direct contact with patients, security service personnel, personnel who are not suitable to work in the hospital, and management personnel of the isolated hotel, each perform their duties to improve work efficiency. The requirement for staff to maintain physical and social distance, wear masks, closed-loop management, vaccination, and pre-service health screening are infectious disease prevention requirements aimed at reducing the probability of nosocomial infection events (42), as well as out of the need to protect health care resources. Medicine has the characteristics of solid professionalism and a long personnel training cycle. Medical personnel is scarce medical and health resources. Especially during the COVID-19 epidemic, countries may face the shortage of medical resources. These requirements for staff can help protect themselves and patients and reduce the probability of being infected.

Another critical point for the success of hospital transformation involves the rehabilitation services and various guarantees provided by the hospital. The purpose of designing a designated rehabilitation hospital is to effectively provide a high level of rehabilitation services to patients in a specific area so that patients can be sent to their homes smoothly. In this sense, taking effective rehabilitation measures to promote the smooth recovery of patients is the most fundamental task of designated rehabilitation hospitals. This study reported that the hospital had explored effective measures to recover the patient's smooth recovery. The coronavirus causes various degrees of damage to patients' lungs, kidneys, heart, and other organs, and even multi-organ failure (47, 48). During the physical rehabilitation phase, exercise rehabilitation, as one of the main methods of pulmonary rehabilitation training, is of great significance to the improvement and rehabilitation of patients with acute and chronic lung injury (49). Moderate physical exercise can promote blood circulation and allow immune cells to transport and destroy viruses in the body in time, which is the primary basis of physical exercise to effectively resist and contain coronavirus (50). Therefore, in the context of the COVID-19 pandemic, physical activity may help to positively regulate the immune system and improve physical and mental health. This rehabilitation hospital puts physical exercise at the top of its rehabilitation program. Furthermore, nutritional support is critical together with rehabilitation to improve the chances of recovery for COVID-19 patients (34). In order to ensure the nutrition of patients, the hospital has made appropriate arrangements for three meals a day.

Both the widespread contagion and the lockdown inevitably affected the psychological changes in the population (51–53). This was also a significant challenge for the hospital. Various frailty and dysfunction caused by COVID-19, as well as activity restrictions and decreased ability to live and participate in society caused by the disease, making convalescent patients often suffer from anxiety, depression, panic, insomnia, and many other psychological problems. Previous studies have shown that patients with COVID-19 experience a significant mental burden during their recovery (54, 55), and new models to mitigate these effects may help reduce this severity. This study confirms the need to assess the consequences of the pandemic over time for people who suffered functional limitations prior to COVID-19, as their physical and mental status may be altered by the pandemic, particularly as a result of lockdown (56). This rehabilitation hospital and its staff have eased patient uncertainty by providing effective COVID-19-related information and emotional support. More importantly, the rehabilitation hospital adopted practical and effective intervention measures to timely identify the psychological needs of patients. According to different genders, occupations, ages, and groups, the hospital carried out different levels of psychological rehabilitation strategies such as in-hospital intervention, telephone counseling, and online consultation. For pregnant women, the elderly, children, the disabled, and other special groups, the hospital took into account their special psychological state and psychological needs, formulated targeted psychological rehabilitation programs, provided comprehensive psychological rehabilitation support, and carried out personalized psychological rehabilitation guidance.

The success of the designated rehabilitation hospitals also depends on whether there is sufficient financial support. First, the spatial layout and negative pressure ventilation system of the ward buildings of the designated rehabilitation hospitals must meet the requirements for preventing and controlling respiratory infectious diseases. The renovation of these facilities requires the hospital's funds to be guaranteed. Second, the closed-loop management adopted by the hospital for its staff is carried out at the hotel. These staff members are required to bear their own costs for accommodation and food. Third, medical expenses incurred by the patients with COVID-19 are subsidized by the government after basic medical insurance, primary medical insurance, and medical assistance are paid in accordance with the regulations (57). In fact, these expenses are usually prepaid by designated rehabilitation hospitals and then financially subsidized by the government to the hospital, but there is often a lag in time. In this study, the hospital's chief accountant did a lot of work to raise funds. However, if government financial subsidies are not available, the epidemic continues to spread, and the number of rehabilitated patients continues to increase, this may lead to the unsustainable operation of the designated rehabilitation hospital.

The hospital refreezes itself after successful transformation

During the refreeze phase, the necessary reinforcement means are needed to fix the new attitudes and behaviors and to stabilize the organizational change (25). In the process of providing rehabilitation services for patients, this hospital has also achieved rapid growth and pointed out the direction for its subsequent transformation and development. There is ample evidence that COVID-19 has increased the need for recovery not only in patients with COVID-19 but also in patients with sequelae of long-term illness or disability (58). Therefore, during the COVID-19 pandemic or any other similar outbreak (59), rehabilitation services should continue to be provided, combined with medical management of different stages of acute, subacute, and long-term COVID-19 (60). This study shows that the hospital has achieved good results by continuing to serve patients through Internet diagnosis and treatment, which can attract some of its previous patients to its Internet hospital for online consultation and disease guidance. Due to the contagious nature of COVID-19, expert consensus-based guidelines recommend limiting direct contact between therapists and COVID-19 patients. Telemedicine can be used as electronic personal protective equipment (PPE) to reduce the risk of exposure and contamination for patients and practitioners (61). Telerehabilitation is defined as "the provision of rehabilitation and rehabilitation services through information and communication technologies.... Telerehabilitation services may include assessment, assessment, monitoring, prevention, intervention, supervision, education, counseling, and guidance" (62). Therefore, the hospital took advantage of the role of the designated rehabilitation hospital for patients with COVID-19 to transform and carry out other services of Internet + Diagnosis and Treatment, providing medical and drug distribution services for more patients during the recovery period, even meeting the medical needs of patients with other diseases, and realizing the sustainable development of the hospital itself.

Limitations

This study is not without its limitations. First, due to COVID-19 movement restrictions, interviews were conducted *via* phone and Tencent Conferences online. This data collection may have limited our in-depth exploration of participants' non-verbal expressions. Second, although the sample of this study has a certain purpose, the sample size is relatively small, and the sample size can be expanded for further research in the future. Third, since the subjects of this study are Chinese hospitals and their managers, the conclusions can be generalized to rehabilitation institutions in China but may not be generalized to other countries due to differences in cultural conditions.

Despite this, this study still has essential significance. Based on the "Unfreeze-Change-Refreeze" theory of organizational change, it provides in-depth evidence for how rehabilitation hospitals can provide high-quality rehabilitation services to patients and achieve their own successful transformation with limited resources during a pandemic. This study raises awareness of the need to improve the operation and management of rehabilitation hospitals to improve the "public welfare" of public hospitals and to develop relevant interventions.

Conclusion

This study aims to understand how a public hospital can provide high-quality rehabilitation services for patients after being identified as a designated rehabilitation hospital for patients with COVID-19 and realize its own transformation. This study analyzes the many challenges of the hospital that had to be unfrozen in the face of a complex internal and external environment from the perspective of organizational change. After unfreezing, the hospital has actively transformed through organization and coordination, hospital infection prevention and control, staff management, providing individual services for patients, and comprehensively supporting. The hospital effectively prevented nosocomial infections and successfully cured 583 patients with COVID-19 through the above management. The most important thing is that the hospital has developed itself rapidly after this transformation. Through the social reputation accumulated during this mission, the hospital established an Internet Hospital to expand medical services to more residents. The hospital staff also became more united after this mission, and the hospital continued to run a public hospital that satisfied the people with the help of this cohesion, which means that the organization has been refrozen.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of School of Medicine of Xi'an Jiaotong University (approval number: 2020-1258). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SH and CC: conceptualization. CC: methodology and writing—original draft preparation. BY: software and formal analysis. CC and BY: validation. QL, CC, and BY: investigation. QL: resources, data curation, and supervision. CC and HH: writing—review and editing. BY and HH: visualization. SH: project administration. 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.

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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.2022.919730/full#supplementary-material

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SYSTEMATIC REVIEW
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An Umbrella Review With Meta-Analysis of Chest Computed Tomography for Diagnosis of COVID-19: Considerations for Trauma Patient Management

*Andrés Gempeler[1†], Dylan P. Griswold[2,3†], Gail Rosseau[4], Walter D. Johnson[5], Neema Kaseje[6], Angelos Kolias[2,3], Peter J. Hutchinson[2,3] and Andres M. Rubiano[2,7,8]**

[1] Centro de Investigaciones Clínicas, Fundación Valle del Lili, Cali, Colombia, [2] NIHR Global Health Research Group on Neurotrauma, University of Cambridge, Cambridge, United Kingdom, [3] Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom, [4] Department of Neurosurgery, George Washington University School of Medicine and Health Sciences, Washington, DC, United States, [5] School of Medicine and Public Health, Loma Linda University, Loma Linda, CA, United States, [6] Surgical Systems Research Group, Kisumu, Kenya, [7] Neuroscience Institute, INUB-MEDITECH Research Group, El Bosque University, Bogotá, Colombia, [8] Neurological Surgery Service, Vallesalud Clinic, Cali, Colombia

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Roger Nlandu Ngatu, Kagawa University, Japan

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***Correspondence:**
Andres M. Rubiano
rubianoam@gmail.com

† These authors have contributed equally to this work

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Background: RT-PCR testing is the standard for diagnosis of COVID-19, although it has its suboptimal sensitivity. Chest computed tomography (CT) has been proposed as an additional tool with diagnostic value, and several reports from primary and secondary studies that assessed its diagnostic accuracy are already available. To inform recommendations and practice regarding the use of chest CT in the in the trauma setting, we sought to identify, appraise, and summarize the available evidence on the diagnostic accuracy of chest CT for diagnosis of COVID-19, and its application in emergency trauma surgery patients; overcoming limitations of previous reports regarding chest CT accuracy and discussing important considerations regarding its role in this setting.

Methods: We conducted an umbrella review using Living Overview of Evidence platform for COVID-19, which performs regular automated searches in MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and more than 30 other sources. The review was conducted following the JBI methodology for systematic reviews. The Grading of Recommendations, Assessment, Development, and Evaluation approach for grading the certainty of the evidence is reported (registered in International Prospective Register of Systematic Reviews, CRD42020198267).

Results: Thirty studies that fulfilled selection criteria were included; 19 primary studies provided estimates of sensitivity (0.91, 95%CI = [0.88–0.93]) and specificity (0.73, 95%CI = [0.61; 0.82]) of chest CT for COVID-19. No correlation was found between sensitivities and specificities (ρ = 0.22, IC95% [–0.33; 0.66]). Diagnostic odds ratio was estimated at: DOR = 27.5, 95%CI (14.7; 48.5). Evidence for sensitivity estimates was graded as MODERATE, and for specificity estimates it was graded as LOW.

Conclusion: The value of chest CT appears to be that of an additional screening tool that can easily detect PCR false negatives, which are reportedly highly frequent. Upon the absence of PCR testing and impossibility to perform RT-PCR in trauma patients, chest CT can serve as a substitute with increased value and easy implementation.

Systematic Review Registration: [www.crd.york.ac.uk/prospero], identifier [CRD42020198267].

Keywords: umbrella review, evidence based synthesis, COVID-19, global health, trauma surgery, evidence-based practice, chest CT, trauma

KEY MESSAGES

What is already known on the subject?

RT-PCR testing has disadvantages for detecting COVID-19 timely in a trauma surgery setting. Sample processing can be long and requires specific laboratory protocols, which usually delay test results; and sampling can be difficult during basic and advanced trauma life support. Chest CT has been proposed as an additional tool in the diagnosis of COVID-19, and several reports from primary and secondary studies that assessed its diagnostic accuracy have been published.

What are the new findings?

Chest CT is a highly sensitive tool to detect COVID-19. Chest CT specificity was lower than sensitivity. Great variation was present between studies due to differences in design, index test definition and reference standards.

How might these results affect future research or surgical practice?

Chest CT is valuable when PCR testing is absent or obtaining timely results is not possible. Positive findings on chest CT should prompt additional protective measures in aerosolizing procedures for medical staff and isolating measures for the patient.

As emergency trauma patients typically undergo localized or full body CT scanning, imaging of the lungs and its interpretation by a radiologist is not expected to increase costs significantly and can be implemented as a screening tool in that setting.

One important consideration are patients with trauma or polytrauma involving the chest, as lung contusions and hemo- or pneumo-thorax will affect the readability of chest CT for pneumonia.

BACKGROUND

During the COVID-19 pandemic, healthcare facilities all over the world are challenged when caring for trauma patients for whom a history of typical symptoms, close contacts and even vaccination status is not available because of agitation, intoxication or unconsciousness due to injury and sedation. Timely detection of cases is crucial to prompt adequate isolation measures and use of personal protective equipment to protect medical staff and other patients. These measures should be applied preventively in every trauma patient with need for emergency surgery, but shortages and sparse resources limit the compliance of these COVID-19 preventive recommendations in low and middle income countries (LMICs); and are thus applied almost exclusively in confirmed cases (1–3). Diagnosis is done with reverse transcriptase polymerase chain reaction (RT-PCR) to identify genetic material of the virus in nasopharyngeal or oropharyngeal swabs.

RT-PCR testing has some disadvantages that become more important in the emergency surgery setting: sample processing can be long and requires specific laboratory protocols, which usually delays test results; and sampling can be difficult during basic and advanced trauma life support. RT-PCR has varying sensitivity among different sampling modes: 97.2% (95%CI: 90.3–99.7%) in sputum; 62.3% (95%CI: 54.5–69.6%) in saliva; and 73.3% (95%CI: 68.1–78.0%) in nasopharyngeal and throat swabs; with a pooled sensitivity estimated at 84.8%, 95% CI = [76.8%; 92.4%]) (4, 5). Of these, nasopharyngeal and throat swabs are the most commonly applied. For both, a considerable rate of false negative results has been reported and is to be expected: an initial false negative RT-PCR results was measured as high as 54% of the time (4, 6). False positives, on the contrary, are very unlikely because specificity has been reported at 98.9%, 95% CI = [97.4%; 99.8%]) with low variability (4). Chest CT has been proposed as an additional tool in the diagnosis of COVID-19, and several reports from primary and secondary studies that assessed its diagnostic accuracy have been published. Chest CT cannot detect asymptomatic carriers, of course, but could detect COVID-19 pneumonias that single RT-PCR can miss (if available).

The above factors make RT-PCR flawed and unpractical for COVID-19 detection in trauma patients, and open the door for a role of chest CT (6). The reported accuracy of chest CT for COVID-19 diagnosis varies substantially and the validity of primary studies is variable, being affected by poor adherence to reporting guidelines and high risk of bias (7). To inform recommendations and practice regarding the use of chest CT in the in the emergency trauma setting with the above factors in mind, we sought to identify, appraise, and summarize the available evidence on the diagnostic accuracy of chest CT for rapid diagnosis of COVID-19, and discuss important considerations for its use.

Abbreviations: CT, computed tomography; ED, emergency department; PRISMA, preferred reporting items for systematic reviews and meta-analyses; LOVE, living overview of the evidence; DTA, diagnostic test accuracy; WHO, World Health Organization; PCR, polymerase chain reaction; UK, United Kingdom; CO-RADS, COVID-19 reporting and data system; NVvR, radiological society of the Netherlands.

METHODS

We conducted a broad evidence synthesis (umbrella review) to summarize the diagnostic accuracy of chest CT imaging to detect COVID-19, the respiratory disease caused by the SARS-CoV-2 virus. A protocol of this review following the PRISMA statement was registered in the International Prospective Registry of Systematic Reviews (PROSPERO; CRD42020198267) and published in *JMIR Research Protocols* (8). This review was conducted following the JBI methodology and the Cochrane Handbook for systematic reviews of diagnostic accuracy (9).

Study Selection

Selection was carried out in Covidence (Melbourne, Australia). Two independent reviewers examined titles and abstracts for eligibility. Full-text review verified fulfillment of selection criteria. All decisions taken during screening were documented and are outlined in this report with a list of excluded studies. Any disagreements that arose between the reviewers were solved by consensus. The results of the search are presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (10).

Selection Criteria

Population of Interest

We considered studies that assessed chest CT imaging for diagnosis of COVID-19 pandemic in trauma patients. Given the likelihood that reports on this specific population were limited, we also included studies of any patients with clinical suspicion of COVID-19 in any procedural and in-hospital setting as the diagnostic accuracy for detection of COVID-19 was considered extrapolatable to most trauma patients.

Types of Studies

Systematic reviews of diagnostic test accuracy studies (DTA) and individual DTAs not included in systematic reviews were included. To be considered a DTA, a study had to include patients with a diagnostic equipoise: patients with and without COVID-19, to accurately measure both sensitivity and specificity. Only studies published in English, Spanish or French were considered. We included pre-print studies identified in our search, but no ongoing studies were searched or considered.

Index Test

For eligibility, a study had to report positive or negative findings of COVID-19 in chest CT imaging, or report findings on chest CT imaging according to described radiologic scales such as the CO-RADS classification or the consensus by the Radiological Society of North America (11, 12). Imaging analyses other than positive or negative for COVID-19 were not used for metanalysis but were considered to summarize valuable information on radiologic reporting of COVID-19 chest CT imaging.

Search Strategy

We conducted searches in the L·OVE (Living OVerview of Evidence) platform for COVID-19, a system that performs automated regular searches in PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and over thirty other sources (13). When compared to manual searches, this platform consistently identifies all the available studies associated with the terms of interest. It allows for a fast (automated) search that is easy to update – a crucial element given the urgent need to answer the research question rapidly and thoroughly.

The platform was consulted on March 15, 2021, using the entry: (1) Diagnostic – Imaging tests – Computed tomography – Population Filter: COVID-19. The full search strategy and terms used to identify papers in L·OVE are presented in our registered protocol. Search through cross-referencing was also carried out to identify additional references.

Assessment of Methodological Quality

Eligible studies were critically appraised by a reviewer and verified by a second reviewer using the QADAS-2 tool for diagnostic test accuracy studies, and the AMSTAR-2 tool for systematic reviews and meta-analyses (9). The results of the critical appraisal are reported narratively and were considered for discussion of results. All included studies underwent data extraction and appraisal. Studies that applied single RT-PCR as a reference standard were consider to have evident risk of bias for estimating diagnostic accuracy due to the likelihood of an initial false negative result in symptomatic patients. If RT-PCR was not repeated or accompanied by adequate follow-up that discards other etiologies, diagnostic accuracy of CT imaging was likely to be biased, particularly in the calculation of specificity. If a single RT-PCR is used as reference standard, false negatives that could be detected by chest CT are wrongfully considered as false positives of chest CT, gravely distorting actual test accuracy. This aspect was rigorously assessed in primary DTA studies and systematic reviews to avoid metanalysis of studies with high risk of bias that directly and considerably affects estimations of diagnostic accuracy.

Data Extraction

Data were extracted from the included studies by a reviewer and verified by a second reviewer using a data extraction tool developed by the authors. The data extracted included specific details about the study population, the index test and reference standard used, other sources of bias, frequency of true negatives, false positives, true positives and false negatives. Disagreements were solved by consensus.

Data Synthesis

A narrative-only summary of review findings was planned. Nonetheless, the included reviews were found to either have high risk of bias in its estimates due to acceptance of single-PCR testing as a reference standard for considering studies in metanalysis, or did not include several of the identified primary DTA studies. This indicated the need to conduct a quantitative synthesis as well, as considered and planned in the published review protocol.

Meta-Analyses

Estimates of pooled sensitivity and specificity as well as other diagnostic summary measures were obtained by use of the bivariate random-effect model methods (14). This approach is the standard for DTA meta-analyses when sources of heterogeneity additional to threshold effect are expected (as is the case with chest CT for COVID-19), and averaged or weighted univariate methods for metanalysis of sensitivity and specificity are discouraged (14, 15). A bivariate method was considered most adequate as it incorporates unexplained variability in the analysis. Variation in specificity or sensitivity measures between studies can be attributed to differences in index tests, reference standards, study populations and settings. When sensitivity and specificity derive from the cut-off of a scale, they have a negative correlation, which is considered with the bivariate method as well (14). With this method, reports with more precise estimates have more weight. A secondary (sensitivity) meta-analyses was performed considering only studies with low risk of bias. Results are presented with pooled estimates of sensitivity, specificity, diagnostic odds ratio, forest plots and summary receiver operator characteristics (SROC) curve. Meta-analyses were conducted in RStudio version 1.3.10 using the "mada" package (16). Likelihood ratios for positive (LR +) and negative (LR-) results were calculated from pooled accuracy estimates.

Index Tests and Reference Standards Considered for Meta-Analyses

A definition of positive or negative chest CT had to be provided for adequate extraction of true positives, false negatives, true negatives and false positives. Index tests definitions were considered adequate if standardized or derived from internationally accepted recommendations for chest CT interpretation in COVID-19 patients (11, 12). Some studies based their index test on the dichotomization of these and other proposed scales for chest CT classification of COVID-19-suspected cases. Studies that did not report a specific positive or negative definition of chest CT results were eligible for metanalysis if information for calculation of the same cut-off dichotomization was possible. A reference standard was considered adequate when consisting of: multiple or repeated PCR-testing; or a composite of epidemiological, clinical and PCR according to World Health Organization (WHO) recommendations, which usually included follow-up to determine COVID-19+ or –. Studies with repeated PCR testing applied only to patients with negative results was considered adequate as a false positive result is highly unlikely, and was considered for primary metanalysis.

Assessing Certainty in the Findings

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for grading the certainty of the evidence was followed. Grading the certainty of the evidence was not planned if adaptation from the identified reviews that used the GRADE approach was considered complete and adequate (17, 18). Although the GRADE handbook suggests to assess evidence quality of diagnostic accuracy based on its impact on outcomes (i.e., the aftermath consequences of misdiagnosing patients), the interest on diagnostic accuracy for this review is not related to COVID-19 outcomes, but rather on the impact it could have for hospital personnel and other patients, because of contagion risk (19). Thus, a described alternative for assessing quality of diagnostic tests evidence of the GRADE approach that focuses on diagnostic accuracy estimates was used instead of considering test accuracy as a surrogate of patient outcomes. Given that pre-test probability of COVID-19 in trauma patients is low, the effect of diagnostic accuracy was assessed with pre-test probabilities of 1 and 10%, reflecting the scenario in which the diagnostic test is to be applied. The certainty of the evidence is reported in a summary of findings (SoF) table and was considered for interpretation and discussion of findings.

Publication Bias

Adequate methods for assessing publication bias in reviews of diagnostic test accuracy studies have not been developed. Funnel plots to assess asymmetry are designed for use in reviews of randomized trials and should not be used with diagnostic accuracy studies. Some available methods to assess publication bias have low power in the presence of heterogeneity, which is expected in diagnostic reviews, and thus interpretation of statistical evidence for publication bias derived from funnel plot is not recommended, as it does not necessarily imply publication bias (20, 21). Coherently, statistical assessment of publication bias was not undertaken. Furthermore, publication bias is unlikely in diagnostic test accuracy as there are no "positive" or "negative" results that could increase or decreased likelihood of publication, respectively, as is the case in review of other designs. Particularly for this review, risk of publication bias is expected to be low due to its unlikelihood in diagnosis topics and because several pre-print studies were identified and considered.

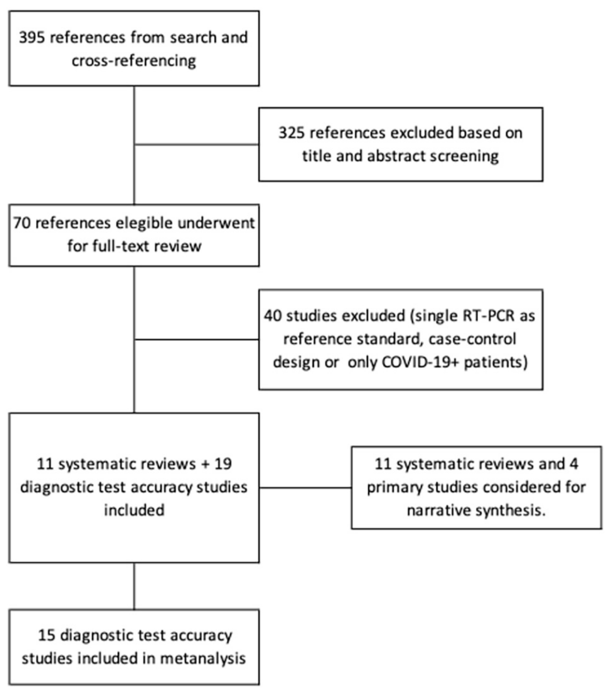

FIGURE 1 | PRISMA flow diagram of the studies selection process.

TABLE 1 | Characteristics of studies included in metanalysis.

Citation	Recollection and setting	Selection criteria	Sample size	Reference standard	Chest CT used as Index test reported as ±	Included in meta-analysis
Aslan et al. (32)	Retrospective analysis in the Emergency department with symptomatic patients	At least two of: fever > 38°C, lower respiratory tract infection symptoms suggesting COVID-19, or normal or decreased lymphocyte count and elevated CRP levels; and evaluation by both chest CT imaging and rRT-PCR test at admission. Patients with severe CT motion artifacts or without rRT-PCR testing were excluded.	306	First or repeated rRT-PCR test (repeated if initially negative).	Yes	Yes
Bellini et al. (33)	Retrospective analysis in the Emergency department with symptomatic patients	Patients who underwent chest CT and RT-PCR testing for suspected COVID-19, based on the symptoms: fever higher > 37.5°C, cough, and clinically relevant dyspnea, with or without a history suggestive of exposure to SARS-CoV-2. Exclusion criteria were lack of RT-PCR testing results, time interval between CT scan and RT- PCR longer than 7 days, and uninterpretable CT scans due to motion artifacts or incomplete scanning.	572	Positive RT-PCR or 14-day follow-up with negative diagnosis if no symptoms' worsening or laboratory findings consistent with COVID-19.	No	No
Caruso et al. (34)	Prospective collection in emergency department with symptomatic patients	Patients with fever and respiratory symptoms as cough and dyspnea; patients with mild respiratory symptoms and close contact with a confirmed COVID-19 patient; patients with a previously positive test result. Exclusion criteria were chest CT with contrast medium performed for vascular indication; patients who refused chest CT or hospitalization; severe motion artifact on chest CT.	158	Two RT-PCR tests with 24 h interval.	Yes	Yes
Debray et al. (35)	Retrospective analysis in the Emergency department with symptomatic patients	Patients presenting with COVID-19 suspicion and for whom hospitalization was considered had both chest CT scan and SARS-CoV-2 RT-PCR.	213	Repeated PCR and clinical features on presentation and follow up. (Although, this standard could not be applied to 28 of the 81 initially negative patients [34.5%], for whom single T-PCR and symptoms were considered)	Yes	Yes

(Continued)

TABLE 1 | (Continued)

Citation	Recollection and setting	Selection criteria	Sample size	Reference standard	Chest CT used as Index test reported as ±	Included in meta-analysis
Fujioka et al. (38)	Retrospective analysis in the Emergency department with symptomatic patients	Suspected COVID-19 based on symptoms and history of exposure; who underwent chest CT and were diagnosed as positive or negative for COVID-19 by one or more RT-PCR tests.	154	Diagnosis by an experienced clinician based on chest X-ray, chest CT, laboratory findings, and clinical data in the follow-up and result of RT-PCR.	No	No
Gezer et al. (36)	Retrospective analysis in the Emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (> 38°C) and respiratory symptoms dyspnea and cough.	222	Diagnosis by consensus of two physicians based on the medical records, CT scans and positive RT-PCR results.	Yes	Yes
Gietema et al. (37)	Prospective collection in emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough.	193	Sequential PCR and hospital follow-up, multiple RT-PCR for initially negative.	Yes	Yes
He et al. (48)	Retrospective analysis in the Emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough. Patients with incomplete clinical information or excessive motion artifacts on CT were excluded.	82	Multiple RT-PCR testing and clinical observation and follow up.	Yes	Yes
Herpe et al. (39)	Multicenter prospective collection in emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (> 38°C) and respiratory symptoms dyspnea and cough.	4824	The final discharge diagnosis based on follow-up and COVID-19 criteria.	Yes	Yes
Korevaar et al. (40)	Retrospective analysis in the Emergency department with symptomatic patients	Adult patients with hospital admission that underwent both chest CT and RT-PCR testing for SARS-CoV-2 infection upon admission.	239	COVID-19 criteria and multidisciplinary consensus after follow-up in case of negative RT-PCR testing.	No	No
Krdzalic et al. (41)	Retrospective analysis in the Emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough.	56	RT-PCR and sequential retest with RT-PCR in patients with initially negative until persistently negative.	Yes	Yes
Patel et al. (42)	Retrospective analysis in the Emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (> 38°C) and respiratory symptoms dyspnea and cough.	317	Multiple RT-PCR testing and clinical observation and follow up.	Yes	Yes
Prokop et al. (12)	Prospective collection in emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough in that were	105	RT-PCR testing and clinical observation and follow up.	No	No

(Continued)

TABLE 1 | (Continued)

Citation	Recollection and setting	Selection criteria	Sample size	Reference standard	Chest CT used as Index test reported as ±	Included in meta-analysis
		followed and in whom RT-PCR was performed				
Schulze-Hagen et al. (49)	Prospective collection in emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough in that were followed and in whom RT-PCR was performed	191	RT-PCR testing and clinical observation and follow up.	Yes	Yes
Song et al. (43)	Retrospective analysis in the Emergency department with symptomatic patients	Patients with respiratory symptoms but no significant improvement in conventional anti-infective treatment; clinically suspected to have COVID-19 due to contact history with COVID-19 patients within 14 days before symptom onset or due to clustering onset; or with pending invasive operation in need of routine inspection to exclude COVID-19. Exclusion criteria: the first RT-PCR tested > 3 days before or after CT scan; or incomplete baseline characteristics and laboratory findings.	211	RT-PCR, repeated if initially negative (although this standard could not be applied to ∼34% of initially negative patients that were thus considered negative)	Yes	Yes
Steuwe et al. (44)	Prospective collection in emergency department and hospital setting	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough.	105	Repeated RT-PCR, hospitalized patients with two negative RT-PCR test results, a third RT-PCR test was performed from bronchial lavage specimens + daily RT-PCR if CT examination showed typical COVID-19 findings.	Yes	Yes
Wen et al. (45)	Retrospective analysis in the Emergency department with symptomatic patients	Patients with fever > 38.3°C or cough of onset within the last 10 days that required hospitalization. Exclusion criteria: fever for more than 14 days without symptoms and signs for acute respiratory infection or exposure history within 14 days.	103	Multiple sequential PCR tests and observation	Yes	Yes
Xie et al. (46)	Prospective collection in emergency department and hospital setting	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough.	19	Multiple RT-PCR testing and clinical observation and follow up.	Yes	Yes
Zhu et al. (47)	Prospective collection in emergency department with symptomatic patients	Adult patients with a chest CT scan upon suspicion of COVID-19 pneumonia with high fever (>38°C) and respiratory symptoms dyspnea and cough in that were followed and in whom RT-PCR was performed. Exclusion criteria; transfer from another hospital or previous visit to the study hospital or previous diagnosis of COVID−19.	116	RT-PCR and if initially negative repeated after 24 h.	Yes	Yes

TABLE 2 | Risk of bias assessment for included systematic reviews.

Citation	(1) Is the review question clearly and explicitly stated?	(2) Were the inclusion criteria appropriate for the review question?	(3) Was the search strategy appropriate?	(4) Were the sources and resources used to search for studies adequate?	(5) Were the criteria for appraising studies appropriate?	(6) Was critical appraisal conducted by two or more reviewers independently?	(7) Were there methods to minimize errors in data extraction?	(8) Were the methods used to combine studies appropriate?	(9) Was the likelihood of publication bias assessed?	(10) Were recommendations for policy and/or practice supported by the reported data?	(11) Were the specific directives for new research appropriate?
Adams et al. (22)	Y	Y	Y	N	Y	Y	Y	Y	N	N/A	Y
Böger et al. (5)	Y	N	U	Y	Y	Y	Y	Y	N	Y	N
Huang et al. (24)	Y	Y	Y	Y	N	N/A	Y	Y	N	N/A	U
Islam et al. (31)	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y
Li et al. (25)	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y
Kim et al. (27)	Y	N	Y	Y	Y	U	Y	Y	Y	Y	U
Lv et al. (28)	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y
Xu et al. (30)	Y	Y	U	Y	Y	Y	Y	Y	N	Y	N/A
Shao et al. (29)	Y	N	N	Y	Y	U	U	N/A	N	Y	Y
Mair et al. (23)	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y
Khatami et al. (26)	Y	N	Y	Y	N	N/A	Y	Y	Y	N/A	N/A

RESULTS

Search Results

The search strategy and cross-referencing searches yielded 395 results. After duplicate screening of title and abstract 70 references were selected for full text review of which 30 met selection criteria and were included: 11 systematic reviews (5, 22–31) and 19 primary diagnostic accuracy studies (12, 32–49). Reasons for exclusion were related to not having a DTA design: only COVID-19 patients; only abnormal CT scans; not reporting data to compute sensitivity and specificity; or using single RT-PCR as a reference standard in all patients. **Figure 1** is a PRISMA flow diagram depicting the selection process.

None of the identified studies assessed chest CT diagnostic accuracy specifically in trauma patients; all were conducted in the emergency setting in patients with suspected COVID-19. This was expected as low probability of infection in trauma patients makes such studies impractical. As stated in our previously published protocol, the available evidence on chest CT accuracy for diagnosis of COVID-19 was to be considered and summarized, considering the indirectness of the evidence and discussing important considerations for its extrapolation to the trauma setting. Studies conducted in the emergency department setting had only slight differences, but overall, patients underwent chest CT scan examination at admission that was compared to an adequate reference standard for COVID-19; chest CT scan analysis was made by experienced radiologist that were in most cases blinded to reference standard results and determined a positive chest CT scan when patients had an image compatible with or typical of COVID-19. In some studies, no dichotomous (+ or −) index test result was presented, and the results of CT image were described or classified with radiological scales such as the proposed CO-RADS classification or the consensus by the Radiological Society of North America (11, 12). Definition of the index test result as positive or negative was similar and consider comparable among studies. The characteristics of the primary DTA studies considered for synthesis are summarized in **Table 1**.

Risk of Bias in Included Studies

All included studies were assessed for risk of bias. **Tables 2**, **3** display the results of the risk of bias assessment. For systematic reviews, the formulation of a specific review question, the search strategies and resources to ensure identification of all relevant studies, methods to minimize errors in data extraction, and methods to combine studies' results were adequate in most reviews. Nonetheless, all included systematic reviews were found to have at least two items that suggested risk of bias. A frequent issue was the inclusion of primary studies that used single RT-PCR testing as reference standard for all patients, and/or inclusion of studies that only considered patients diagnosed with COVID-19 (hence impairing assessment of false positive, true negative rates, and meta-analyses; not a DTA design). A flawed reference standard, as is the case of single RT-PCR due to high false negative rate, leads to severely biased estimates of sensitivity and specificity, as discussed in the methods section. To include such reports in metanalysis was considered inadequate.

TABLE 3 | Risk of bias assessment for included diagnostic test accuracy studies.

Study	(1) Was a consecutive or random sample of patients enrolled?	(2) Was a case-control design avoided?	(3) Did the study avoid inappropriate exclusions?	(4) Were the index test results interpreted without knowledge of the results of the reference standard?	(5) If a threshold was used, was it pre-specified?	(6) Is the reference standard likely to correctly classify the target condition?	(7) Were the reference standard results interpreted without knowledge of the results of the index test?	(8) Was there an appropriate interval between index test and reference standard?	(9) Did all patients receive the same reference standard?	(10) Were all patients included in the analysis?
Aslan et al. (32)	Y	Y	Y	U	N/A	Y	Y	Y	N	Y
Caruso et al. (34)	Y	Y	Y	U		Y	Y	Y	Y	Y
Debray et al. (35)	Y	Y	Y	Y		SC	Y	Y	N	Y
Gezer et al. (36)	Y	Y	Y	Y		Y	U	Y	Y	Y
Gietema et al. (37)	Y	Y	Y	Y		Y	Y	Y	N	Y
He et al. (48)	Y	Y	Y	Y		Y	Y	Y	N	Y
Herpe et al. (39)	Y	Y	Y	Y		Y	Y	U	Y	Y
Krdzalic et al. (41)	Y	Y	Y	Y		Y	Y	Y	N	Y
Patel et al. (42)	Y	Y	Y	Y		SC	Y	Y	N	Y
Schulze-Hagen et al. (49)	Y	Y	Y	Y		Y	Y	Y	Y	Y
Song et al. (43)	Y	Y	Y	Y		SC	Y	Y	N	Y
Steuwe et al. (44)	Y	Y	Y	Y		Y	Y	Y	N	Y
Wen et al. (45)	Y	Y	Y	Y		Y	Y	Y	Y	Y
Xie et al. (46)	Y	Y	Y	Y		Y	Y	Y	Y	Y
Zhu et al. (47)	Y	Y	Y	Y		Y	Y	Y	N	Y

Thus, results from systematic reviews that included DTA studies that used single PCR testing as a reference standard were not considered for synthesis; neither were those results from reviews that included studies of only COVID-19-confirmed patients. Four reviews used appropriate selection criteria based on an appropriate reference standard and inclusion of patients independent of that reference standard result (22, 24, 30). One lacked a risk of bias assessment for the included studies and only two specified that this process was performed in duplicate (22, 24, 30). One used a single database as a resource to identify studies and was conducted early in the pandemic, leading to missing studies that were published later (22). These findings pointed to the need to conduct a new metanalysis to overcome those limitations.

Regarding primary DTA studies, assessment of risk of bias is presented only for studies considered for metanalysis and is displayed in **Table 3**. All studies used an adequate reference standard (see methods). Nonetheless, some studies performed further testing and follow up only in patients with initial negative results; while patients that had symptoms and a positive PCR test were considered positive. This is due to the inherent properties of RT-PCR testing (low sensitivity and high specificity), which confer confidence in positive results but skepticism in negative results. This reference standard was also considered adequate. Two studies report being unable to repeat PCR testing for initially negative patients in 1/3 of their study sample. These studies are marked as "with some concerns" (SC) regarding risk of bias.

Metanalysis and Summary Receiver Operator Characteristics Estimation

Of the 19 primary DTA studies 15 were meta-analyzed. Four studies that reported CT findings according to a radiological scale without positive or negative result (index test) are summarized but were not considered in metanalysis (12, 33, 38, 40). **Figure 2** displays forest plot of sensitivities and specificities reported by the primary studies; pooled estimates are derived from bivariate metanalysis. Sensitivity of chest CT for COVID-19 was estimated at 0.91, 95%CI = (0.88–0.93). Specificity was estimated at 0.73, 95%CI = (0.61; 0.82). Higher heterogeneity is visually evident for specificity, while sensitivities are more homogeneous. **Figure 3** displays the Summary ROC (SROC) curve that demonstrates such variability within a small range of values for sensitivity estimates and within a wider range for specificity estimates. No correlation was found between sensitivities and specificities (ρ = 0.22, IC95% [−0.33; 0.66]). Diagnostic odds ratio was estimated at: DOR = 27.5, 95%CI (14.7; 48.5).

Likelihood Ratios and Practical Interpretation of Results

The calculated likelihood ratios derived from pooled estimates of sensitivity and specificity were: LR+ = 3.44 (sensitivity/[1-specificity]) and LR− = 0.13 ([1-sensitivity]/specificity). A practical interpretation of this results can be made using the

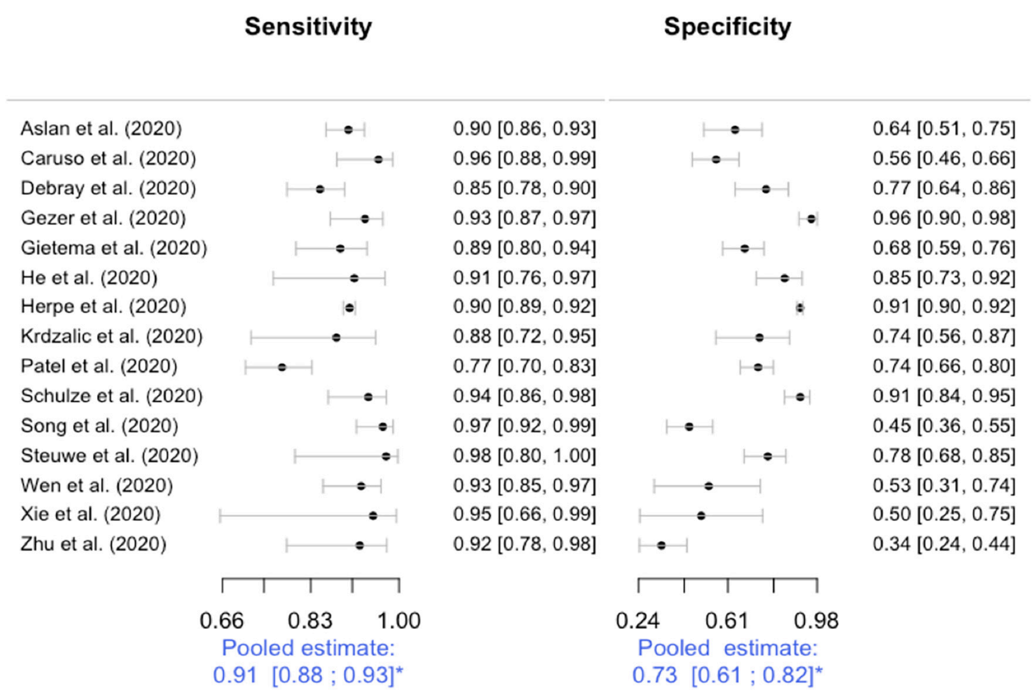

FIGURE 2 | Forest plots for sensitivity and specificity. Studies are sorted alphabetically. *Estimated pooled sensitivity and specificity with their 95% confidence intervals from bivariate methods using a random effects model. As no statistical method is currently available for heterogeneity assessment in diagnostic metanalysis with bivariate methods, heterogeneity was assessed qualitatively and considered low for sensitivity and high for specificity. Although high, heterogeneity for specificity estimates was explained by differences between studies and thus considered not serious (see quality of evidence in the results section). Sensitivity analysis excluding studies with concerns regarding flawed reference standard did not change displayed estimates.

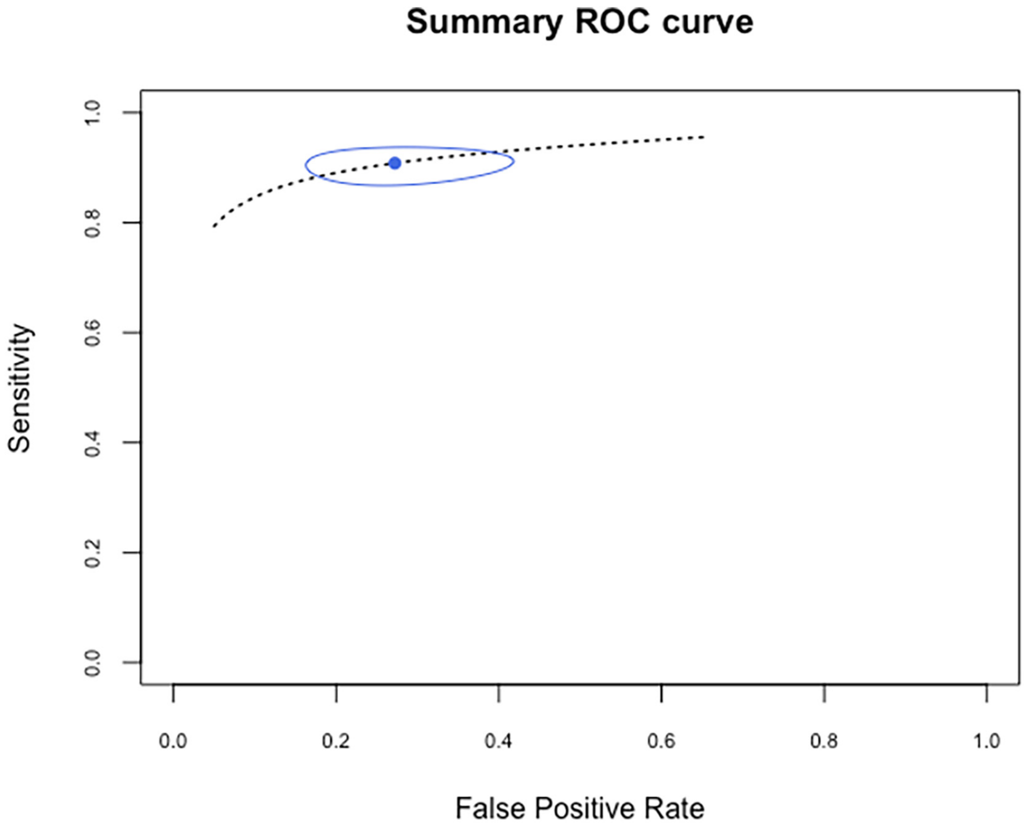

FIGURE 3 | Summary ROC curve. Estimation of diagnostic accuracy of chest CT for detection of COVID-19: high sensitivity with narrow range of variability and modest specificity (inverse of false positive rate) with a wider range of variability; attributable to variable local COVID-19 incidence and differences in reference standards applied.

estimated change in pre-test probability according to calculated LRs provided by McGee (50). The presence of a compatible or highly suspicious chest CT ("positive") increases pre-test probability by 20–25%, while an unlikely/incompatible (negative) chest CT reduces the pre-test probability of COVID-19 by ∼45%.

Quality of the Evidence

Evidence assessment to estimate diagnostic accuracy of chest CT for COVID-19 was undertaken separately for sensitivity and specificity, as recommended. Both assessments considered 15 studies comprising 4824 patients. Evidence for sensitivity estimates was graded as "Moderate" due to indirectness of evidence, and for specificity estimates it was graded as "Low" due to imprecision (evidenced by a wide 95% confidence interval) and indirectness. The summary of findings (SoF) table (**Table 4**) displays the judgments made for each aspect of quality assessment and their corresponding explanations. Effect is presented for pre-test probabilities of 1 and 10%.

Additional Findings

Three studies specifically addressed using CT as a method of screening for COVID-19 in an emergency surgery setting. In one study of 28 patients with initial negative RT-PCR results that upon a second test became positive, the mean interval time between negative to positive results was 6.2 days, with some up to 15 days (51). In two cases PCR was negative two times before being positive, with positive chest CT findings identifying lesions on the first day. In countries like India where there is an ongoing surge of COVID-19 patients, shortages in test kit supplies have strained health systems. CT testing can compensate for this, especially in situations where the patient needs emergency surgery. In these cases, the urgency to get the patient to the operating room is incompatible with the time needed to receive test results from PCR. This is important as one study found that there was a higher number of positive PCR in the trauma population than in the general population (52). On the contrary, in low-resource areas in which CT scans are not readily available at many hospitals transferring patients to hospitals with CT availability may be a risk to patients and healthcare workers. Another study of 207 patients admitted for acute surgical emergencies found a negative predictive value of 82.4%, concluding that CT of the thorax has the potential to play an important role in helping surgeons in their decision making (53). However, the authors note that over-reliance on CT with its high false positive rate can lead to overtreatment, overuse of resources and delays in the decision-making process. In the third study with data provided for over 800 patients undergoing both emergency and elective

TABLE 4 | Summary of findings.

Question: Should Chest CT be used to screen for COVID-19 in patients that require emergency surgery due to trauma?

Sensitivity 0.91 (95% CI: 0.88 to 0.93)
Specificity 0.73 (95% CI: 0.61 to 0.82)

Prevalences 1% 10%

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	Pre-test probability of 10%	
True positives (patients with COVID-19)	15 studies 4824 patients	Cross-sectional (cohort type accuracy study)	Not serious	Serious [a]	Not serious	Not serious	None	9 (9–9)	91 (88–93)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having COVID-19)								1 (1–1)	9 (7–12)	
True negatives (patients without COVID-19)	15 studies 4824 patients	Cross-sectional (cohort type accuracy study)	Not serious	Serious[a]	Not serious[b]	Serious[c]	None	723 (604–812)	657 (549–738)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having COVID-19)								267 (178–386)	243 (162–351)	

[a]*All DTA studies assessed chest CT for COVID-19 in symptomatic suspected patients. Emergency trauma patients have a much lower pre-test probability of COVID-19. Although accuracy of chest CT is not expected to change, chest trauma may affect image reading, and the different clinical setting constitutes indirect evidence.*
[b]*Although inconsistency of results was observed, it is explained by variable local incidence of COVID-19 cases and by studies that used an imperfect reference standard in up to one third of included patients; both of which affect specificity estimates. As such, we considered that there was not "unexplained heterogeneity," which is the finding that downgrades quality.*
[c]*Given the issues explained in b, pooled estimates of specificity have a wider confidence interval and were considered imprecise.*

surgical interventions over a 5-day period at all UK hospitals with imaging departments, a high rate of false positives was found, producing a sensitivity of 68.4% for thoracic CT (54). These authors suggest that the diagnostic yield is low and that additional CT examinations expose patients to an unnecessary extra dose of radiation to the patient.

The CO-RADS Scale

The most widespread method for the diagnosis of COVID-19 using CT imaging appears to be the COVID-19 Reporting and Data System (CO-RADS), introduced by the Radiological Society of the Netherlands (NVvR) and largely based on the recommendations of the Radiological Society of North America (11, 12). The scoring system uses a scale from 0 to 5 to grade the level of suspicion of COVID-19 infection based on pulmonary involvement from very unlikely to very likely. In a study of 105 patients, the NVvR found high performance for predicting COVID-19 with an AUC of 0.91 (CI, 0.85–0.97) (12, 55). A high negative predictive value and low negative likelihood ratio was associated with a CO-RADS $\leq$ 3 while a high positive likelihood ratio and good positive predictive value was associated with a CO-RADS score $\geq$ 4. It is important to note that in both studies the prevalence of COVID-19 was high. As cases drop it is likely that the false-positive rate and negative predictive value will increase. Of the reviewed studies, in four that did not report a dichotomous index test (+ or –) and thus could not be meta-analyzed, the CO-RADS scale was used (12, 33, 38, 56). Dichotomization of the scale was used by one additional study that did report + or – results for the index test.

Interrater Agreement of Chest Computed Tomography for COVID-19

Since diagnostic efficacy is dependent upon the radiologist's interpretation of the CT scan, the reproducibility of the categorization of CT reports among multiple observers is an essential component when considering appropriate clinical decision making. In a study of 241 COVID-19 suspected patients, eight observers categorized each CT into one of four categories (evocative, compatible for COVID-19 pneumonia, not evocative, and normal) (35). Agreement across the 4 categories was good between all readers (κ value 0.61 95% CI 0.60–0.63) and moderate to good between pairs of readers (0.54–0.75). Among patients considered for hospitalization, CT categorized as evocative is highly predictive of COVID-19, while almost a third of patients with CT categorized as not evocative had a positive RT-PCR. In another study of 34 COVID-19 and 48 non-COVID-19 patients identified by RT-PCR, two radiologists had a good interobserver agreement (κ value 0.69) with 26/34 COVID-19 patients correctly diagnosed at final agreement (48). Since several studies did not examine inter-observer variability of CT findings it is possible that the observed specificity and sensitivity are overestimated.

DISCUSSION

This review identified, appraised, and summarized the available evidence regarding the diagnostic accuracy of chest CT scan for the diagnosis of COVID-19 in order to inform clinical decisions and recommendations regarding its application in an emergency trauma setting. No studies that assessed chest CT diagnostic accuracy in this specific setting were found. Nonetheless, consideration of evidence from the ED setting during the pandemic was planned in advance given that we judged the diagnosis accuracy largely extrapolatable, as is indicated in our published protocol (8). Some case series reporting the utility of CT in the pre-operative screening on COVID-19 were summarized narratively but were not a source for diagnostic accuracy of the test. We report that chest CT is a highly sensitive tool to detect COVID-19 in suspected patients and would be expected to have a similar sensitivity when applied to a trauma patient, but has lower specificity.

Great variation was present between studies due to differences in design, index test definition and reference standards. The nature of the disease and differences in settings likely affected specificity estimates in the included studies. The local incidence of COVID-19 cases explains variability of specificity estimates among studies. When incidence is low, abnormal chest CT findings suggestive of COVID-19 might be more often caused by other etiologies such as other respiratory viruses. Conversely, in a context of high COVID-19 incidence, abnormal findings due to non-COVID-19 pneumonias constitute a smaller proportion of the studied patient. This leads to a lower false positives rate being recorded for the test, and hence, higher calculated specificity. This relationship is to be considered when applying and interpreting results of chest CT for screening or diagnosing COVID-19.

The value of chest CT appears to be that of an additional screening tool that can easily detect PCR false negatives, which are reportedly frequent. It is a sensitive tool to diagnose COVID-19, and specificity can vary as discussed. Carrier/asymptomatic status, which is believed to also represent contagion risk, is obviously not expected to be detected with chest CT. Thus, a negative chest CT does not exclude SARS-CoV-2 transmission in the incubation phase. However, given the absence of COVID-19 pneumonia, the likelihood of contagion is significantly reduced. In this sense, CT can have increased value if reading is compatible with COVID-19 when either PCR testing is unavailable or results are delayed. Compatible findings on chest CT should prompt additional protective measures in aerosolizing procedures for medical staff and isolating measures for the patient should be considered. As emergency trauma patients typically undergo localized or full body CT scanning, imaging of the lungs and its interpretation by a radiologist is not expected to increase costs significantly and can be implemented as a screening tool in that setting. One important consideration are patients with trauma or polytrauma involving the chest; as lung contusions and hemo- or pneumo-thorax will affect the readability of chest CT for pneumonia.

Strengths and Limitations

A considerable proportion of the systematic reviews encountered when conducting this synthesis were found to be of low methodological quality and thus with high risk of bias because they included studies without a DTA design where a reference standard and an index test are applied to all patients, studies of only COVID-19 positive cases and/or did not considered the rate of false negatives on single initial RT-PCR. We provide new estimates that overcome these limitations and that should serve as a trustworthy source of information regarding the diagnostic accuracy of chest CT for COVID-19. We hope that the insights into the methodology of assessing diagnostic tests performance and synthesizing this type of evidence will be of value for readers.

Quality of the evidence for diagnostic accuracy of chest CT was moderate for sensitivity estimates and low for specificity estimates, mostly due to indirect evidence and, in the case of specificity, imprecision. Higher quality of evidence requires studies that assess chest CT in the trauma setting. Chest CT is a sensitive test for COVID-19 that can have a role in screening of trauma patients with need for urgent surgical care; it has easy implementation as CT is routinely performed in trauma patients, and could be particularly useful in low-resources settings where supplies are to be used selectively.

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/s.

AUTHOR CONTRIBUTIONS

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

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Benjamin Longo-Mbenza,
Walter Sisulu University, South Africa

REVIEWED BY
Vilma G. Duschak,
Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina
Bridgid Lai Fui Chin,
Curtin University Malaysia, Malaysia

*CORRESPONDENCE
Yoshihisa Fujino
zenq@med.uoeh-u.ac.jp

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Spread of infection and treatment interruption among Japanese workers during the COVID-19 pandemic: A cross-sectional study

Jun Akashi[1], Ayako Hino[2], Seiichiro Tateishi[3], Tomohisa Nagata[4], Mayumi Tsuji[5], Akira Ogami[6], Shinya Matsuda[7], Masaharu Kataoka[1] and Yoshihisa Fujino[8]* for the CORoNaWork Project

[1]Second Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [2]Department of Mental Health, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan, [3]Department of Occupational Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [4]Department of Occupational Health Practice and Management, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan, [5]Department of Environmental Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [6]Department of Work Systems and Health, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan, [7]Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [8]Department of Environmental Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

Background: The COVID-19 pandemic has resulted in treatment interruption for chronic diseases. The scale of COVID-19 in Japan has varied greatly in terms of the scale of infection and the speed of spread depending on the region. This study aimed to examine the relationship between local infection level and treatment interruption among Japanese workers.

Methods: Cross-sectional internet survey was conducted from December 22 to 26, 2020. Of 33,302 participants, 9,510 (5,392 males and 4,118 females) who responded that they required regular treatment were included in the analysis. The infection level in each participant's prefecture of residence was assessed based on the incidence rate (per 1,000 population) and the number of people infected. Age-sex and multivariate adjusted odds ratios (ORs) of regional infection levels associated with treatment interruption were estimated by multilevel logistic models, nested by prefecture of residence. The multivariate model was adjusted for sex, age, marital status, equivalent household income, educational level, occupation, self-rated health status and anxiety.

Results: The ORs of treatment interruption for the lowest and highest levels of infection in the region were 1.32 [95 % confidence interval (CI) were 1.09–1.59] for the overall morbidity rate (per 1,000) and 1.34 (95 % CI 1.10–1.63) for the overall number of people infected. Higher local infection levels were linked to a greater number of workers experiencing treatment interruption.

Conclusions: Higher local infection levels were linked to more workers experiencing treatment interruption. Our results suggest that apart from individual characteristics such as socioeconomic and health status, treatment interruption during the pandemic is also subject to contextual effects related to regional infection levels. Preventing community spread of COVID-19 may thus protect individuals from indirect effects of the pandemic, such as treatment interruption.

KEYWORDS

COVID-19, patient acceptance of health care, treatment refusal, regional medical programs, Japan

Introduction

COVID-19, first identified at the end of 2019, is continuing to rage around the world (1–4). Having experienced four waves of the disease through June 2021 there is an urgent need in Japan to understand the working and social environment and the health status of workers affected by the COVID-19 pandemic. In addition to direct effects of severe pneumonia and acute respiratory failure, COVID-19 has also had indirect health effects. COVID-19-related treatment interruption, particularly in patients with chronic diseases, is an emerging issue in several countries (5, 6), including Japan (7). Studies have reported a significant decrease in the number of prescriptions during the pandemic compared to before, and that 40 % of patients requiring regular visits have been seen less frequently (8, 9).

Treatment interruption for diseases other than COVID-19, which should normally be continued, can cause serious health care problems in several ways. First, it can exacerbate the medical condition of patients with chronic diseases that require regular management. Second, few opportunities for regular physical examinations may lead to undiagnosed complications and delayed treatment. Further, such medical problems, which could have been avoided by continued treatment, may cause further strain on future health care resources (10). Studies performed during the COVID-19 pandemic have reported that treatment interruption among patients with chronic diseases is associated with a variety of factors, including fear of becoming infected when seeing the doctor (6, 11), scheduling changes by hospitals (12, 13), and shortage of medical resources (6). These factors presumably have differing degrees of impact depending on the level of infection in the region, such as incidence rate and cumulative COVID-19 cases. In addition, patients with unstable socioeconomic status are more likely to discontinue treatment (7, 14, 15). Areas with higher prevalence of COVID-19 may be more affected by the loss of job security and other factors that affect individuals with unstable socioeconomic status.

In Japan, the spread of COVID-19 has varied widely by region in terms of the scale of infection and the speed of spread (16, 17). We hypothesize that differences in regional infection rates will affect treatment interruption in each region. The level of infection in a community, such as incidence rate and the number of people with COVID-19, may directly or indirectly affect fear of visiting medical institutions, anxiety about going out, and financial difficulties, which may cause treatment interruption. For example, the number of people with COVID-19 is reported daily by region. Such information will arouse some degree of anxiety and fear in people living in regions with high levels of infection about the safety of the area and the disease. Tokyo, which has recorded the greatest number of infections in Japan, saw a significant drop in prescriptions through May 2020 (8). Given that pandemics are known to overwhelm medical resources (18), Japan's lack of capacity to conduct COVID-19 tests in areas with high levels of infection and limited hospital beds has exposed the limits of the country's medical resources (19).

However, the relationship between regional COVID-19 infection level and treatment interruption remains to be elucidated. Japan provides an ideal opportunity to test our hypotheses due to the country's large regional variation in COVID-19 infection levels. Therefore, this study investigated the relationship between both local viral infection levels measured and treatment interruptions described, in Japan.

Materials and methods

Study design and subjects

Cross-sectional internet survey was conducted from December 22nd to 26th, 2020, the period corresponding to Japan's third wave of infection, as a part of the Collaborative Online Research on the Novel-coronavirus and Work (CORoNaWork) Project (20). The target population was formed by workers aged 20–65 years at the time of this survey. Data were obtained from participants who indicated that they were employed at the time of the survey, with participants selected based prefecture of residence, job type, and sex. A detailed description of the protocol of this survey is provided elsewhere (20). Of the 33,302 participants in the survey, 6,266 were excluded for providing fraudulent responses. Of the 27,036 remaining participants, data from 9,510 (5,392 males and 4,118 females) who described themselves as needing regular treatment or hospital visits were analyzed.

This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (Reference Nos. R2-079 and R3-006) and performed in accordance with relevant guidelines and regulations. Participants provided informed consent by completing a form on the survey website.

Treatment status

This study used a single-item question to assess participants' treatment status: "Do you have a condition that requires regular hospital visits or treatment?" Participants check from "I do not have such a condition," "I am continuing with hospital visits and treatment as scheduled," and "I am not able to continue with hospital visits and treatment as scheduled."

Infection level indices

The infection level in each participant's prefecture of residence was assessed based on the incidence rate for the entire period from January 2020, when the first case was identified in Japan, to December 16th, 2020; the number of people infected for the entire period; the incidence rate in the month before the survey (per 1,000 population); and the number of people infected over that same month. These values were calculated using publicly available data from the Ministry of Health, Labor and Welfare (16).

Socioeconomic status, health status, and anxiety

Socioeconomic status, health status, and anxiety were assessed through questionnaires in the Internet survey. Socioeconomic factors were age, sex, marital status (married, unmarried, bereaved/divorced), occupation (mainly desk work, mainly interpersonal communication, mainly labor), education (graduated from junior high school, high school, vocational school/college, university, graduate school), and equivalent income [household income divided by the square root of household size; 500,000–2,650,000, 2,650,000–4,500,000, >4,500,000 Japanese Yen (JPY)]. Health and psychological factors were assessed by self-report (very good, neither good nor bad, not good). Anxiety about contracting COVID-19 was assessed using the following question: "Do you feel anxious about being infected with COVID-19?" Participants chose from "yes" or "no".

Statistical analysis

We estimated age-sex- and multivariate-adjusted odds ratios (ORs) of treatment interruption associated with regional infection level by nesting multilevel logistic models in prefecture of residence. This study used four indices of regional infection level: incidence rate for the entire period (per 1,000 population), number of people infected for the entire period, incidence rate in 1 month (per 1,000 population), and number of people infected in 1 month. For analysis, these indices were divided into quartiles and used as area-level variables. In the multivariate model, sex, age, marital status, job type, equivalent household income, education, self-rated health, and anxiety were adjusted. $p < 0.05$ indicated statistical significance. All analyses were conducted using Stata (Stata Statistical Software: Release 16; StataCorp LLC, TX, USA).

Results

The participants' characteristics together with residential area according to the number of people infected for the entire period are summarized in Table 1. This study stratified the 9,510 participants in need of regular treatment into four groups according to the regional infection level. Socioeconomic factors including sex, age, marital status, household income, education, and occupation in each group, as well as self-assessment of health status and anxiety related to COVID-19 infection are shown. The group with the highest number of people infected tended to have higher annual equivalent household income, and a higher percentage were in vocational school/college, university, and graduate school.

The prefectures and participants belonging to each infection level indices are shown in Table 2 and the association between the regional infection level and treatment interruption is summarized in Table 3. According to multivariate analysis, the ORs of treatment interruption for the lowest and highest levels were 1.32 (95 % CI: 1.09–1.59; $p = 0.003$) for the overall incidence rate (per 1,000 population), 1.34 (95% CI: 1.10–1.63; $p = 0.002$) for the overall number of people infected, 1.28 (95 % CI: 1.06–1.54; $p = 0.013$) for the monthly incidence rate (per 1,000 population), and 1.38 (95 % CI: 1.14–1.67; $p = 0.001$) for the number of people infected per month. For each index of infection level, a higher infection level was linked to more workers experiencing treatment interruption for chronic diseases in Japan. The results remained unchanged after adjusting for age and sex.

Discussion

This study showed that regional indices of the scale of infections related to COVID-19 in Japan were correlated with more workers with diseases requiring regular hospital visits

TABLE 1 Basic characteristics of the study subjects.

	Residential area according to the number of people infected for the entire period			
	74–492	**507–1,496**	**1,673–11,982**	**12,381–52,382**
Number of subjects	2,130	2,579	2,422	2,379
Age, median [interquartile range (IQR)]	51 (42, 57)	51 (43, 57)	52 (44, 58)	53 (46, 58)
Sex, male	1,181 (55.4 %)	1,440 (55.8 %)	1,403 (57.9 %)	1,368 (57.5 %)
Marital status, married	1,252 (58.8%)	1,496 (58.0 %)	1,370 (56.6 %)	1,284 (54.0 %)
Annual equivalent household income (JPY)				
500,000–2,650,000	773 (36.3 %)	875 (33.9 %)	816 (33.7 %)	717 (30.1 %)
2,650,000–4,500,000	690 (32.4 %)	824 (32.0 %)	733 (30.3 %)	648 (27.2 %)
>4,500,000	667 (31.3 %)	880 (34.1 %)	873 (36.0 %)	1,014 (42.6 %)
Education				
Junior high school	26 (1.2 %)	32 (1.2 %)	30 (1.2 %)	36 (1.5 %)
High school	703 (33.0 %)	750 (29.1 %)	619 (25.6 %)	500 (21.0 %)
Vocational school/college, university, graduate school	1,401 (65.8 %)	1,797 (69.7 %)	1,773 (73.2 %)	1,843 (77.5 %)
Occupation				
Mainly desk work	1,144 (53.7 %)	1,293 (50.1 %)	1,222 (50.5 %)	1,264 (53.1 %)
Mainly interpersonal communication	480 (22.5 %)	590 (22.9 %)	622 (25.7 %)	614 (25.8 %)
Mainly labor	506 (23.8 %)	696 (27.0 %)	578 (23.9 %)	501 (21.1 %)
Self-rated health				
Very good	742 (34.8 %)	895 (34.7 %)	895 (37.0 %)	885 (37.2 %)
Neither good nor bad	919 (43.1 %)	1,104 (42.8 %)	991 (40.9 %)	986 (41.4 %)
Not good	469 (22.0 %)	580 (22.5 %)	536 (22.1 %)	508 (21.4 %)
Do you feel anxious about being infected with COVID-19?				
Yes	1,684 (79.1 %)	2,083 (80.8 %)	1,904 (78.6 %)	1,850 (77.8 %)
The incidence rate for the entire period (per 1,000 of the population), median (IQR)	0.28 (0.22, 0.34)	0.55 (0.51, 0.59)	1.26 (0.79, 1.51)	3.12 (1.91, 3.76)
The number of people infected for the entire period, median (IQR)	379 (330, 445)	1,053 (671, 1,124)	2,455 (2,168, 8,438)	27,500 (14,427, 52,382)
The incidence rate in the month before the survey (per 1,000 of the population), median (IQR)	0.09 (0.058, 0.14)	0.23 (0.16, 0.32)	0.47 (0.33, 0.59)	1.06 (0.74, 1.06)
The number of people infected in the month before the survey, median (IQR)	124 (39, 171)	440 (282, 501)	1,705 (916, 2,936)	9,851 (5,596, 14,690)
The number of people who had interrupted treatment	220 (10.3 %)	285 (11.1 %)	269 (11.1 %)	285 (12.0 %)

and treatment experiencing treatment interruption. To our knowledge, this is the first report showing that community infection levels are associated with treatment interruption.

The COVID-19 pandemic is affecting individuals' socioeconomic status, which is determined by factors such as employment instability. Higher levels of infection have greater socioeconomic impact than lower levels, for example, being more likely to lead to an increase in unemployment and workers in precarious employment situations, which may be a factor affecting treatment interruption (7). Our findings are consistent with those of a previous study showing that such individual factors influence treatment interruption. It is important to emphasize that the association between infection level and treatment interruption remained after adjusting for individual factors such as socioeconomic and health status. These results suggest that apart from individual characteristics, treatment interruptions during the COVID-19 pandemic were also subject to contextual effects related to regional infection levels. For example, rescheduling by medical institutions and health care providers is expected to occur in areas with higher infection levels than in areas with lower levels. Although more research is required to clarify the mechanisms by which regional infection levels lead to treatment interruptions, our study demonstrates that local spread of COVID-19 infection may affect the behavioral characteristics of workers living in the area. These findings suggest that, in addition to an individual patient approach, a population strategy is also needed to prevent the spread of infection and to avoid treatment interruption for manageable diseases.

TABLE 2 The prefectures and participants belonging to each infection level indices.

	Prefecture	Total ($n = 9{,}510$)
The incidence rate for the entire period (per 1,000)		
0.10–0.44	Aomori, Akita, Ehime, Fukui, Fukushima, Kagawa, Iwate, Nagasaki, Niigata, Shimane, Tokushima, Tottori, Yamaguchi, Yamagata	2,185
0.49–0.68	Kagoshima, Mie, Miyazaki, Nagano, Oita, Okayama, Saga, Shiga, Shizuoka, Tochigi, Toyama, Wakayama, Yamanashi	2,539
0.76–1.63	Chiba, Fukuoka, Gunma, Gifu, Kochi, Kumamoto, Kyoto, Hiroshima, Hyogo, Ibaraki, Ishikawa, Miyagi, Nara, Saitama	2,369
1.89–3.76	Aichi, Hokkaido, Kanagawa, Okinawa, Osaka, Tokyo	2,417
The number of people infected for the entire period		
74–492	Akita, Aomori, Ehime, Fukui, Iwate, Kagawa, Nagasaki, Niigata, Saga, Shimane, Tokushima, Tottori, Yamaguchi, Yamagata, Yamanashi	2,130
507–1,496	Fukushima, Ishikawa, Kagoshima, Kochi, Kumamoto, Mie, Miyazaki, Nagano, Oita, Okayama, Shiga, Tochigi, Toyama, Wakayama	2,579
1,673–11,982	Chiba, Fukuoka, Gifu, Gunma, Kyoto, Hiroshima, Hyogo, Ibaraki, Miyagi, Nara, Okinawa, Saitama, Shizuoka	2,422
12,381–52,382	Aichi, Hokkaido, Kanagawa, Osaka, Tokyo	2,379
The incidence rate in the month before the survey (per 1000)		
0.018–0.15	Akita, Ehime, Fukui, Fukushima, Ishikawa, Kagawa, Nagasaki, Niigata, Saga, Shimane, Tokushima, Tottori, Toyama, Yamaguchi	2,360
0.16–0.32	Ibaraki, Iwate, Kagoshima, Kumamoto, Mie, Miyagi, Miyazaki, Nagano, Oita, Shiga, Tochigi, Wakayama, Yamagata, Yamanashi	2,269
0.33–0.61	Chiba, Fukuoka, Gifu, Gunma, Hiroshima, Kochi, Kyoto, Nara, Okayama, Saitama, Shizuoka	2,209
0.66–1.12	Aichi, Hokkaido, Kanagawa, Okinawa, Osaka, Hyogo, Tokyo	2,672
The number of people infected in the month before the survey		
13–203	Akita, Aomori, Ehime, Fukui, Kagawa, Ishikawa, Nagasaki, Niigata, Saga, Shimane, Tokushima, Tottori, Toyama, Wakayama, Yamaguchi, Yamanashi	2,255
204–626	Fukushima, Kagoshima, Kochi, Kumamoto, Mie, Nagano, Okayama, Oita, Iwate, Miyazaki, Shiga, Tochigi, Yamagata	2,454
704–4,373	Chiba, Fukuoka, Gifu, Gunma, Hiroshima, Hyogo, Ibaraki, Kyoto, Miyagi, Nara, Okinawa, Saitama, Shizuoka	2,422
5,218–14,690	Aichi, Hokkaido, Kanagawa, Osaka, Tokyo	2,379

In this study, both the number of infected people and the infection rate by region were associated with treatment interruption. This suggests that it would be informative to report the incidence rate based on the infection status in each region, which reflects the population of that region. However, Japanese news reports tend to emphasize the number of people infected rather than the infection rate by region, the latter of which may contribute to changing the behavior of more people. A previous study reported that Japanese people have greater trust in local information (21), suggesting that reporting the number of infections by region will have a strong influence on individual's behavioral changes and risk perception.

Increased treatment interruption in areas with high levels of infection may cause further strain on future health care resources. Delaying and avoiding treatment can result in poorer management of chronic diseases, fewer regular checkups, and missed or delayed start of therapy thus deteriorating health conditions. It can also lead to increased complications and poor prognosis. These factors in turn can increase future health care needs in the region. The strain on local health care resources due to the COVID-19 pandemic is a serious challenge, and treatment interruption may be an indirect burden on health care resources due to COVID-19. Thus, reducing treatment interruption for manageable diseases may alleviate downstream consequences on the health care system.

The findings of this study indicate that controlling the level of infection in a community has important implications for treatment interruption. With the COVID-19 pandemic expected to continue for some time, sustained control of community-level spread will protect populations from the indirect effects of COVID-19, which include treatment interruption. In addition, strategies are needed to prevent treatment interruption. For example, telemedicine has and will continue to play a major role in the provision of health care during the COVID-19 pandemic (22–25). Furthermore, educating patients to avoid treatment interruption and widespread use of long-term prescriptions to prevent patients from running out of regular medications may help avoid health care problems caused by treatment interruption.

TABLE 3 Association between regional COVID-19 infection level and treatment interruption.

	Age-sex adjusted				Multivariate*			
	OR	95 %, CI		*P*-value	OR	95 %, CI		*P*-value
The incidence rate for the entire period (per 1,000)								
0.10–0.44	reference				reference			
0.49–0.68	1.00	0.83	1.21	0.999	1.00	0.83	1.21	0.993
0.76–1.63	1.06	0.88	1.28	0.555	1.07	0.88	1.30	0.505
1.89–3.76	1.25	1.04	1.50	0.019	1.32	1.09	1.59	0.005
				0.013†				0.003†
The number of people infected for the entire period								
74–492	reference				reference			
507–1,496	1.07	0.89	1.29	0.473	1.06	0.87	1.29	0.545
1,673–11,982	1.14	0.94	1.38	0.180	1.15	0.94	1.40	0.168
12,381–52,382	1.28	1.06	1.55	0.011	1.34	1.10	1.63	0.003
				0.008†				0.002†
The incidence rate in the month before the survey (per 1,000)								
0.018–0.15	reference				reference			
0.16–0.32	1.07	0.89	1.29	0.487	1.07	0.89	1.30	0.470
0.33–0.61	1.05	0.87	1.27	0.641	1.06	0.87	1.29	0.576
0.66–1.12	1.21	1.02	1.45	0.032	1.28	1.06	1.54	0.009
				0.044†				0.013†
The number of people infected in the month before the survey								
13–203	reference				reference			
204–626	1.11	0.92	1.34	0.284	1.12	0.93	1.36	0.241
704–4,373	1.16	0.96	1.40	0.127	1.18	0.97	1.43	0.093
5,218–14,690	1.30	1.08	1.57	0.006	1.38	1.14	1.67	0.001
				0.006†				0.001†

*The multivariate model was adjusted for age, sex, marital status (married, unmarried, bereaved/divorced), equivalent household income (500,000–2,650,000, 2,650,000–4,500,000, >4,500,000 JPY), educational level (graduated from junior high school, high school, vocational school/college, university, graduate school), occupation (mainly desk work, mainly interpersonal communication, mainly labor), self-rated health (very good, neither good nor bad, not good) and anxiety about infection. †p for trend.

A major strength of this study was the relatively large sample size, which allowed us to show, for the first time, an association between community infection level and treatment interruption.

However, this study also had several limitations. First, because this study conducted a cross-sectional study, causality could not be determined. However, since it is theoretically unlikely that treatment interruption experienced by an individual will increase the COVID-19 infection rate in a region, we think it is likely that high regional infection rates cause treatment interruption. Second, the results of this study may not be representative of those of Japan as a whole because this study did not use random sampling. Third, this study did not identify workers' reasons for discontinuing treatment in this study. As discussed above, there are various possible causes of treatment interruption, which may vary by region. Finally, this study did not inquire about the diseases being treated. Treatment interruption may vary depending on the presence or absence of symptoms and the potential disadvantages of discontinuing treatment for a particular disease.

Conclusions

The present study found that higher regional infection levels were linked to more workers experiencing treatment interruption during the third wave of COVID-19 infection in Japan. Although Further study is needed to clarify the relationship between the kinds of chronic disease, the degree of disease, and treatment interruption, as well as the causes of such interruption, our findings suggest that in addition to individual factors such as socioeconomic status and health status, high regional infection levels may contribute to behavioral changes in the local population, leading to treatment interruption. Preventing community spread of COVID-19 may thus be useful for avoiding treatment interruption for chronic diseases, an emerging medical problem brought about by 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 human participants were reviewed and approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (Reference Nos. R2-079 and R3-006). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JA: conceptualization and writing—original draft. AH, ST, and TN: funding acquisition, project administration, and writing—review and editing. MT, AO, and SM: funding acquisition, project administration, and supervision. MK: supervision and writing—review and editing. YF: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing—original draft, and writing—review and editing. All authors read and approved the final 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.

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EDITED BY
Constantinos Tsioutis,
European University Cyprus, Cyprus

REVIEWED BY
Basma M. Hani,
Benha University, Egypt
Muki Shey,
University of Cape Town, South Africa

*CORRESPONDENCE
Jaffer Shah
jaffer.shah@kateb.edu.af

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COVID-19 vaccine uptake among physicians during the second wave of COVID-19 pandemic: Attitude, intentions, and determinants: A cross-sectional study

Samar A. Amer [1,2,3], Jaffer Shah[4]*, Eman Elsayed Abd-Ellatif [5] and Hala A. El Maghawry[6]

[1]Department of Public Health and Community Medicine, Faculty of Medicine Zagazig University, Zagazig, Egypt, [2]Member of the Royal College of General Practitioners, London, United Kingdom, [3]Mental Health in Primary Care, Nova University, Lisbona, Portugal, [4]New York State Department of Health, New York, NY, United States, [5]Department of Public Health and Community Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt, [6]Department of Public Health and Community Medicine, Faculty of Medicine Zagazig University, Zagazig, Egypt

Background: Developed within a short period of time, the COVID-19 vaccine is not yet widely accepted among the public despite its availability, including by physicians, who are considered a vulnerable group.

Methodology: A descriptive cross-sectional study selected 436 governmental physicians from different specializations, representing four random administrative regions in Egypt. The data were collected through a self-administrated online questionnaire and analyzed using suitable tests.

Results: Out of the studied 436 physicians, 229 (52.2%) [aged 20–30, 284 (65.1%)] were women, 270 (61.9%) were residents, 219 (50.2%) were married, 398 (91.3%) were non-smokers, and 263 (60.3%) were non-frontline caregivers. The majority of the physicians, 227 (52.1%) of them, hesitated to take the vaccine, 236 (54.1%) had not decided on the preferred type of vaccine, and 101 (23.2%) were neutrally confident in the Egyptian healthcare system; 302 (96.3%) had no history of drug or food hypersensitivity. There was no statistically significant ($p < 0.05$) relationship between the physicians' attitude toward COVID-19 vaccine uptake and the studied demographic variables. There was a statistically significant connection between all of the doctors' intentions to get the COVID-19 vaccine and all of the four attitude domains that were looked at.

Conclusion: The study concluded that a low level of willingness among Egyptian physicians to take the COVID-19 vaccine is a prevalent problem. COVID-19 vaccination hesitancy and non-acceptance were linked to negative attitudes about natural immunity, mistrust of vaccine benefits, and concerns about commercial profiteering.

KEYWORDS

vaccination, COVID-19, attitude - intentions, cross sectional analysis, physician, COVID-19 Vaccination

Introduction

The World Health Organization (WHO) has made stringent efforts and campaigns to advise the world on how to manage and overcome the COVID-19 pandemic (1). There are no specific antiviral medications and only a few drugs have shown the potential to reduce mortality among COVID-19 patients (2). As a result, human compliance with global preventive measures, such as facemasks, social distancing, extended quarantine, and travel restrictions, has been shown to only go so far in reducing the spread of the virus. The best way to control and eventually eradicate this pandemic is to produce an effective and accessible vaccine (3).

Vaccination is one of the biggest public health successes of the 20th century, with at least seven COVID-19 vaccines having been developed as of 18 February 2021. High vaccination coverage is advised as the main public health intervention to control and flatten the epidemic "curve" of COVID-19, with the long-term goal of achieving herd immunity; however, in most cases, vaccine development can take years. As a result, despite the availability of the new COVID-19 vaccine, public acceptance remains uncertain (4). Vaccine hesitancy is one of the most difficult health challenges, so much so that the WHO considers it a significant global health threat (5).

Several factors influence the decision to accept, postpone, or refuse vaccination, including political, cultural, ecological, healthcare system, historical, and socioeconomic factors (6). According to Protection Motivation Theory, factors such as vaccination perceptions, efficacy, the severity of health threats, and a low incidence of community infections can influence a person's willingness to get vaccinated, making them important tenets of health behavior engagement. In particular, concerns about side effects or safety, as well as the social and peer factors can heavily influence a person's willingness to get vaccinated (7, 8).

Misinformation, safety or efficacy concerns, the vaccine manufacturer's country of origin, and the belief in rushed vaccine development and production are the main causes of COVID-19 vaccination hesitancy (6). It has also been observed that specific vaccine-related issues, such as new vaccine introduction, administration method, schedule, cost, reliability, source of supply, knowledge base, new recommendations for a current vaccine, and the strength of these recommendations also play a part in the public's hesitation to take the vaccine. Globally, the acceptance rate of the COVID-19 vaccine varies and has been linked to some of these factors in many studies. The Middle East, in particular, has been one of the regions with the lowest rates of vaccine acceptance (7).

Developing effective COVID-19 vaccination strategies requires a thorough study of the factors that influence vaccination decisions as they might differ significantly between people who accept and are determined to take the vaccine and those who do not (9). According to a recent global report, approximately 30% of those polled would refuse or are hesitant to take the vaccine if it becomes available (10).

The role of healthcare providers (HCPs) in the pandemic response has become increasingly important. Due to low vaccination acceptance rates among HCPs, individuals who deal with vaccine-hesitant HCPs both professionally and personally are likely to be less vaccine-compliant. This is concerning because HCPs are the most dependable social resource for promoting public immunization, as they are in the best position to comprehend and respond to the anxieties and concerns of hesitant patients, as well as to explain the benefits of vaccination, especially during subsequent waves of COVID-19 (11–13).

Only a few studies among HCPs have been conducted to address these issues. HCPs who are exposed to COVID-19 patients are at risk of contracting the virus and transferring it to others (14). Therefore, achieving high COVID-19 vaccination coverage rates for this group will be paramount, as they are considered immunization role models for the public and have substantial influence over individuals and their communities. They will also be responsible for recommending vaccinations and counseling COVID-19-positive patients (15).

Limited research has studied COVID-19 vaccine acceptance among HCPs in Egypt during the second wave of the COVID-19 pandemic. At that time, vaccine availability was restricted in Egypt, a middle-income country in northeast Africa. Vaccination campaigns had not yet been initiated, and only HCPs were eligible for vaccination. The goal of this study was to investigate physicians' attitudes and acceptance of the COVID-19 vaccine, as well as the determinants that may influence their vaccination decision-making from January to March 2021.

Methodology

Participants and study design

This online cross-sectional survey targeted Egyptian physicians of different specialties and was conducted from January 2021 to March 2021. The exclusion criteria were refusal to participate in the study, internet non-users, and Egyptian physicians living or working abroad during the study period.

Sample size

The sample size was estimated using this equation: $n = Z^2 P (1 - P) / d^2$ (16).

n = sample size, z = level of confidence according to the standard normal distribution (for a level of confidence of 95%, z = 1.96, for a level of confidence of 99%, z = 2.575), P = estimated proportion of the population that presents the characteristic (when unknown, we use P = 0.5), d = tolerated margin of error (for example, we want to know the real proportion within 5%) (16). Due to limited data regarding the prevalence of COVID-19 anti-vaccine attitudes in Egypt, we assumed that 50% of the respondents would have anti-COVID-19 vaccine attitudes, 95% confidence level, and 80% power of the study, so the calculated sample size was 436 physicians.

Sampling techniques

The data were anonymously collected using a multistage sampling method *via* an online self-administered questionnaire. We randomly selected four of Egypt's seven geographical regions, then randomly selected four governmental healthcare settings per region, two from urban areas and two from rural areas (17). The targeted sample from each was weighted according to proportions based on physician density per setting.

Data collection

Google Forms was used to create, distribute, and collect the questionnaire. The data were gathered using a self-administered online English questionnaire. From January through March 2021, the URL was shared *via* the study team's network and the HCPs' professional groups, as well as the official platforms of many healthcare settings on WhatsApp, Facebook, official emails, and Facebook Messenger. Data confidentiality was guaranteed. A weekly reminder was sent to increase the response rate until the target sample was reached.

Data were collected anonymously through an online survey based on another study (18). The questionnaire was revised and then pilot tested on 15 HCPs to check acceptability, clarity, and face validity. The results of the pilot study were not used in the final analysis. Internal consistency was assessed, and Cronbach's coefficient was 0.82. The questionnaire contained required admission of sensitive information.

Data collection tool

The questionnaire was composed of four main sections as follows:

1. Sociodemographics

   Age, sex, residence, educational level, frontline physician status, experience in years, marital status, smoking history, and history of chronic diseases.
2. COVID-19 exposure history and health-related factors

   - Previous infection with COVID-19.
   - Family member infected with COVID-19.
   - Perceived susceptibility to COVID-19 infection.
   - General Health Perception Scale; single item to determine the current perceived state of health (poor to medium health, good health, and very good to excellent health) 0.1 (2).
   - Confidence in the Egyptian government to handle the pandemic.

3. *COVID-19 vaccine uptake-related factors*

   - ☐ The preferred type of vaccine.
   - ☐ Willingness (willing, hesitated, or unwilling) to take the vaccine.
   - ☐ History of potential adverse effect or sensitivity to food or drug or medication , using a single item based on the perceived sensitivity to medication scale (19).
   - ☐ History of influenza vaccination.

4-vaccine attitude

The 12-item Vaccination Attitudes Examination (VAX) Scale (20) was used to assess four negative attitudes toward the COVID-19 vaccine with subscale items: worries about unforeseen side effects, natural immunity preference, mistrust of vaccine benefits, and commercial profiteering concerns.

Each item was assessed through a six-point Likert scale ranging from strongly agree = 1; agree = 2; slightly agree =3; neutral = 4; slightly disagree = 5; to strongly disagree = 6. The total scores ranged from 6 to 24; the higher the score, the more negative the attitude. Values equal to or above the mean of the total score or individual items were considered negative attitudes of the participants toward the vaccine, while those below the mean were considered positive attitudes.

Statistical analysis

The data were analyzed using SPSS version 25 (IBM, Armonk, NY, United States). Differences were considered statistically significant at $p < 0.05$. The qualitative and discrete sociodemographic variables were presented as frequency and percentage. A chi-square test was performed to test the relationship between sociodemographic factors and COVID-19 vaccination uptake. The mean and standard deviation were used to calculate the quantitative subscales of attitudes toward vaccinations. Pearson's correlation coefficient (r) was used to test the association between age and the subscales of the VAX Scale. The predictors of COVID-19 vaccination uptake among physicians, hesitancy, and non-acceptance were identified using multinomial logistic regression analysis.

Ethical issues

The study methodology was approved by the Ethical Committee of Scientific Research, Faculty of Medicine, Benha

University, No. RC.3.1.2021. All participants provided electronic informed written consent after clarification of the goals, data confidentiality, voluntary participation, and withdrawal.

Results

Out of the 436 physicians studied, 229 (52.2%) were between the ages of 20 and 30 years, 239 (54.8%) lived in an urban area, 284 (65.1%) were women, 270 (61.9%) were residents, 219 (50.2%) were married, 398 (91.3%) were non-smokers, 263 (60.3%) were not frontline caregivers, and 260 (59.6%) had fewer than 10 years of experience (Table 1).

In terms of health-related factors, the majority of the physicians studied (336, 77.1%) had no comorbidities, 261 (59.9%) had never received a flu vaccine, 229 (52.5%) were not infected with COVID-19, 336 (77.1%) reported that they were susceptible to infection, and 192 (44.0%) had no family members infected with COVID-19 (Table 2).

The majority of physicians (227, 52.1%) were hesitant to take the vaccine, 236 (54.1%) had not yet decided on the preferred type of vaccine, 101 (23.2%) reported borderline (neutral) confidence in the Egyptian government to handle the pandemic, and 302 (96.3%) had no history of drug or food hypersensitivity (Figure 1; Table 3).

TABLE 1 Association between sociodemographic and attitude toward COVID-19 vaccine uptake.

Sociodemographic variables	**Total *n* = 436 *F* (%)**	**Attitude**		**X^2 test (*p*)**
		Positive No=222 *F* (%)	**Negative No=214 *F* (%)**	
Age groups (Y)				
20–<30	229(52.2)	120(54.1%)	109(50.9%)	1.25
30–<40	150(34.4)	71(31.9%)	79(36.9%)	(0.56)
40 y or more	57(13.1)	31(13.9%)	26(12.1%)	
Residence				
Urban	239 (54.8)	120(54.1%)	119(55.6%)	0.12
Rural	197(45.2)	102(45.9%)	95(44.4%)	(0.77)
Sex				
Male	152(34.9)	71(31.9%)	81 (37.9%)	1.65
Female	284(65.1)	151(68.0%)	133(62.1%)	(0.23)
Education				
Resident (University-educated)	270(61.9)	139(62.6%)	131(61.2%)	0.09
Post graduate	166(38.1)	83(37.3%)	83(38.8%)	(0.76)
Marital status				
Single	205(47.0)	109(49.1%)	96(44.9%)	2.02
Married	219(50.2)	109(49.1%)	110(51.4%)	(0.36)
Divorced –widowed	12(2.8)	4(1.8%)	8(3.7%)	
Smoking				
Current smoker	23(5.3)	11(4.9%)	12(5.6%)	0.124
Ex-smoker	15(3.4)	8(3.6%)	7(3.3%)	(0.96)
Non-smoker	398(91.3)	203(91.4%)	195(91.1%)	
Frontline				
Yes	173(39.7)	90(40.5%)	83(38.8%)	0.14
No	263(60.3)	132(59.4%)	131(61.2%)	(0.77)
Experience duration (y)				
≤10 y	260(59.6)	130(58.6%)	130(60.7%)	0.22
>10 y	176(40.4)	92(41.4%)	84(39.3%)	(0.69)

X^2 test (chi-square test).

TABLE 2 Association between the physicians' attitude toward COVID-19 vaccine uptake and health-related factors.

Health-related variables	Total $n = 436$ F (%)	Attitude		X^2 test (p)
		Positive attitude No=222 F (%)	Negative attitude No=214 F (%)	
Health status				
Poor to medium health	31(7.1)	9(4.1%)	25(11.7%)	9.36
Good health	133(30.5)	67(30.2%)	66(30.8%)	(0.009) *
Very good to excellent	194(44.5)	146(65.8%)	123(57.5%)	
Chronic disease				
No chronic disease	336(77.1)	169(76.1%)	167(68.1%)	0.23
With comorbidities **	110(22.9)	53(23.9%)	47(21.9%)	(0.65)
Up took flu vaccine				
Never take flu vaccine	261 (59.9)	133(59.9%)	128(59.8%)	
Took flu vaccine before***	157(40.1)	89(40.1%)	86(40.1%)	
Get infected with COVID-19				
No	95(21.8)	52(23.4%)	43(20.1%)	4.86
Yes	229(52.5)	123(55.4%)	106(49.5%)	(0.09)
Don't know	112 (25.7)	47(21.7%)	65(30.4%)	
Perceived susceptibility				
Yes, I'm susceptible	336(77.1)	161(72.5%)	175(81.8%)	7.27
No, I don't susceptible	23(5.2)	17(7.6%)	6(2.8%)	(0.027) *
Don't know	77(17.7)	44(19.8%)	33(15.4%)	
Family with COVID-19				
Yes	184(42.2)	97(43.7%)	87(40.7%)	0.42
No	192(44.0)	95(54.8)	97(45.3%)	(0.82)
Don't know	60(13.8)	30(13.5%)	30(14.2%)	

* Significant at the 0.05 level (2-tailed). X^2 test (chi-square test).
** Asthma or respiratory disease 22 (5.0), cardiac disease 4 (0.9), hypertension 11 (2.5), diabetes 11 (2.5), kidney or liver disease 2 (0.5), autoimmune disease 9 (2.1), overweight/obesity 21 (4.8).
*** Long time ago100 (22.9), last year 12 (2.8), this year 44 (10.1), and every year 19 (4.4).

In terms of the attitude of the physicians toward the COVID-19 vaccine, 222 (50.9%) showed positive attitudes, and 214 (49.1%) showed negative attitudes (Figure 2). There was no statistically significant ($p > 0.05$) relationship between physicians' attitudes toward COVID-19 vaccine uptake and any of the demographic variables studied (age, residence, sex, education, marital status, smoking, frontline work, and experience duration) (Table 1).

There was a statistically significant ($p < 0.05$) relationship between physicians' intentions to receive COVID-19 vaccinations and marital status, residence, whether the physicians were frontline, and perceived susceptibility. The highest willingness rates were 61 (57.5%) among rural physicians, 75 (70.7%) among infection-prone physicians, and 69 (65.1%) among non-frontline physicians (Table 4).

The main reasons for negative attitudes toward COVID-19 vaccination uptake were, in descending order, 328 (75.2%) preference for natural immunity, 312 (71.6%) mistrust of vaccine benefits, 305 (70%) concerns about commercial profiteering, and 255 (58.5%) concerns about unforeseen effects. There was a statistically significant relationship between all the physicians'

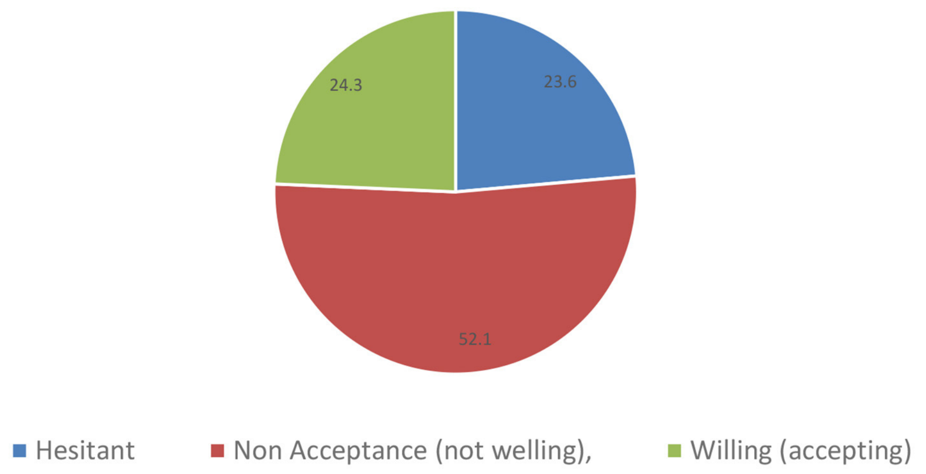

FIGURE 1
Intention of the physicians to get the COVID-19 vaccine. Shows the distribution of HCPs' status toward COVID-19 vaccine as "Hesitant," "Non-Acceptance (not willing)," and "Willing (accepting)".

TABLE 3 The vaccine uptake; Intentions, Preference, and other related determinants among the studied physicians ($n = 436$).

Variable	F (%)
Type of preferred vaccine[#]	
Chinese vaccine	26(6.0)
Pfizer vaccine	121(27.8)
Moderna vaccine	10(2.3)
AstraZeneca	31(7.1)
Russian vaccine	12(2.8)
Not decided yet	236(54.1)
History of drug or food hypersensitivity	
Yes	48 (11.0)
No	302(96.3)
Don't know	86(19.7)
Confidence in the Egyptian government to handle the pandemic	
Strongly disagree	93 (21.3)
Disagree	89(20.4)
Slightly disagree	46(10.6)
Borderline (neutral)	101(23.2)
Slightly agree (slight confidence)	44(10.1)
Agree (confident)	57(13.1)
Strongly agree	6(1.3)

[#]The known and approved vaccines during the time of data collection.

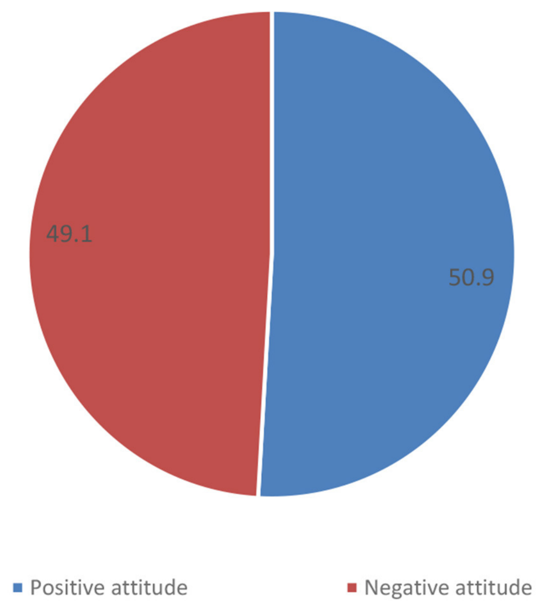

FIGURE 2
Attitude of the physicians regarding the COVID-19 vaccine. Shows the distribution of HCPs' status toward COVID-19 vaccine with regards to "Positive" and "Negative" attitudes.

intentions toward COVID-19 vaccination uptake and the entire four-attitude domains studied (Table 5).

There was a significant ($p = 0.01$) positive correlation between age and mistrust of the vaccine benefits, and an insignificant negative correlation between concerns about commercial profiteering and preference for natural immunity (Table 6).

Multinomial logistic regression analysis was used to identify predictors of COVID-19 vaccine hesitancy and non-acceptance. The reasons for vaccination hesitancy and non-acceptance of vaccine uptake were revealed to be urban residence, concerns about future side effects, and vaccine mistrust, benefit, and

TABLE 4 Association between intentions toward COVID-19 vaccination uptake and some sociodemographic and health-related factors.

Sociodemographic and health variables	Intentions toward COVID-19 vaccination uptake			X^2 test (p)
	Willing No=106 *F* (%)	Hesitated No=227 *F* (%)	Not willing No=103 *F* (%)	
AGE group				
20–<30	56(52.8%)	116(51.1%)	57(55.3%)	3.69
30 < 40	32(30.2%)	81(35.7%)	37(35.9%)	(0.45)
40+	18(16.9%)	30(13.2%)	9(8.7%)	
Gender				
Male	46(43.3%)	76(33.4%)	30(29.3%)	5.1
Female	60(56.6%)	151(66.5%)	73(72.7%)	(0.07)
Residence				
urban	45(42.5%)	129(56.8%)	65(64.4%)	9.7
Rural	61(57.5%)	98(43.2%)	38(36.6%)	(0.01) *
Marital status				
single	50(47.2%)	104(45.8%)	51(50.7%)	
married	55(51.9%)	119(52.4%)	45(44.6%)	9.54(0.046) *
Divorced –widowed	1(0.9%)	4(1.8%)	7(6.7%)	
Frontline worker				
Yes	37(34.9%)	103(45.4%)	33(32.9%)	6.6
No	69(65.1%)	124(54.6%)	70(69.1%)	(0.037) *
Infected with COVID-19				
yes	21(19.8%)	51(22.5%)	23(22.3%)	7.3
No	64(60.4%)	120(52.9 %)	45(43.6%)	(0.12)
Don't know	21(19.8%)	56(24.7%)	35(34.1%)	
Susceptible to infection				
Yes	75(70.7%)	187(82.4%)	74(73.0%)	9.94
No	9(8.5%)	6(2.6%)	8(7.7%)	(0.04) *
Don't know	22(20.7%)	34(14.9%)	21(20.3%)	

* Significant at the 0.05 level (2-tailed). X^2 test (chi-square test).
There was no statistically significant difference between the age groups and the Intentions toward COVID-19 vaccination uptake.

preference for natural immunity were significant independent predictors of vaccine hesitancy ($p = 0.004$, 0.01, 0.00, and 0.03, respectively (Table 7).

Discussion

The COVID-19 vaccine was deemed the ideal solution for combating the existing pandemic, yet HCPs' vaccine hesitancy has been a challenge for healthcare leaders. Egypt has launched several vaccination programs, but the newness of the COVID-19 vaccination rollout has raised concerns about physicians' attitudes and acceptance of the vaccination. As a result, this novel study was carried out in Egypt to investigate this issue. During the second wave of the pandemic, this study was conducted right before the CDC and WHO approved all available vaccinations in Egypt and right before the vaccines were administered.

The majority of the studied physicians (227, 52.1%) were hesitant to take the vaccine, which was clearly higher than what was reported in other studies in different countries. In KSA 28.1% were unsure, while in America 31.6%, and in United Kingdome, and Portugal were hesitant (17, 21–24).

Less than 25% of the studied physicians were willing to accept the vaccine. Different rates were reported in different countries, all of which were higher than those in Egypt. Over time, with experience with actual vaccine administration and the current pandemic's time-varying death rates, COVID-19 vaccine willingness can change dramatically (21). For example, 88.6% was the median global acceptance rate from a survey of 19

TABLE 5 Frequency distribution of attitudes toward the vaccine association between intentions toward COVID 19 vaccination and attitudes toward vaccines.

	Total $n = 436$ *F* (%)	Intentions toward COVID 19 vaccination uptake			X^2 test (*p*)
		Willing No=106 *F* (%)	Hesitated No=227 *F* (%)	Not willing No=103 *F* (%)	
Mistrust of vaccine benefit mean± SD (2.92 ± 1.03)					67.2 (0.00) **
Attitude					
Positive	124(28.4)	12(11.3%)	61(26.8%)	51(59.2%)	
Negative	312(71.6)	94(88.7%)	176(73.1%)	42(40.7%)	
Worries about unforeseen effects mean± SD (2.92 ± 1.03)					4.32 (0.00) **
Attitude					
Positive	181(41.5)	51(48.1%)	95(41.8%)	35(33.9%)	
Negative	255(58.5)	55(51.9%)	132(58.1%)	68(66.1%)	
Concerns about commercial profiteering mean± SD (2.92 ± 1.03)					15.44 (0.00) **
Attitude					
Positive	131(30.0)	47(44.4%)	63(27.8%)	21(20.3%)	
Negative	305(70.0)	59(55.6%)	164(72.2%)	82(79.6%)	
Preference of natural immunity mean± SD (3.17 ± 1.07)					11.004 (0.004) *
Attitude					
Positive	108(24.8)	38(35.8%)	53(23.3%)	17(16.5%)	
Negative	328(75.2)	68(64.2%)	174(76.7%)	86(83.5%)	

** Significant at the 0.01 level (2-tailed)/ * Significant at the 0.05 level (2-tailed).
X^2 test (chi-square test).

TABLE 6 Correlation between age and attitude toward COVID-19 vaccine.

Variables	Age(y)	
	R	P
Mistrust of vaccine benefit	0.12	0.01*
Worries about unforeseen effects	0.078	0.104
Concerns about commercial profiteering	−0.089	0.063
Preference of natural immunity	−0.015	0.757

* Correlation is significant at the 0.05 level (2–tailed)./r correlation coefficient.

countries, ranging from 59 to 75% in most Western countries (25). Specifically, the rates were 60% to 90% among physicians in Greece (February 2020), (26) 77.6% in France (March to July 2020), (27) 69% in KSA (November 2020), (28) 64.7% in America, (29) the figure was found at 36 and 57.6% in Singapore, and US (8, 23), 8% in Congo (March to April 2020), (9) 59% in South Africa (March to May 2021), (30) and nearly similar to other studies in Egypt (21, 27%) among Egyptian HCPs (11, 21).

This high vaccination hesitancy (VH) and low vaccination acceptance rate among HCPs in Egypt could be explained by the reported low and borderline or neutral levels of confidence in the Egyptian health care system, as well as the high prevalence of negative attitudes reported by more than 70% of physicians toward the uptake of COVID-19 vaccination, which was, in descending order, preference for natural immunity, mistrust of vaccine benefits, and concerns about commercial profiteering. VH is linked to negative attitudes about the SARS-CoV-2 vaccine, such as fears about safety and effectiveness, doubts about the need for vaccination, and preference for natural immunity (23, 25, 31).

Among the studied HCPs in Egypt, 103 (23.6%) were not willing to take the vaccine, which was higher than what was reported in other studies and lower than 41.0% in South Africa (March to May 2021) (30). For example, 10.8 to 25% of Americans, 20% of Canadians, 9% of Portuguese, and 7% of Saudis would not receive the vaccine (21–23, 32). Because of the extent of non-compliance, achieving herd immunity would be extremely difficult.

TABLE 7 Multinomial regression analysis for the predictors of the COVID-19 vaccine uptake, hesitancy and non-acceptance.

Intentions		B	Sig.	Exp(B)	95% Confidence interval for exp(B)	
					Lower bound	Upper bound
Vaccine hesitancy[a]						
	Mistrust of vaccine benefit	1.064	0.00*	0.345	0.242	492
	Worries about future side effects	0.351	0.01*	1.421	1.0931	0.846
	Commercial profiteering	0.119	0.39	1.127	0.856	1.483
	preference of natural immunity	0.333	0.03*	1.395	1.035	1.881
	Rural	0[b]	.	.	.	.
	Urban	0.761	0.004**	2.140	1.272	3.602
	Frontline (no)	0[b]	.	.	.	.
	Frontline (yes)	0.384	0.152	1.468	0.868	2.484
Non-acceptance of the vaccine uptake[a]						
	Mistrust of vaccine benefit	2.038	0.000**	0.130	0.083	204
	Worries about future side effects	0.501	0.002*	1.650	1.202	2.265
	Commercial profiteering	0.129	0.464	1.138	0.805	1.609
	preference of natural immunity	0.562	0.003**	1.754	1.209	2.544
	Rural	0[b]	.	.	.	.
	Urban	0.978	0.004**	2.660	1.363	5.192
	Frontline (no)	0[b]	.	.	.	.
	Frontline (yes)	−0.421−	0.236	0.656	0.327	1.316

[a] The reference category is: willing to the vaccine uptake.
[b] This parameter is set to zero because it is redundant.
** Significant at the 0.01 level (2-tailed)/ * Significant at the 0.05 level (2-tailed).

Although only 3.7% of HCPs had a history of drug or food hypersensitivity, approximately 24% of physicians were unwilling to uptake the vaccine. This figure is lower than that reported in a previous study of 40% of Egyptians (9), which could be explained by the fact that physicians had a higher level of medical education about the importance and effectiveness of the vaccine than the rest of the Egyptian community.

Vaccine willingness can change dramatically with time, experience with actual vaccine administration, and the current pandemic's time-varying morbidity and death rates (33). Physicians' acceptance of using the COVID-19 vaccine depends on the availability of the vaccine, the type of the vaccine, the degree of confidence in the healthcare system, and the vaccination policy. However all these determinants are changeable from time to time (34).

There was a statistically significant ($p < 0.05$) relationship between physicians' intentions to receive COVID-19 vaccinations and the physician's sex. However, most respondents (284, 65.1%) were women, in contrast with other studies which reported significantly lower acceptance among women (11, 17, 35).

A study in Bangladesh reported that participants living in urban areas were more than twice as likely to be aware of COVID-19 vaccination and willing to receive it (36). In contrast to our study, physicians who live in rural areas were significantly more likely to accept the vaccination. This can be explained by the fact that the population in rural areas has a poor practice for preventive measures, making physicians feel at increased risk for infection (37).

This study showed that age was found to be insignificantly associated with vaccination decisions. This was consistent with Fares et al., who found that the youngest age group had the highest uptake of the COVID-19 vaccine (21) This contradicted Grech et al., who found that the oldest age group had the highest uptake of the COVID-19 vaccine because they are the most vulnerable, and thus, more likely to accept the vaccine (38).

There was an insignificant relationship between physicians' attitudes toward COVID-19 vaccine uptake and all the studied demographic variables. In contrast to a study conducted in Bangladesh, participants' attitudes toward the COVID-19 vaccine were significant in terms of all demographic variables studied except perceived susceptibility and health status (36).

Our findings suggest that the most significant attitudinal barriers to receiving a COVID-19 vaccine are general distrust regarding vaccine benefits and safety and concerns about unforeseen side effects. This supports previous research that found low vaccine confidence and concerns about the novelty and safety of the COVID-19 vaccine to be significant attitudinal barriers to vaccine willingness (17).

The majority of respondents (71.6 %) did not believe in the benefits of the COVID-19 vaccine. This is consistent with another Egyptian study, which found that 79% of respondents did not trust received vaccine information (21). This was also similar to the findings of a study conducted in the United States, which found that a high percentage of HCPs did not trust information about COVID-19 and its severity provided by regulatory authorities and pharmaceutical companies for vaccine development and safety (17).

In the existing study, participants expressed a high level of concern about the COVID-19 vaccine's unforeseen effects, the percentage of which differed significantly between groups. This was supported by an Australian study by Dodd et al., which found that 36% of those who were hesitant to get the vaccine were concerned about its safety, compared to 11% of those who were willing to get the vaccination (39). Concerns about vaccination safety and effectiveness, as well as trial and testing duration, were common findings in many studies (40).

Assessing vaccine uptake predictors among HCPs is critical because it will enable health authorities and policymakers to target resources to maximize uptake. In this study, participants' willingness to administer COVID-19 vaccines was found to be significantly influenced by their income and years of experience. For diverse groups of HCPs who answered identical surveys in different regions of the world, the predictors were willingness to obtain influenza vaccinations years and people who classified themselves as having a high risk of severe COVID-19 infection (11).

Based on the reported maximum vaccine uptake, health officials must reassure the public that vaccine development adhered to all predetermined guidelines and that the process of developing the vaccine was not rushed. If the public believes that health officials are rushing a vaccine into production, this will erode public trust and exacerbate vaccine acceptance.

The most important way to ensure vaccine uptake is to provide convincing evidence that a SARS-CoV-2 vaccine has been rigorously tested, proven to be effective, and has not been rushed into production. Concerns about commercial profiteering are a significant barrier to vaccination uptake. Vaccine development and dissemination programs with more reassuring titles are more likely to gain public trust (41, 44).

By 28 April 2021, the COVID-19 mortality in Egypt reached 13,219, according to the Egyptian Ministry of Health and Population and WHO.[36.] On the same day, the Egyptian Medical Syndicate reported that 492 Egyptian physicians had died of COVID-19 since the start of the pandemic (42), accounting for 3.7% (492/13,219) of COVID-19 mortalities in the country. The reported high negative attitudes and lack of willingness to vaccinate may lead to an exacerbation of the situation (45–47).

Strength

The relatively large sample of physicians working in governmental healthcare settings in urban and rural areas represents physicians from Egypt's seven regions. The representation of both sexes, age groups, specialties, and proximity in dealing with COVID-19 patients.

Limitation

The fact that this study was conducted exclusively online restricts the generalizability of the findings and may lead to selection bias. The study was conducted before COVID-19 vaccines were offered to HCPs in Egypt, so the acceptance rate may have altered once the vaccines were available.

Conclusion

According to this study, Egyptian physicians were commonly hesitant to take the COVID-19 vaccine despite their susceptibility to the virus itself. There were statistically significant differences in the COVID-19 vaccination attitude and health status and perceived susceptibility. The high negative attitudes related to preference for natural immunity, mistrust of vaccine benefits, and concerns about commercial profiteering were significantly related to the widespread COVID-19 vaccination hesitancy and non-acceptance. Urban residence, concerns about future side effects, and vaccine mistrust, benefit, and preference for natural immunity were significant independent predictors of vaccine hesitancy and non-acceptance.

Recommendations

As long as physicians' attitudes and perceptions of COVID-19 vaccines play an important role in the general population's vaccination behavior through consultation, we recommend that (1) This study's findings be shared with policymakers. (2) Policymakers should take these findings into account when planning and implementing public health intervention campaigns in Egypt to change negative vaccine attitudes and increase acceptance and uptake of COVID-19 vaccines to achieve herd immunity and control the pandemic. (3) Well-structured mass health education campaigns, advising on the significant implications for vaccine safety be implemented to reassure physicians and the public to maximize public uptake of the SARS- CoV-2 vaccine. (4) More research and interventions be conducted to address the various anti-vaccination beliefs that have been identified, as well as the best practices for reducing these negative beliefs.

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 methodology was approved by the Ethical Committee of Scientific Research, Faculty of Medicine, Benha University, No (RC.3.1.2021). All participants provided electronic informed written consent after clarification of the goals, data confidentiality, voluntary participation, and withdrawal.

Author contributions

Study conception and design: SA and EA-E. Data collection: SA and HE. Analysis and interpretation of results: SA and JS. Draft manuscript preparation: SA, JS, EA-E, and HE. All authors contributed to the article and approved the submitted version.

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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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EDITED BY
Benjamin Longo - Mbenza,
Walter Sisulu University, South Africa

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Simon Grima,
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University of Raparin, Iraq
David Kitara Lagoro,
Gulu University, Uganda

*CORRESPONDENCE
Khadijah Angawi
kkangawi@kau.edu.sa

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The impact of social media on risk perceptions during COVID-19 in Saudi Arabia

Khadijah Angawi [1]* and Mutlaq Albugmi[2]

[1]Department of Health Services and Hospital Administration, Faculty of Economics and Administration, King Abdulaziz University, Jeddah, Saudi Arabia, [2]King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia

Background: Social media is considered a critical source for seeking health information, especially during outbreaks. During the Coronavirus disease 2019 (COVID-19) pandemic, social media played an important role in disseminating information. However, it has been a source of misinformation in many communities throughout the pandemic. Whether this disseminated information has a positive or negative impact, individuals' risk perceptions of disease are influenced. It is important to explore factors that build public behaviors and their adaptation of risk reduction measures during the COVID-19 pandemic. Therefore, the aim of this study is to determine the role of social media and its impact on the risk perceptions of the COVID-19 in Saudi Arabia.

Methods: This was a cross-sectional study, and participants were recruited using different social media outlets between August to October 2020. The survey was delivered through Qualtrics platform targeting Saudi Arabian residents over the age of 18 years old. The questionnaire was delivered in English and Arabic. A convenience sampling was used to recruit participants to the study. The survey link was posted on several social media platforms.

Results: A total of 2,680 respondents completed the online survey. The results showed that male gender, individuals earning 4,000–12,000 SAR, and employed had positive and significant relationships with risk perception compared to their counterparts (β: 0.044, p-value: 0.035 and β: 0.051, p-value: 0.041, β: 0.108 p-value: < 0.001, β: 0.119 p-value: < 0.001), respectively. In second block, individuals exposed to social media had higher risk perception (β: 0.096, p-value < 0.001). In third block, self-efficacy was significantly but negatively associated with risk perception, indicating individuals who were self-efficient were less likely to perceive risk for the COVID-19 (β: −0.096, p-value < 0.001). There was no interactive effect of social media and self-efficacy on risk perception.

Conclusion: The current study results show that social media exposure to the COVID-19 information has a positive impact in shaping an individuals' risk perception. The study also suggests that there is a need for public officials and policymakers to develop effective communication strategies through risk communication campaigns targeted at women, individuals with lower socioeconomic status, and those who are single as they showed a negative relationship with risk perception.

KEYWORDS

COVID-19, risk perception, social media, self-efficacy, Saudi Arabia

Introduction

Today's society is facing a major risk in the form of the coronavirus pandemic. In December 2019, the first case of a novel Coronavirus disease 2019 (COVID-19) was identified in Wuhan, China. Soon, thousands of people were affected (1). Despite the growing outbreak, Chinese health officials and the government remained unclear about the origin. Since then, the uncertainty around COVID-19 has contributed to the spread of the virus worldwide, and the number of cases has rapidly been increasing, killing millions of people worldwide (1). To date, various variants of COVID-19 have emerged around the world (2).

Both population growth and change in human behavior have contributed to a rise in outbreaks of emergent infectious diseases (3). Today's widespread uses of technology and internet access have allowed healthcare communication to expand on a global scale. Social media is considered a critical source for health information in some countries, especially during infectious disease outbreaks (3). Social media can be useful in communicating information on emerging infectious diseases and medical information, positively impacting people's perceived risks and decision-making processes (3). Furthermore, social media has an impact on an individual's risk perceptions, which have been moderated by other factors such as self-efficacy (3). Individuals interpret information based on their risk perception of the disease. Furthermore, an individual's risk perceptions influence the protective behaviors in facing an outbreak of an infectious disease (4).

Ideally, governments and public officials are the most trusted sources that play a critical role in disseminating information (5). The public's trust in social media has been known to positively influence their risk perceptions in terms of both overreactions to the epidemic and compliance with self-quarantine (5). The World Health Organization (WHO) guidelines suggest that governments and public institutions, regardless of their political situation, clearly communicate information to the public in times of epidemic outbreaks (5, 6). During the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak in China, the public highly relied on the social media as a reliable source instead of government and public officials (7). In addition, the Chinese population distrusted the reliability of information constructed by their government due to the lack of transparency in disseminating information on the outbreak (7).

According to Kasperson et al., many factors affect individuals' perception of risk, such as scientific information, interpersonal communication, cultural beliefs, and social interactions (8). An individual's response to a particular risk shapes their public perception of that risk itself. Risk is defined as "the product of the probability of an event occurring times the magnitude of potential consequences or impacts of that event" (9). The previous study documented that social media played a crucial role in forming an individual's risk perception of Middle East Respiratory Syndrome (MERS) because it was a useful tool in obtaining infectious disease information during an outbreak (10). It was documented by Balkhay et al. that the Saudi public had shown mistrust in the announcements of the Swine Flu outbreak by the Ministry of Health in the past (11). However, the public believed that not all cases could be detected (11). During outbreaks of infectious diseases, governments and public health officials inform the public about the situation and its risks (11, 12). They would use different media outlets such as television, newspapers, and social media to impact the publics' risk perception of these diseases and not merely to influence preventive behaviors and cognitive thought processes (12). Song et al. showed that people tend to positively share factual information and preventive measures regarding diseases on social media (13). Nevertheless, they can also express negative emotions and information resulting from their inner anxieties and fears. Intensive use of social media promotes shaping the public's risk perceptions of infectious diseases (13).

The current pandemic gives us a great opportunity to explore the factors that build public behavior and their adaptation of risk reduction measures (14). The risk perception and individual's subsequent behavior are complex and affected by multiple psychological and cultural factors (15). There are also rising concerns about COVID-19, information communicated on social media, and its impact on risk perception. This study builds on the previous study by Choi et al. in South Korea to yield additional insights into understanding the impact of social media on risk perceptions during an infectious outbreak (10). This study aims to determine the role of social media and its impact on the risk perceptions of the COVID-19 among the general population in Saudi Arabia. Understanding how social media relates to COVID-19 risk perceptions will help to facilitate future effective risk communications strategies, especially when faced with emerging public health threats.

Materials and methods

This was a cross-sectional study, and participants were recruited using different social media outlets between August to October 2020. This was the peak period of the pandemic. The survey was delivered through the Qualtrics platform and was delivered in English and Arabic. A convenience sampling technique was used to recruit participants to the study. An unrestricted self-selected survey link was posted on several social media platforms (WhatsApp, Facebook, and Twitter), and in response, 2,687 participants answered the survey. An unrestricted, self-selected survey is usually open to everyone to participate (16). Only Saudi Arabian residents who are over the age of 18 years old were able to participate in answering the survey. The face validity of the questionnaire in this study was determined by three faculty members within a similar discipline. The pilot respondents offered valuable feedback on the content of the questionnaire, and accordingly, unclear questions were modified. The questionnaire consisted of demographic information, aspects of risk perception, social media, and self-efficacy. The questionnaire was adapted from the previously validated and published study (10). A detailed description of each component is included in the following sections.

Measurement

Risk perception

Risk perception was created using a Five-point, Likert scale with 1 as extremely unlikely and 5 as extremely likely. Two questions were asked to evaluate how much they agreed with the following questions; how likely do you think it is that you will be directly and personally affected by coronavirus/COVID-19 and how likely do you think it is that your friends and family will be directly affected by COVID-19. Mean values were created for these two questions in order to construct the index for risk perception. Mean = 3.55, *SD*: 0.82.

Social media

Social media exposure was assessed by inquiring about how often over the previous months they were exposed to news and information about COVID19 on social media, such as Facebook, Twitter, and WhatsApp. This was measured on a Five-point Likert scale with 1 as never and 5 as very often. Mean = 4.42, *SD*: 0.73.

Self-efficacy

Self-efficacy was measured by using 10 questions on a Five-point Likert scale with 1 as almost never and 5 as almost always. Participants were asked about mandatory standard operating protocols to avoid contracting COVID-19. Mean values were created by using these 10 questions to construct the self-efficacy index. Mean = 4.15, *SD*: 0.56.

Confounders

Certain sociodemographic variables were used as confounder variables. Age was categorized into the following categories: <20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, and 60 years and above. Gender (male, female) and marital status (single, ever married) were categorized into binary variables. Education was categorized into high school and less, bachelor and individuals with graduate. Employment status was categorized into employed, unemployed, self-employed, retired, and student; and lastly income was categorized into individuals earning <4,000 Saudi Riyal (SR), 4,000 to < 8,000 SR, 8,000 to <12,000 SR, and ≥12,000 SR.

Statistical analysis

Hierarchical linear regression was used to explore the research hypothesis. Followed by socio-demographics, social media variables, self-efficacy, and attitude variables were entered into the simultaneous blocks. Dummy variables were created for age, employment, education, and income categories. An interaction term between social media and self-efficacy and social media and attitude were also created by using the standardized main effect variables. This was done to avoid multicollinearity between the interaction terms and their parent parts.

TABLE 1 Sociodemographic characteristics of study participants (*N* = 2,680).

Sociodemographic	Frequency (%)
Age	
<20 years	166(6.2)
20–29 years	1,005(37.4)
30–39 years	937(34.9)
40–49 years	371(13.8)
50–59 years	145(5.4)
60 years	55(2.0)
Gender	
Male	1,277(47.6)
Female	1,403(52.3)
Income*	
<4,000	920(34.3)
4,000- <8,000	334(12.4)
8,000- <12,000	388(14.5)
>/=12,000	615(22.9)
Marital status	
Single	1,241(46.3)
Married	1,439(53.7)
Education	
High school and less	697(26.0)
Bachelor's	1,595(59.4)
Graduate and postgraduate	388(14.5)
Employment	
Unemployed	611(22.8)
Employed	1,192(44.4)
Self-employed	77(3.1)
Retired	93(3.5)
Student	707(26.3)

*missing data.

Results

Table 1 demonstrates the sociodemographic characteristics of study participants. The mean age of participants was 32.5 (*SD*: 10.09), more than three quarters were of age 20–39 (72.1%), more than half were women (52.3%), less than one third were earning 12,000 and more Saudi Riyal (22.9%), were married (53.7%). Nearly half were employed or self-employed (47.5%) and more than half had bachelor's degree (59.4%).

Mean risk perception was 3.55 (*SD*: 0.82), mean social media exposure was 4.42 (*SD*: 0.73), and mean self-efficacy score was 4.15 (*SD*: 0.56). In the first block of hierarchical linear regression, gender, monthly income, and marital status had a significant relationship with risk perception. Male gender, individuals earning 4,000–8,000, 8,000–12,000, and above 12,000, employed individuals compared to the female gender and those who are earning <4,000 Saudi Riyal had positive and significant relationship with the risk perception (β: 0.044, p-value: 0.035 and β: 0.051, p-value:0.041, β: 0.108 p-value: < 0.001, β: 0.119 p-value: < 0.001), respectively. While single individuals had a negative relationship with risk perception (β: -0.049, p-value: 0.043).

In the second block, social media was positively associated with the risk perception indicating that individuals exposed to social media had higher risk perception (β: 0.096, p-value < 0.001). In the third block, self-efficacy was significantly but negatively associated with the risk perception, indicating that individuals who were self-efficient were less likely to perceive the risk for COVID-19 (β: -0.096, p-value < 0.001). We could not find any interactive effect of social media and self-efficacy on risk perception (Table 2).

TABLE 2 Hierarchical linear regression model predicting risk perception toward Coronavirus disease 2019 (COVID-19) ($N = 2,680$).

Block 1	**risk perception**
Age	
<20 years(Ref)	
20–29 years	0.009
30–39 years	0.007
40–49 years	−0.005
50–59 years	0.007
60 years	−0.021
Gender (1 = male, 0 = female)	0.044*
Education	
High school and less (Ref)	
Bachelor's	−0.017
Graduate and postgraduate	−0.001
Income	
<4,000 (Ref)	
4,000- <8,000	0.051*
8,000- <12,000	0.108***
>/=12,000	0.119***
Employment	
Unemployed (Ref)	
Employed	−0.006
Self-employed	−0.042
Retired	−0.039
Student	−0.021
Marital status (1 = single, 0 = married)	−0.049**
Incremental R^2 (%)	3.3%
Block 2	
Social media	0.096***
Incremental R^2 (%)	0.9%
Block 3	
Self-efficacy for COVID-19	−0.096***
Incremental R^2 (%)	0.9%
Block 4	
Social media* Self-efficacy for COVID-19	0.005

*p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001.

Discussion

The current study investigates demographic factors and social media's influence on the Saudi public's risk perceptions during the COVID-19 pandemic. The study aimed to understand the risk perceptions as it is critical for virus prevention and control of infections. The survey results confirmed that the risk perception is associated with various sociodemographic factors and social media. The study reported a key finding of higher risk perceptions among individuals with higher exposure to social media. It is in line with the previous research that documented that social media exposure was positively related to forming higher risk perceptions of South Korean individuals during the MERS outbreak (10). It has been previously suggested that people obtain information from media outlets during outbreaks, which impacts their risk perceptions of infectious diseases (17) and significantly improves preventive behaviors through self-relevant emotions (fear and anger). However, social media exposure to COVID-19 information also is associated with anxiety (18). A study reported that the use of social media is linked to the risk perception and self-efficacy, which in turn is associated with the preventive behavior during pandemics (19).

While the COVID-19 pandemic was looming, public health officials in Saudi Arabia selected optimal means of communication channels to disseminate information on the COVID-19 virus. The Ministry of Health and other government agencies are very active in using different social media platforms to make people aware of the virus and enforce protective behaviors. Such activities could have influenced the high-risk perceptions among the Saudi population, given that there was a high social media dependency of the public during the COVID-19 outbreak. The risk perception significantly impacts trust in the government and self-efficacy; this association was effective and helpful in avoiding virus exposure when social media was used for COVID-19 information (20).

The WHO recommended that communication outbreaks focus on gaining public trust and confidence, and governments must have transparency in disseminating information (6). Sociodemographic factors, such as male gender, individuals earning 4,000–8,000, 8,000–12,000, and above 12,000, employed individuals compared to the female gender, and those earning <4,000 Saudi Riyal had a positive and significant relationship with the risk perception. However, these results are consistent with a recent risk perception study in Iran; they found that men, being well-educated and married, believed they were more susceptible to the risks related to COVID-19 (21). In contrast, a large survey of individuals from ten countries indicates that men showed lesser risk perception (22). In particular, women in this study appeared to have lesser risk perceptions than men. Higher risk perceptions among men could be linked to the recent epidemiological data showing a greater incidence rate and severity of COVID-19 among men than women (23). One possible explanation is that the men may believe they are more susceptible to being infected. This is probably due to Saudi's cultural context that men occupy blue-collar jobs. Hence, they are more exposed and susceptible to the virus when on the job. On the contrary, these results are different from recent studies that indicated women had higher health risk perceptions of being infected with COVID-19 than men (24, 25). Women were more fearful about the debilitating consequences of COVID-19 than men, whereas men showed more aggressive behavior and self-efficient toward the COVID-19 pandemic (26). The previous studies have also documented that women perceived themselves as more susceptible to environmental risks than men (3).

The present study shows that participants with high education and income, being employed and married, had higher levels of perceived risk perceptions. Additionally, recent data also show that the higher education status was significantly associated with 72% lesser perceived high-risk against COVID-19. Several studies also reported similar findings that highly educated individuals carry out more protective and preventive behaviors against different pandemics, which is highly associated with other factors, such as attitudes and influences on their risk perceptions (27–29). Also, married individuals are more protective and worry about their families being infected. Meanwhile, it can be observed that employees whose working have a high-risk perception than those unemployed as they have more exposure when on the job.

The present study found that most respondents used social media very often. The International Telecommunication Union has noted that Saudi Arabia is one of the top ten countries using information and communication technology (30). There have been significant increases in social media users in Saudi Arabia over the past few years, reaching 23 million users, an amount equal to 70% of the population (31). Facebook is the most popular social media platform in the Kingdom, with over 15 million active monthly users. Instagram came in second with 12 million active monthly users. Additionally, Twitter had 11.27 million active monthly users as of January 2019 (31). According to the Ministry of Communications and Information technology in Saudi Arabia, approximately 18.3 million of the population use social media networks (Ministry of Communication and Information Technology, 2019).

During the COVID-19 pandemic and lockdowns, it not only helps in disseminating news but also information related to the virus, personal experiences, and perspectives with each other instantaneously (32). However, according to WHO, the current pandemic is also an "Infodemic," where there is abundant information broadcasted about COVID-19 (33). Similarly, a study reported that frequent online information or social media usage leads to cyberchondria, information overload, or overconcern among individuals (34) timely and reliable dissemination of disease-related information. Developing countries usually have limited surveillance systems and resources to timely monitor infectious diseases outbreaks. Therefore, the social media act as a health networking mechanism to prevent the spread of disease in the community (19).

To date, there are no studies on the risk perception and its related factors to COVID-19 in Saudi Arabia, particularly the impact of social media on risk perceptions of a health pandemic. This study was carried out in Saudi Arabia during the highest recorded of COVID-19 patients; very high attention was given to the outbreak in the country. The results of risk perceptions and perceived susceptibility may differ with the decline in numbers and the less attention given to COVID-19 in the media. The study's major strength is that the survey was conducted in an ongoing pandemic. The study contributes to a better understanding of people's behavior during outbreaks and pandemics. The study also includes participants from various demographic categories. There are several limitations of the present study, which are worth to be mentioned. First, the study was conducted online, and all the data were based on self-reported measures, which could be under- or over-reported. Second, this was a cross-sectional study and only captured the snap short; therefore, we cannot comment on the causal relationship between the variables. A longitudinal prospective approach should be considered in future studies to make a stronger causal association. Third, this study used only a single variable to measure social media exposure. Although a single item cannot determine and cover the complete social media impact, as many individuals nowadays use various social media platforms. These platforms could have different influences, allowing users to create and distribute information. Therefore, it is worthy of examining the impact of all social media platforms separately and their influence on the risk perception. The results cannot be generalized because an unrestricted self-selected survey that is a form of convenience sampling, was used for this study.

Conclusion

The current study results show that social media exposure to COVID-19 information has a positive impact on shaping an individuals' risk perception. Especially during lockdown, with easy accessibility of social media increases the dissemination of information about health issues. The study also suggests that there is a need for public officials and policymakers to develop effective communication strategies through risk communication campaigns targeted at women, individuals with lower socioeconomic status, and those who are single as they showed a negative relationship with the risk perception. It is essential that every country communicates with the general public about the disease's risks and provides them with basic information on disease transmission, management, high-risk practices, and protective behavioral measures during pandemics (35). Communication dramatically improves the general public's awareness and reduces the transmission of pandemic diseases in the past (35). It is suggested that disseminating clear information on disease transmissions and protective preventive measures to the public can significantly reduce transmissions (35).

During the outbreaks and pandemics, social media usage for the effective communication of risk susceptibility is important for public health and safety (36). Likewise, every individual's responsibility is to take personal precautions to decrease the spread of COVID-19 and understand that their own's decision has a huge impact on other individuals (37). An extension of this study should be considered to further identify factors and the impact of social media on risk perception and status of self-efficacy in a post-vaccination state. There might be a change of perception after the restrictions are lifted, but new variants are still emerging from different countries.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by IRB of the Jeddah Research Health Affairs for science and technology. The participants provided their written informed consent to participate in this study.

Author contributions

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

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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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EDITED BY
Oyelola A. Adegboye,
James Cook University, Australia

REVIEWED BY
Tanmoy Bhowmik,
University of Central Florida,
United States
Shaniko Kaleci,
University of Modena and Reggio
Emilia, Italy

*CORRESPONDENCE
Lourdes García-García
garcigarml@gmail.com

†PRESENT ADDRESS
César Arturo Méndez-Lizárraga,
Departamento de Epidemiología,
Secretaría de Salud de Baja California,
Mexicali, Mexico

‡These authors have contributed
equally to this work and share first
authorship

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Evaluating the impact of mobility in COVID-19 incidence and mortality: A case study from four states of Mexico

César Arturo Méndez-Lizárraga[1†‡], MLucía Castañeda-Cediel[2‡], Guadalupe Delgado-Sánchez[1], Edith Elizabeth Ferreira-Guerrero[1], Leticia Ferreyra-Reyes[1], Sergio Canizales-Quintero[1], Norma Mongua-Rodríguez[1], Norma Tellez-Vázquez[1], María Eugenia Jiménez-Corona[3], Kathryn Bradford Vosburg[4], Omar Y. Bello-Chavolla[5] and Lourdes García-García[1]*

[1]Centro de Investigación Sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, Mexico, [2]Posgrado en Geografía, Facultad de Filosofía y Letras, Universidad Nacional Autónoma de México, Mexico City, Mexico, [3]Departamento de Epidemiología, Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico, [4]Institute for Global Health Sciences, University of California, San Francisco, San Francisco, CA, United States, [5]Dirección de Investigación, Instituto Nacional de Geriatría, Mexico City, Mexico

Introduction: The COVID-19 pandemic in Mexico began at the end of February 2020. An essential component of control strategies was to reduce mobility. We aimed to evaluate the impact of mobility on COVID- incidence and mortality rates during the initial months of the pandemic in selected states.

Methods: COVID-19 incidence data were obtained from the Open Data Epidemiology Resource provided by the Mexican government. Mobility data was obtained from the Observatory for COVID-19 in the Americas of the University of Miami. We selected four states according to their compliance with non-pharmaceutical interventions and mobility index. We constructed time series and analyzed change-points for mobility, incidence, and mortality rates. We correlated mobility with incidence and mortality rates for each time interval. Using mixed-effects Poisson models, we evaluated the impact of reductions in mobility on incidence and mortality rates, adjusting all models for medical services and the percentage of the population living in poverty.

Results: After the initial decline in mobility experienced in early April, a sustained increase in mobility followed during the rest of the country-wide suspension of non-essential activities and the return to other activities throughout mid-April and May. We identified that a 1% increase in mobility yielded a 5.2 and a 2.9% increase in the risk of COVID-19 incidence and mortality, respectively. Mobility was estimated to contribute 8.5 and 3.8% to the variability in incidence and mortality, respectively. In fully adjusted models, the contribution of mobility to positive COVID-19 incidence and mortality was sustained. When assessing the impact of mobility in each state compared to the state of Baja California, increased mobility conferred an increased risk of incident positive COVID-19 cases in Mexico City, Jalisco, and Nuevo León.

However, for COVID-19 mortality, a differential impact of mobility was only observed with Jalisco and Nuevo León compared to Baja California.

Conclusion: Mobility had heterogeneous impacts on COVID-19 rates in different regions of Mexico, indicating that sociodemographic characteristics and regional-level pandemic dynamics modified the impact of reductions in mobility during the COVID-19 pandemic. The implementation of non-pharmaceutical interventions should be regionalized based on local epidemiology for timely response against future pandemics.

KEYWORDS

mobility, COVID-19, incidence, correlation, Mexico, change-point, mortality

Introduction

During the first months of the SARS-CoV-2 pandemic, Mexico concentrated 8.6% of confirmed cases across the Americas by July 2020, a region that represented 25% of the world cases (238,511 cases in Mexico and 2,746,277 in Latin America) (1). The first three cases of SARS-CoV-2 in the country were confirmed on February 28th, 2020 (2), a month after the World Health Organization (WHO) declaration of the epidemic as a Public Health Emergency of International Concern (3). As the world faced this novel pathogen, no specific therapeutics and vaccines were available, forcing the global community to appeal to nonpharmaceutical interventions (NPIs) (4, 5).

The Mexican government officially published public health mitigation strategies by late March (March 24th, 2020) (6); days later, the Consejo de Salubridad General (General Health Council, GHC) formally recognized the pandemic as a national health emergency (7). This occurred when more than 1,000 cases and 28 deaths of COVID-19 had been confirmed, and ongoing local transmission took place in the country (8, 9). A combination of NPIs, titled Jornada Nacional de Sana Distancia (National Program of Safe Distance, NPSD), centered around the suspension of non-essential activities to slow viral transmission, hospitalizations, and fatalities, was carried out starting March 30th, 2020 (10) resulted in a decline in population mobility during the following weeks in all 32 states. Other interventions included the promotion of physical distancing and handwashing during the early stages (11, 12). As outlined by WHO's guidance, a critical component of national and regional response to a pandemic is timely and effective interventions, such as restricting the movement of people and goods, which allow for time to implement preparedness activities and slow viral transmission (4).

The NPSD concluded on May 30th as the authority concerning health policies for SARS-CoV-2 mitigation, and guidance for the return to non-essential activities (and thus population mobility) was transferred from the federal government to state governments for the new normality (11, 12). National Health authorities developed an epidemiological risk tool: semáforo epidemiológico (epidemiological traffic light), based mainly on transmission, hospitalizations, fatalities, and hospital bed availability to guide state decision-makers (13). NPIs continued to be encouraged by all health authorities throughout the new normality (14).

The country's initial response to COVID-19 presents an opportunity to assess the impact of NPIs on mitigating health damages from the pandemic and provides a unique opportunity for future pandemic preparedness and readiness vs. potential emerging and re-emerging pathogens. As outlined further in the present work, multiple studies have explored the relationship between population mobility and the trajectory of the pandemic, the first being very variable among reports; daily mobility (measured by Google Maps and Apple), average mobility across time segments, mobility characterized by place of occurrence (example: house, supermarket, public transport, recreational spaces), internal mobility within a city, mobility between regions or states and international mobility (15–26). In this study, we studied four states (Baja California, Nuevo León, Jalisco, and Mexico City) based on mobility, compliance to NPIs, and metropolitan area. We conducted a three-step analysis in four states to evaluate the impact of mobility on COVID-19 incidence and mortality using (1) a change point analysis, (2) correlation analysis to examine the relationship between mobility and incidence and mortality rates, and (3) adjusted mixed-effects Poisson models, for evaluation of the impact of reductions in mobility on the incidence rate of positive COVID-19 cases and COVID-19 deaths.

Materials and methods

Setting

Mexico's territory includes 1,960,189 km2 (10.2% of Latin America's extension) and has 126,014,024 inhabitants, with a

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population density of 64.28 inhabitants/km2 (27). Out of thirty-two states, four were selected for this study: Baja California, Nuevo León, Jalisco, and Mexico City; all comprise five of the top fifteen metropolitan areas in the country (28). Figure 1 shows their location and relevant data.

The Ministry of Health coordinates the health system, which is fragmented into several subsystems that organize, provide, and regulate most of its services. The three main components operate in parallel and include: (a) multiple employment-based social insurance schemes, (b) public assistance services for the uninsured, and (c) a private sector composed of service providers and insurers (29).

Data and sample selection

Open data on COVID-19 cases in Mexico were drawn from the General Directorate of Epidemiology repository for incidence and mortality rates (30). In the case of mobility, data was extracted from the Observatory for COVID-19 in the Americas of the University of Miami (adapted from the Oxford Government Response Tracker, OxCGRT 5.0, and from Google population mobility) for Mexico and its thirty-two states (31). Google provided mobility measurements on travel to workplaces, supermarkets and pharmacies, parks and plazas, public transportation stations, shops, and places for recreation, excluding mobility from the residential category. The mobility index reflects the seven-day moving average for mobility data on visits to the mentioned sites instead of a daily value. This average is a more stable indicator and reflects the overall trend regardless of small daily fluctuations (31). We used a daily public policy index (PPI) that measures compliance to non-pharmaceutical measures (31) and date of implementation (graded on a 0–100 scale), and population mobility (reported as a change in percentage based on early 2020 mobility). All states were drawn on a Cartesian plane and categorized into four groups based on the median in mobility and PPI index (low mobility and

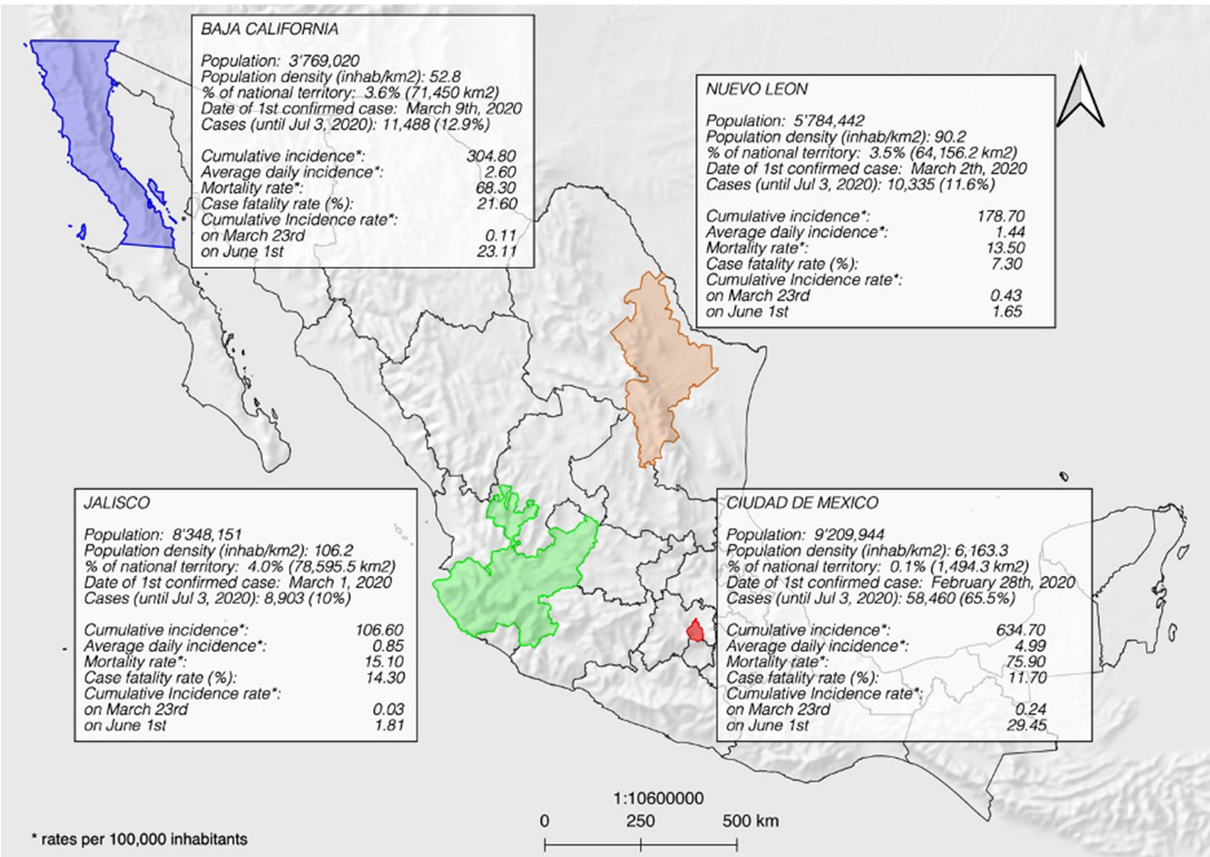

FIGURE 1
The geographical location of the states studied and general characteristics of the COVID-19 pandemic, Mexico. The map shows the population of each state, its density per km^2, the percentage it represents from the country's territory, the date of the first confirmed cases, and confirmed cases until July 3, 2020. It also shows cumulative incidence, average daily incidence, the mortality rate per 100,000 habitants, case fatality rate, and the cumulative incidence rate on March 23rd, 2020 (beginning of the National Program of Safe Distance) and June 1st, 2020 (beginning of the New Normality).

low PPI, low mobility and high PPI, high mobility and high PPI, high mobility, and low PPI) (31). The state with the largest metropolitan area from each group was selected, representing different adherence to non-pharmaceutical interventions as described above. Because restrictions on population mobility were implemented during the first weeks of the pandemic, the present study aims to exhibit the impact of these restrictions in the early stages of viral transmission (the first confirmed case in Mexico) up to the first week after restrictions were eased (July 3rd, 2020). An exploratory analysis was made for each state's epidemiology. Analyzed data is available in an external repository (32).

Change-point analysis

Time series for the independent variable (mobility) and dependent variables (incidence and mortality) were constructed. A change-point analysis utilized the R package *ecp* (33) for the three described variables from each state in RStudio. The ecp package performs a retrospective analysis of an entire sequence that estimates both the number of change points and the places in time in which they occur. It can perform time series on either univariate or multivariate parameters without a priori knowledge of the number of change points, working without any assumptions about the nature of change or any distribution hypothesis beyond the existence of the absolute moment, for some (0, 2)*. Estimation is based on hierarchical clustering.

We used a divisive algorithm (*e-divisive*) that has shown consistent estimates of the number and location of change points. Divisive estimation sequentially identifies change points *via* a bisection algorithm and can detect any distributional change within the data. The multiple change points are estimated by iteratively applying a procedure for locating a single change point. A new transition point location is calculated to divide an existing segment at each iteration. As a result, the progression of this method can be diagrammed as a binary tree.

Additionally, the statistical significance of an estimated change point is determined through a permutation test. Specifications for running the analysis included the number of iterations (199) and the level of statistical significance (set at $\leq$0.05). The time complexity of this method is ϑ(kT2), where k is the number of estimated change points, and T is the number of observations in the series (34).

The ecp package was selected due to a better fit of the data from the sample, although there are other packages for change-point analysis (35).

Estimating the effects of mobility on incidence and mortality

We created time intervals based on incidence and mortality change-points. For incidence rates, the interval was constructed taking 12 days before its change-point, considering the mean incubation period for SARS-CoV-2 and delays in seeking medical attention. Then, the endpoint of each segment was fixed 14 days after the change-point in incidence. Finally, we used the same approach for mortality but with a difference of 28 days (36, 37). Afterward, we estimated the impact of mobility on both incidence and mortality by calculating Spearman's rank-order correlation coefficient for each segment (38). As observed in the Supplementary materials, intervals include both before and after tendencies based on identified change-points for all analyzed variables and Spearman's correlation coefficient.

To evaluate the impact of reductions in mobility on the incidence rate of positive COVID-19 cases and COVID-19 deaths in all states being assessed, we fitted a mixed-effects Poisson regression model fit by maximum likelihood using the Laplace Approximation, which took the state of origin and date of symptom onset as random intercepts to account for the dependence of COVID-19 rates across time and regional-level pandemic dynamics, incorporated log-transformed population as the regression offset. Next, we obtained incidence rate ratios (IRR) by exponentiating the beta coefficients obtained from the mixed-effects models. All models were adjusted for the number of physicians and available hospital beds per 10,000 inhabitants as a proxy of the impact of the availability and access to medical services in the evaluated states and the percentage of the population living in poverty (39). To assess the impact of mobility in each state, we fitted a mixed-effects Poisson model with a random effect in the date of symptom onset and an interaction effect with the state of case identification for both COVID-19 incidence and mortality. All models were evaluated using residual diagnostics, evaluation of overdispersion, and assessment of the influence of random effects in the model. Models were selected by minimization of the Bayesian Information Criterion.

This study was ruled "Exempt from Review" by the "Ethical Commission" of the Instituto Nacional de Salud Pública (approval number PT651) because the database is public.

Results

Before the NPSD, mobility decreased across the four states, reaching its lowest levels in late April (Figure 2). Mexico City reduced its mobility by close to 60%. It maintained the smallest percentages compared to the rest of the states, which reached their lowest levels between−40 and−50% in early April. Halfway throughout the month, there was an increase in mobility that coincided with the first ending date of the NPSD established by the GHC (6) and national holidays from early April in some states (Table 1). After reassessing the spread of SARS-CoV-2, federal health authorities extended the campaign until the end of May 2020 (40), but mobility continued to increase steadily during the month. The change-point analysis in

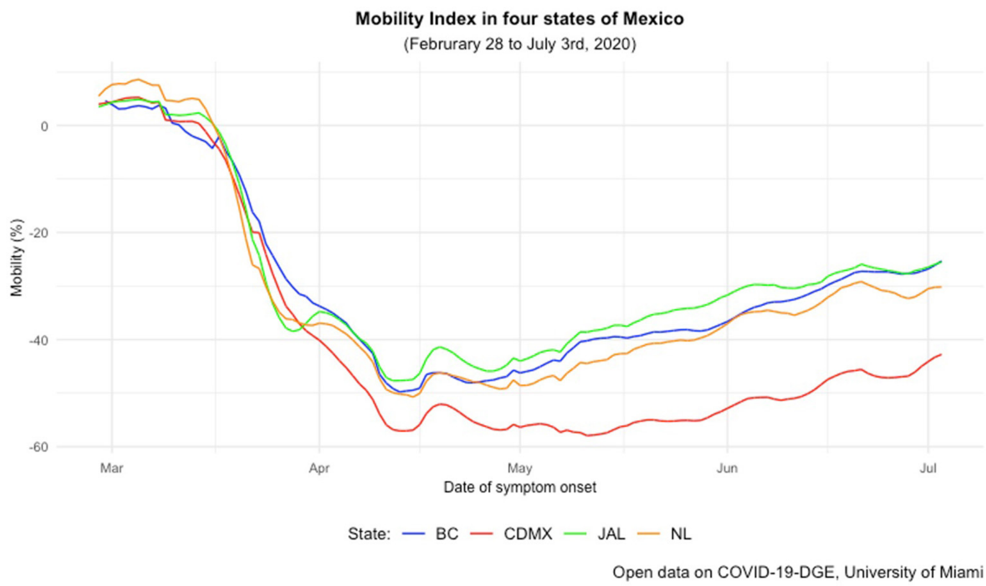

FIGURE 2
Mobility index in four states from February 28th to July 3rd Mexico, 2020. The horizontal axis shows the period since the confirmation of the first COVID-19 case in Mexico, from February 28th, 2021, to July 3rd 2021. The vertical axis shows the percentage change in the mobility index documented by Google in a 10 to–60% range. The blue line represents the mobility index across the specified period in Baja California, the red line Ciudad de Mexico, the green line Jalisco and the yellow line Nuevo Leon. Data were retrieved from the Observatory for COVID-19 in the Americas, University of Miami.

mobility revealed shifts in all four states during holidays (Table 1; Supplementary Figures 1–8).

It is worth mentioning that many holidays are celebrated in April and May, like Labor Day and Easter, the latter being one of many holidays associated with the Christian religion. On the other hand, national festivities such as Cinco de Mayo, which commemorates a victory over French invaders in 1862, and Mother's Day, take a considerable part in celebrations across the country with family and friends (41, 42).

Starting June 1st, a gradual return to non-essential activities was guided and regulated on a state level (11), based on the traffic-light epidemiological risk tool (13, 14). As the new normality began, all states were on a red light, meaning that no non-essential activities were to be reinitiated until mid-June when Nuevo Leon and Jalisco changed to an orange light (43). However, mobility rose gradually in all four states across the new normality. The change-point analysis (Supplementary Figures 1–8) revealed a mobility shift during the Holy Week holiday weekend (April 5–11) in all four states. Another change in mobility that coincided with culturally important dates happened during Mother's Day weekend except in Mexico City. As mobility increased gradually over the following weeks, multiple change-points were identified across May and June, even after the new normality (Supplementary Figures 1–8).

During the first weeks after the first confirmed case, Baja California and Mexico City sustained an upward trend in their incidence rate well before mobility reached its lowest levels (Figure 3); both continued to increase during the following weeks after March 23rd. After experiencing similar incidence rates, Mexico City's escalated by mid-April, reaching its peak in June (14 cases per 100,000 habitants), while Baja California's increased on a lower scale across May and June (up to 6 cases per 100/000 habitants). Both states' mobility index increased gradually during the following months (Figure 2). Jalisco and Nuevo Leon had a lower incidence and mortality rates as mobility decreased (Figures 3, 4). Both states' incidence rates started to rise until mid-May, parallel to both mobility's increasing trends as seen in their respective Spearman's correlation coefficients (Table 2). Then, Nuevo Leon's incidence rate continued to escalate (up to 8 cases per 100,000 habitants), surpassing Baja California's and closing in on Mexico City's. At the same time, Jalisco maintained a steady and lower rate during the remaining period, regardless of the sustained rise in mobility (Figure 3).

We identified change points in incidence 12–13 days after the original NPSD ending in Mexico City and Baja California. However, these were not preceded by changes in mobility near the dates. On the other hand, change-points in incidence in Jalisco and Nuevo León did come after change-points in mobility (8–16 days) (Supplementary Figures 1–4).

Both Baja California's and Mexico City's mortality rates had a similar trajectory. Rates rose even though mobility reached its lowest levels in both territories (Figure 4). Mexico

TABLE 1 Critical dates during the first months of the pandemic in Mexico (2020).

Critical dates during the first months of the pandemic in Mexico (2020)

February 28th	First confirmed cases in Mexico.
March 23rd	NPSD begins*
March 27th	COVID-19 is recognized as a severe disease that requires extraordinary measures and needs to be prioritized all over the country *
March 30th	A national health emergency is declared due to the SARS-CoV-2 pandemic*
April 5-11	Holy week holidays
April 19th	First ending date of the NPSD*
April 21st	Extension of the NPSD (up to May 30th)
May 1st	National holiday: Worker's Day
May 5th	National holiday: Cinco de Mayo (Battle of Puebla)
May 10th	National holiday: Mother's Day
May 30th	Ending of the NPSD
June 1st	Beginning of the "New Normality," the epidemiological light is introduced. All states are in red (non-essential activities continue to be suspended)
June 15th	The epidemiological light changes to orange in Nuevo Leon and Jalisco. Ciudad de México and Baja California remain in red.

*Determined by the General Health Council. Besides critical dates signaling the evolution of the COVID-19 pandemic and the response from the Mexican government to it, the table mentions key dates from Mexico's culture, traditions, and holidays.

City's reached its highest levels during May (1.7 deaths per 100,000 habitants), experimenting a steady decline during June, while Baja California's oscillated across the whole period on a lower scale (between 0.5–1.2 deaths per 100,000 habitants). During the first weeks, no increases in mortality rates were observed for both Jalisco and Nuevo León (Figure 4). Like both states' incidence rate trajectories, mortality rose as mobility and incidence surged throughout late May and June. Mortality rates in these two states attained similar values by the end of the study period (0.5 deaths per 100,000 habitants). By the end of the period analyzed, Baja California and Mexico City had at least four times the mortality rate compared to Nuevo Leon and Jalisco (68.3 and 75.9 vs. 15.1 and 13.5 deaths per 100,000 habitants). Regarding change-points, all four states had similar differences in days between change points in mobility and their respective mortality rate; differences ranged from 20 to 37 days and were present on most of the dates (Supplementary Figures 5–8).

Based on the construction of time intervals from change-points in incidence, positive correlations were obtained for incidence and mobility in Jalisco and Nuevo León, the first one having an overall higher magnitude. On the other hand, Baja California and Mexico City had mixed results for incidence and mobility, with both negative and positive correlations across their intervals, with no apparent pattern between both variables (Table 2; Supplementary Figures 9–12). Regarding mortality and mobility, correlations were also positive for Jalisco and Nuevo León, excluding the initial intervals where mobility experimented its initial decrease. As for Baja California and Mexico City, no pattern was identified as seen by mixed results in coefficients for mortality and mobility (Table 2; Supplementary Figures 13–16).

Overall, dependent variables (incidence and mortality rate) had an ascending change in their trajectories after their respective change-points, reinforcing the influence of mobility on our incidence and mortality hypothesis. This is not the case for Baja California and Ciudad de Mexico, as observed in their mobility and mortality trends (Supplementary Figures 13, 14), with changes in the opposite direction after their respective change-points and verified with Spearman's correlation coefficients.

When evaluating the mixed-effects Poisson model results, we identified that a 1% increase in mobility yielded a 5.2% increase in the risk of incident COVID-19 cases in all evaluated states. Mobility was estimated to contribute 8.5% to the variability in incident COVID-19 cases. For the case of COVID-19 mortality rates, we also identified a significant association between mobility and COVID-19 deaths, where a 1% increase in mobility was associated with a 2.9% increase in the risk of incident COVID-19 deaths. Nevertheless, the contribution of mobility was lower, representing 3.8% of the variability in COVID-19 mortality. In fully adjusted models, the contribution of mobility to positive COVID-19 incidence and COVID-19 mortality was sustained. Notably, in fully adjusted models, the percentage of the population living in poverty displayed a decreased risk for positive COVID-19 cases but an increased risk for COVID-19 mortality (Table 3). When assessing the impact of mobility in each state compared to the state of Baja California, we identified that increased mobility conferred an increased risk of incident positive COVID-19 cases in Mexico City, Jalisco, and Nuevo León. However, for COVID-19 mortality, a differential impact of mobility was only observed with Jalisco and Nuevo León compared to Baja California (Table 4).

Discussion

The challenge presented by the pandemic has required much more than treating a novel disease; it has demanded a social, economic, and political coordinated response (44) with many complexities deep-rooted in federated states, such as Mexico (45). NPIs, which aimed to slow viral transmission across societies, reduced population mobility globally (46).

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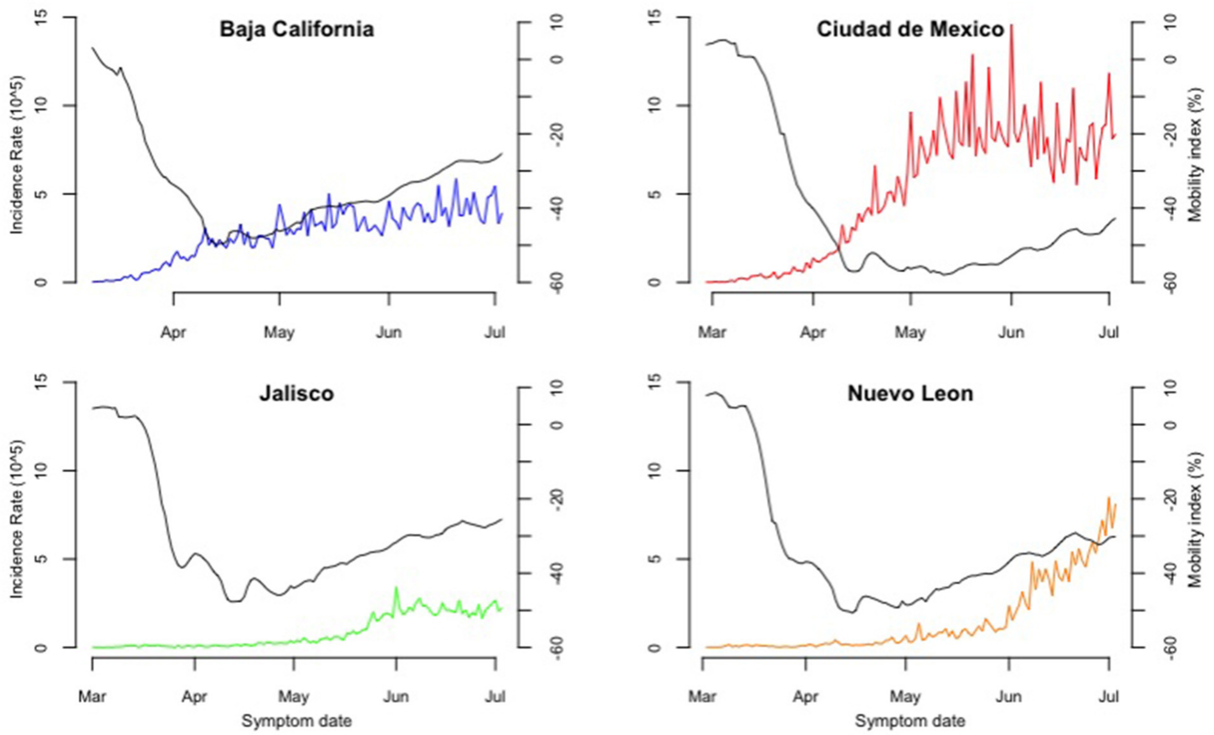

FIGURE 3
Incidence rate by symptom onset and mobility index in four states from February 28th to July 3rd, Mexico, 2020. The horizontal axis shows the period covered since the confirmation of the first COVID-19 case in Mexico, February 28th, 2021, to July 3rd 2021. The left vertical axis shows the incidence rate of confirmed cases per 100,000 habitants scale, and the right vertical axis shows the percentage change for mobility on a 10 to−60% range. The continuous black line represents the average daily mobility rate documented by Google. The colored line shows daily confirmed cases based on their date of symptom onset.

Nonetheless, NPIs implementation has required substantial changes in human behavior, resulting in heterogenous and mixed responses across different populations (15, 16, 45, 46).

Our study focuses on mobility and its correlation with morbidity and mortality in four states in Mexico. We found a significant association between mobility and incident COVID-19 cases and mortality rates using mixed-effects Poisson models. We identified that the contribution of mobility was lower for mortality (3.8%) than for incident cases (8.5%). Increasingly studies have shown that social determinants of health such as sociodemographic inequalities, differential health system capacities for critically ill patients across multiple health systems, general practitioners and nurses' ratio per inhabitant, knowledge, attitudes, and practices toward public health recommendations, in addition to the prevalence of chronic diseases impact on COVID-19 incidence and mortality rates (17, 47–54). Therefore, we adjusted all models for the number of physicians and available hospital beds per 10,000 inhabitants to proxy the impact of the availability and access to medical services in the evaluated states and the percentage of the population living in poverty. We identified that the contribution of mobility to positive COVID-19 incidence and COVID-19 mortality was sustained when adjusting for medical services and poverty. When we compared individual states with Baja California, we identified that increased mobility conferred an increased risk of incident positive COVID-19 cases in Mexico City, Jalisco, and Nuevo León. However, for COVID-19 mortality, a differential impact of mobility was only observed with Jalisco and Nuevo León compared to Baja California. This demonstrates that mobility had heterogeneous impacts on COVID-19 rates in different regions of Mexico, indicating that sociodemographic characteristics and regional-level pandemic dynamics modified the impact of reductions in mobility during the COVID-19 pandemic.

We also analyzed the correlation between mobility and COVID-19 incidence and mortality rates between the change points. This allowed us to demonstrate heterogeneity over time and across states. Findings suggest a similar pandemic course in two states, Jalisco and Nuevo Leon. In contrast, Baja California and Mexico City displayed a different trajectory.

While Mexico City and Baja California reduced their mobility by more than 40%, an upward trend of incidence and mortality rates was already in progress by the time mobility reached those levels, suggesting a late onset of NPIs in those

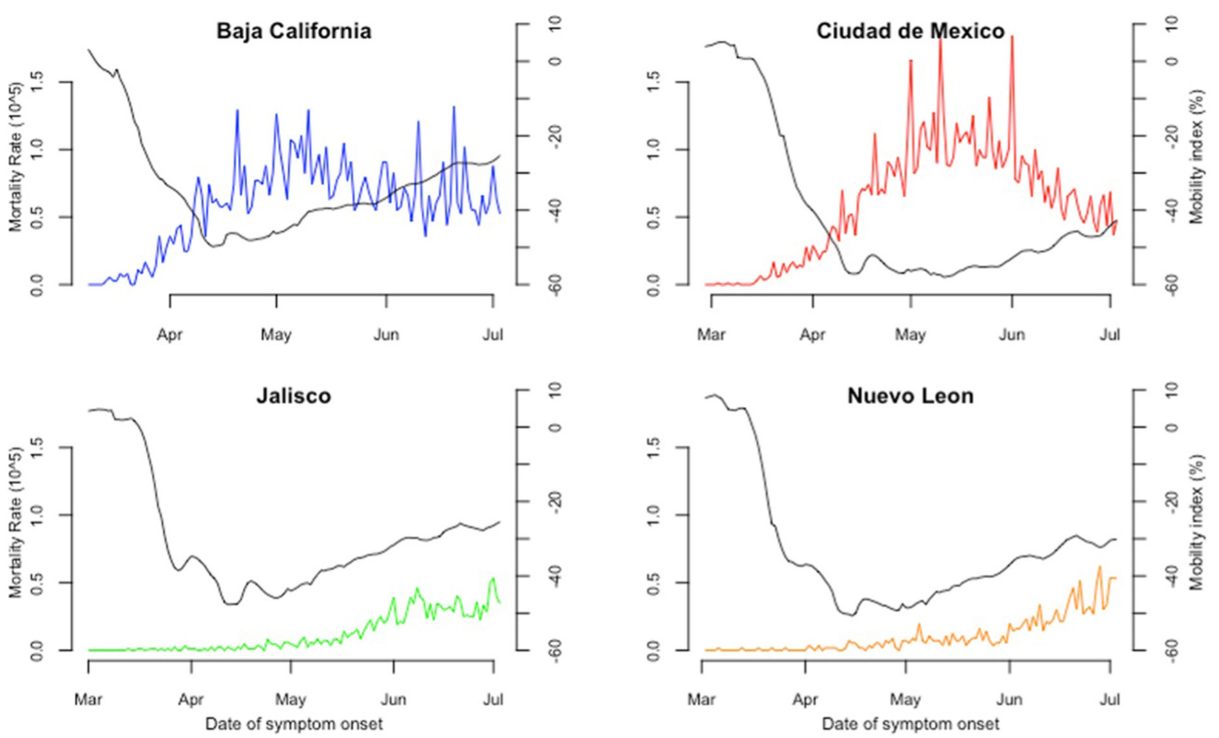

FIGURE 4
Mortality rate and mobility index in four states of Mexico from February 28th to July 3rd. The horizontal axis depicts the period covered since the confirmation of the first COVID-19 case in Mexico, February 28th, 2021, to July 3rd 2021. The left vertical axis shows the mortality rate, 0–1.5 confirmed COVID-19 deaths per 100,000 habitants, and the right vertical axis shows the percentage change for mobility in a 10 to–60% range. The continuous black line represents the average daily mobility rate documented by Google. The colored line shows daily confirmed cases based on their date of symptom onset.

two states. On average, incidence and mortality rates were at least 1.7 and 4.5 times higher in Mexico City and Baja California than in Jalisco and Nuevo Leon during the analysis period. Mobility analysis in Europe showed that countries with a delayed response had an 82% higher mortality rate and were forced to adopt a stricter lockdown, except in one case. Overall, countries had a difference of 11.4 days between 100 cases and their first change-point in mobility and more than 0.02 deaths per 100,000 inhabitants (18). Weaker correlations in the last weeks of the study period across the four states also suggest that decoupling between mobility and transmission occurred in the last weeks of the study period, consistent with the analysis made on numerous countries that documented a gradual decline of the relationship between mobility and transmission after strict control measure were eased in the initial stages of the pandemic, in which no data was reported on Mexico (55). Furthermore, early action allowed some countries to operate at a higher level of mobility during lockdowns without sacrificing public health. Results from published studies have shown that the effectiveness of lock-down measures, including the closure of businesses and schools, for COVID-19 containment depended largely on timely implementation and a clear distinction needs to be made when addressing this issue as physical distancing may be used interchangeably with lockdowns in other studies (19, 20).

As for mortality and mobility, correlations were positive in two of four states. Research from other countries on these two variables has yielded mixed results (18, 19, 21, 22); in this study, a significant correlation between decreased mobility and deaths was found for Jalisco and Nuevo Leon but not for Baja California and Mexico City. Positive correlations found in our study match with reports of excess mortality and mobility, which is a more objective and comparable way to assess the scale of the pandemic (56) and quantify the effects of mobility on COVID-19 cases (23).

Other authors have studied population density, which has been a predictor in the trajectory of SARS-CoV-2 epidemiology during community transmission (57, 58). In contrast, our data show that the least and most densely populated states (Baja California and Mexico City) sustained the highest incidence and mortality rates during the initial and later stages. It is worth noting that both Nuevo Leon and Baja California are border states with the United States of America and that Mexico City is the country's capital. Therefore, results could differ from other states not analyzed in this study, and further

TABLE 2 Spearman's rank correlation coefficients for mobility and incidence and mortality rates by time intervals from analyzed states in Mexico.

State		Time segment (2020)	Incidence change point	Spearman coefficient (Incidence and mobility		Time segment (2020)	Mortality change point	Spearman coefficient (Mortality and mobility
Baja California	1	March 17 to April 12	March 29	−0.86	1	March 11 to April 22	April 8	0.31
	2	March 27 to April 22	April 8	0.27	2	April 2 to May 14	April 30	−0.19
	3	April 8 to May 14	April 30	−0.05	3	April 25 to June 6	May 23	−0.19
	4	May 24 to June 19	June 5	−0.07				
Jalisco	1	April 8 to May 4	April 20	0.42	1	March 1 to April 13	March 30	−0.22
	2	April 18 to May 14	April 30	0.62	2	March 27 to May 8	April 24	0.21
	3	May 5 to 31	May 17	0.87	3	April 26 to June 7	May 24	0.5
	4	May 12 to June 7	May 24	0.68				
	5	May 20 to June 15	June 1	−0.09				
Nuevo León	1	April 22 to May 18	May 4	0.3	1	March 2 to April 15	April 1	−0.28
	2	May 23 to June 18	June 4	0.18	2	May 25 to 6	April 24	0.45
	3	June 13 to July 3	June 25	0.45	3	May 4 to June 15	June 1	0.41
Ciudad de México	1	March 25 to April 20	April 6	−0.35	1	February 28 to April 8	March 25	– 0.83
	2	April 8 to May 5	April 20	−0.18	2	March 18 to April 29	April 15	0.06
	3	April 19 to May 15	May 1	−0.23	3	April 8 to May 20	May 6	0.275
					4	May 14 to June 25	June 11	−0.13

Time segments were constructed based on mobility change-points; 12 days before change-points in incidence and 28 for mortality. Both periods for incidence and mortality ended after 14 days after their change-point date. Spearman's coefficients were calculated for both incidence and mobility and mortality and mobility in each state.

research is needed better to understand local epidemiology and transmission dynamics. In addition to the latter, it should be noted that both Jalisco and Nuevo Leon adopted stricter policies for physical distancing and COVID-19 containment compared to Mexico City and Baja California, as documented by Knaul et al. (59). This corresponds with the observed difference between these states and their respective mobility trajectory and COVID-19 epidemiology over the analyzed period in this study.

Furthermore, the adoption of staying-at-home varied through geographical regions: the northeastern border region (Nuevo Leon) had the highest adoption of this measure, at 50.1%, while the pacific-center (Jalisco) had the lowest levels, 30.6%; Mexico City and the northern pacific region (Baja California) reported adoption of 41.2 and 36.5%, respectively (60, 61). According to ENSANUT 2020, the main reason for leaving their house was buying food (70.6%), work (31.4%), buying medicines (12.1%), and going to medical consults (10%), but regarding knowledge and adoption of mitigation strategies, only 36.4% of responders identified staying-at-home as a preventive measure, while 38.5% adopted it (60).

In México, during the period analyzed in this study, controversy continuously surfaced on how the pandemic was managed by national authorities, which held leadership through the first months, and was later transferred to state authorities (12, 24, 61–65). From a perspective of public policy implementation, and according to Knaul et al. (59), "Nuevo Leon and Jalisco and its metropolitan areas of Monterrey and Guadalajara, respectively, stood out as positive examples." According to Knaul et al., both state governments suspended non-essential activities earlier, established policies to promote social distancing before national measures were enacted, and expanded testing capacity (12). Our findings support this observation since incidence and mortality rates were lower when NPIs were implemented in Nuevo Leon and Jalisco.

The main limitation was mobility data availability since it is limited to the possibility of tracking users. Although mobile users across the states are similar (91–94.4%) (27), data may not represent all of the population, and we are aware that it might exclude some groups. Incidence data is also limited since it depends on testing strategies (12). However, correlation with mortality data validates our results. Even though multiple studies examine the relationship between NPIs and the pandemic trajectory, the most consistent and analyzed variable as a predictor among other works was population

TABLE 3 Results from mixed-effects Poisson regression models to evaluate the influence of mobility on the incidence of positive COVID-19 cases and COVID-19 mortality rates in all states being assessed.

Model	Parameter	IRR	95%CI	*p*-value
COVID-19 incidence $R^2 = 0.085$	Mobility	1.052	1.048–1.055	<0.001
COVID-19 incidence adjusted $R^2 = 0.166$	Mobility	1.052	1.048–1.056	<0.001
	Physicians per 10,000 inhabitants	1.329	1.310–1.348	<0.001
	Hospital beds per 10,000 inhabitants	0.830	0.807–0.854	<0.001
	Population living in poverty (%)	0.888	0.882–0.893	<0.001
COVID-19 mortality $R^2 = 0.038$	Mobility	1.028	1.019–1.038	<0.001
COVID-19 mortality adjusted $R^2 = 0.163$	Mobility	1.029	1.020–1.038	<0.001
	Physicians per 10,000 inhabitants	2.390	2.283–2.503	<0.001
	Hospital beds per 10,000 inhabitants	0.273	0.250–0.297	<0.001
	Population living in poverty (%)	1.035	1.017–1.053	<0.001

TABLE 4 Results from mixed-effects Poisson regression models to evaluate the influence of mobility on the incidence of positive COVID-19 cases and COVID-19 mortality rates per state using an interaction effect and using as reference the state of Baja California.

Model	Parameter	IRR	95%CI	*p*-value
COVID-19 incidence $R^2 = 0.232$	Mobility	1.016	1.012–1.020	<0.001
	Mexico City	4.406	3.715–5.225	<0.001
	Jalisco	7.815	6.717–9.092	<0.001
	Nuevo León	0.888	0.882–0.893	<0.001
	Mobility*Mexico City	1.010	1.006–1.013	<0.001
	Mobility*Jalisco	1.102	1.097–1.107	<0.001
	Mobility*Nuevo Leon	1.112	1.107–1.116	<0.001
COVID-19 mortality $R^2 = 0.225$	Mobility	1.007	0.998–1.016	0.1233
	Mexico City	1.152	0.760–1.747	0.504
	Jalisco	13.454	9.271–19.524	<0.001
	Nuevo León	12.600	8.233–19.283	<0.001
	Mobility*Mexico City	0.999	0.991–1.007	0.726
	Mobility*Jalisco	1.130	1.117–1.142	<0.001
	Mobility*Nuevo Leon	1.115	1.102–1.128	<0.001

mobility (15, 16, 18–26, 55, 56). Also, we excluded the analysis of specific public policies, as all promoted NPIs in the early stages of the pandemic by national health authorities had an objective to slow viral transmission by reducing population mobility (6, 10, 59), which can be outlined as the mobility index, thus allowing for a detailed statistical analysis of the end-product of NPIs as one variable. Finally, another aspect revolving around population mobility is mobility between states, within states, cities, and sub-city areas, which is not included in our study and has shown to be associated with SARS-CoV-2 epidemiology (25, 26).

Conclusions

NPIs focused on physical distancing were promoted during the local transmission phase, although the epidemiological trajectory varied between states. After the initial decline in mobility experienced in early April, a sustained increase in mobility followed during the rest of the country-wide suspension of non-essential activities and the return to other activities throughout mid-April and May. We identified that a 1% increase in mobility yielded a 5.2 and a 2.9% increase in the risk of COVID-19 incidence and mortality, respectively, in all evaluated states. Mobility was estimated to contribute 8.5 and 3.8% to the variability in incidence and mortality, respectively. When adjusting for medical care and poverty, the contribution of mobility to positive COVID-19 incidence and mortality was sustained. When assessing the impact of mobility in each state compared to the state of Baja California, we identified that increased mobility conferred an increased risk of incident positive COVID-19 cases in Mexico City, Jalisco, and Nuevo León. However, for COVID-19 mortality, a differential impact of mobility was only observed with Jalisco and Nuevo León compared to Baja California. We hypothesize that a contributing factor to the trajectory of the pandemic in Mexico, as occurred in other countries, was the timeliness of implementation of such measures. Our results provide valuable information for future pandemic preparedness and response against possible emerging and re-emerging pathogens of similar nature. Overall, mobility increased during the NPSD as COVID-19 cases and deaths escalated. Finally, the match between important festivities with changes in mobility could be another factor that drove mobility throughout the NPSD. Despite the continued promotion of NPIs, return to non-essential activities was encouraged by health authorities during a rising wave of cases and deaths due to political and economic pressures. Further research focused on other states and variables and governance is needed to understand the pandemic across the country thoroughly.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://github.com/Caml1034/COVID19Mobility.git.

Author contributions

CM-L, MC-C, and LG-G participated in the study conception and design. CM-L and MC-C acquired data. CM-L, MC-C, GD-S, EF-G, LF-R, SC-Q, NT-V, NM-R, MJ-C, KB, OB-C, and LG-G analyzed and interpreted data. CM-L, MC-C, OB-C, and LG-G contributed to the writing of the manuscript. GD-S, EF-G, LF-R, SC-Q, NT-V, NM-R, MJ-C, and KB critically revised the manuscript for important intellectual content. All authors reviewed the manuscript and granted their final approval to publish this version.

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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.2022.877800/full#supplementary-material

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EDITED BY
Benjamin Longo-Mbenza,
Walter Sisulu University, South Africa

REVIEWED BY
Sandra Incerpi,
Roma Tre University, Italy
Carlo Tascini,
University of Udine, Italy

*CORRESPONDENCE
Syed Mohammed Basheeruddin Asdaq
sasdaq@gmail.com;
sasdag@mcst.edu.sa

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Analysis of potential risk factors associated with COVID-19 and hospitalization

Abdul-Hakeem Moazi Alharbi[1,2], Syed Imam Rabbani[2], Ashraf Abdel Halim Mohamed[3,4], Basil Khalid Almushayti[1,2], Nasser Ibrahim Aldhwayan[1,2], Ali Tami Almohaimeed[1,2], Abdullah Abdulrhman Alharbi[1,2], Naif Saad Alharbi[1,2], Syed Mohammed Basheeruddin Asdaq[5]*, Abdulhakeem S. Alamri[6,7], Walaa F. Alsanie[6,7] and Majid Alhomrani[6,7]

[1]College of Pharmacy, Qassim University, Buraydah, Saudi Arabia, [2]Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah, Saudi Arabia, [3]Consultant Pulmonologist, Buraidah Central Hospital, Buraidah, Saudi Arabia, [4]Department of Pulmonary Medicine, Zagazig University, Zagazig, Egypt, [5]Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Riyadh, Saudi Arabia, [6]Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Taif University, Taif, Saudi Arabia, [7]Centre of Biomedical Sciences Research (CBSR), Deanship of Scientific Research, Taif University, Taif, Saudi Arabia

Coronavirus disease 2019 (COVID-19) was found to cause complications in certain groups of people, leading to hospitalization. Several factors have been linked to this, such as gender, age, comorbidity, and race. Understanding the precise reasons for the COVID-19-induced complications might help in designing strategies to minimize hospitalization. A retrospective, cross-sectional observational study was conducted for patients in a COVID-19-designated specialty hospital after obtaining ethical clearance. Patients' demographic and clinical characteristics, such as age, gender, race, vaccinated status, complications, comorbidities, and medications, were retrieved from the hospital medical database. The data were statistically analyzed to determine the association between the predictors and the outcomes of COVID-19. An odds ratio (both unadjusted and adjusted) analysis was carried out to determine the risk factors for hospitalization [non-intensive care (non-ICU) and intensive care (ICU)] due to COVID-19. The data from the study indicated that the majority of patients hospitalized due to COVID-19 were male (>55%), aged > 60 years (>40%), married (>80%), and unvaccinated (>71%). The common symptoms, complications, comorbidities, and medications were fever, pneumonia, hypertension, and prednisolone, respectively. Male gender, patients older than 60 years, unemployed, unvaccinated, complicated, and comorbid patients had an odds ratio of more than 2 and were found to be significantly ($p < 0.05$) higher in ICU admission. In addition, administration of prednisolone and remdesivir was found to significantly reduce ($p < 0.05$) the odds ratio in ICU patients. The analysis of the data suggested that male gender, age above 60 years, and unvaccinated with comorbidities increased the complications and resulted in hospitalization, including ICU admission. Hypertension and type 2 diabetes associated with obesity as metabolic syndrome could be considered one of the major risk factors. Preventive strategies need to be directed toward these risk factors to reduce the complications, as well as hospitalization to defeat the COVID-19 pandemic.

KEYWORDS

COVID-19, risk factors, complications, hospitalization, medications

Introduction

Coronavirus disease (COVID-19) is a highly infectious illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The virus is genetically related to the Middle East respiratory syndrome virus and SARS-CoV-1 (1). The infection is mainly transmitted by the inhalation of droplets from infected people. The virus enters the host through inhalation of air contaminated with infected patients' sneezes, coughs, and speech (2). Touching unhygienic surfaces and the eyes, nose, or mouth of infected people could also transmit the virus to a healthy individual (3).

The first case of COVID-19 was reported in Wuhan city of China in December 2019. The infection spread to other parts of the world rapidly, and the infection reached every corner of the globe very quickly (4). Currently, the virus has infected millions of people, causing mortality in 2–3% of the world. To date, no specific therapeutic intervention has been found to treat the infection. Several classes of drugs are used to treat the symptoms, and they are mostly patient-specific (5). Vaccination is one of the most reliable approaches to building herd immunity in a population. However, due to frequent mutation of viruses and insufficient data on the precise duration of protection offered by vaccines, the efficacy of the vaccines is under elaborate study (6).

The first case of COVID-19 was reported in Saudi Arabia in March 2020. The country immediately took proactive measures, such as the closure of international borders, schools, and public places, and implemented strict precautionary measures such as wearing masks, avoiding crowded gatherings, social distancing, and mass screening of the public (7). The country is the second most affected, with more than 5.44 million confirmed cases. The mortality rate was reported to be 1–2% (8).

According to the literature, COVID-19 causes mild to moderate symptoms, such as fever, headache, body pain, and sore throat, in most individuals. Other symptoms such as loss of taste/smell, difficulty in breathing, and diarrhea were also reported (2). However, in a few people, the infection leads to severe pneumonia, congestion, hypoxia, and respiratory failure. Several factors have been reported for the occurrence of these complications due to COVID-19 (3).

The most important reasons for COVID-19-related complications are reported to be the quantum of viral exposure, host immune response, age, and comorbid conditions of the patients. A study conducted in the past suggested that 39.3% of the Saudi population suffers from different types of metabolic diseases, such as type 2 diabetes mellitus and cardiovascular diseases (9). These risk factors were found to vary from region to region and between races (10). Identifying the precise cause of hospitalization might provide an opportunity to analyze the severity and may help in proactive measures to prevent it (11). Hence, this study aimed to evaluate the factors responsible for hospitalization due to COVID-19 during the first wave of infection in a COVID-19 specialty hospital in Saudi Arabia.

Materials and methods

Data collection

Data were collected from a COVID-19 specialty hospital in the Qassim province of Saudi Arabia designated to treat in-patients diagnosed with COVID-19. An 11-month record (March 2020–January 2021) of in-patients admitted to the hospital was randomly retrieved after approval from the concerned authorities. All patients, irrespective of gender, age, and nationality, admitted to the COVID-19 hospital [non-intensive care (non-ICU) and intensive care (ICU)] were analyzed. Sampling of the data was performed in the duration that corresponds to the first wave of infection in the country when therapeutic interventions had limited options and were mostly carried out depending on patients' condition.

Ethical clearance

The study was conducted after obtaining ethical clearance from the regional ethics committee of Qassim province. H-04-Q-001 is the number of the ethical clearance letter. A duly filled form with the research proposal, a letter from the institution, and a list of investigators was submitted for obtaining the approval. Prior to this, permission from the specialty hospital designated for treating COVID-19 in Qassim province was obtained for conducting the study using their recorded data. All the information about the patients was recorded as anonymous, maintaining the secrecy of their identification.

Inclusion and exclusion criteria

All patients with COVID-19-positive results who were admitted for treatment of complications and had complete information on the predictors were included in the study, while vice versa was considered the exclusion criteria.

Study design and participants

For this retrospective study, 619 patients' records (non-ICU = 369 and ICU = 250 patients) with confirmed COVID-19 were retrieved. All patients were diagnosed as COVID-19 positive with a real-time PCR assay for SARS-CoV-2 RNA, which analyzed genetic sequences that matched COVID-19, and then the infection was confirmed with SARS-CoV-2. The patients were clinically diagnosed as well, based on typical manifestations such as fever, cough, and respiratory distress, accompanied by chest radiological examinations (12). All 619 COVID-19 patients were considered eligible for the present study based on the inclusion criteria, and data of 39 patients were rejected, mainly due to a lack of sufficient information in their records. The medical records of each COVID-19 hospitalized patient were analyzed by the members of the research team to determine the predictors and outcome of the disease. The data of hospitalization and the mortality data (if any) with the duration of stay in the hospital were recorded for each patient during the study period. The following variables were considered for this study (13).

Patient and hospital characteristics

The demographic characteristics of the patients, such as gender, nationality, age, marital and employment status, were recorded for each hospitalized patient receiving treatment for COVID-19. The hospital visit information, such as date of admission, type of hospitalization (non-ICU and ICU), and discharge disposition, were also recorded.

Clinical characteristics

The clinical characteristics of the hospitalized COVID-19 patients, such as vaccinated status, important symptoms of disease, comorbidities (hypertension, type 2 diabetes, heart failure, chronic pulmonary disease, coronary artery disease, and cancer), and complications of COVID-19 (pneumonia, septic shock, and multi-organ failure) were recorded.

Pharmacological therapies

The frequently used medical interventions for treating the complications of COVID-19 were recorded. The medical records of the hospitalized patients revealed the following medications: prednisolone, favipiravir, ivermectin, hydroxychloroquine, azithromycin, and remdesivir.

Clinical outcomes

The clinical outcomes assessed in the COVID-19 patients included in-hospital mortality, ICU admission, and total hospital length of stay, including in ICU. The prevalence of ICU admissions can be referred to as the percentage of COVID-19 patients who had ICU admission during their stay in the hospital. On the other hand, in-hospital mortality means the percentage of COVID-19-related deaths in the hospital during the course of treatment.

Severity score of mortality due to COVID-19

The severity score designed by the World Health Organization was used to predict the mortality outcome in the patients hospitalized to either non-ICU or ICU (14). Different scores between 0 and 10 ("0" for uninfected and "10" for death) were assigned depending on the severity of the COVID-19-induced complications. Patients with scores of 0–3 were considered at "low" risk for COVID-19, those with scores 4–7 were indicated as "moderate" risk, and those with scores above 7 were considered to be at "high" risk of mortality. Final scores were calculated by multiplying with the number of patients presented with that particular severity of the disease (recorded as scores), and then the percentage was determined for each severity and represented in Figure 2.

Statistical analysis

All the data are recorded in an Excel sheet and are represented in the form of figures and tables. A descriptive analysis of the data was carried out to determine the demographic characteristics, hospital characteristics, clinical characteristics, medications used, and clinical outcomes after treatment (survival vs. death) (15). The statistical analysis of the data was carried out using IBM SPSS 21.0 software. The categorical variables were expressed as frequencies or percentages, while continuous variables were recorded as mean values. When the data were normally distributed, the mean values were compared between groups using one-way ANOVA, and when it was not, the Mann–Whitney test was used for analysis. The chi-square test was used to calculate the odds ratio (OR), and it represented the association between potential risk factors and hospitalization. OR values suggest the odds that an outcome occurs due to an exposure compared to the outcome that is due to the absence of that particular exposure. Depending on the OR values, it is possible to study the incidences of outcome (OR < 1 indicates decreased occurrences of an event and OR > 1 indicates increased occurrences of an event). The

TABLE 1 Demographic characteristics of hospitalized COVID-19 patients.

Demographic characteristic	Non-ICU patients ($n = 369$)	ICU patients ($n = 250$)
Gender		
Male	208 (56.4)	172 (68.8)
Female	161 (43.6)	78 (31.2)
Nationality		
Saudis	203 (55.1)	154 (61.6)
Non-Saudis	166 (44.9)	96 (38.4)
Age (Yrs)		
0–20	31 (8.4)	8 (3.2)
21–40	77 (20.9)	27 (10.8)
41–60	102 (27.6)	71 (28.4)
Above 60	159 (43.1)	144 (57.6)
Marital status		
Married	301 (81.6)	231 (92.4)
Single	68 (18.4)	19 (7.6)
Employment status		
Employed	149 (40.4)	92 (36.8)
Unemployed	220 (59.6)	158 (63.2)

Values are represented as total number (%).

influence of confounding factors on the analysis was corrected by evaluating the OR in the unadjusted and adjusted setups. The odds ratio values in an unadjusted and adjusted setups assessed the influence of multiple confounders or one specific confounder on the outcome of COVID-19 hospitalization, respectively (15, 16). $P < 0.05$ was considered to indicate the significance.

Results

Demographic characteristics of hospitalized COVID-19 patients

The demographic characteristics of hospitalized COVID-19 patients are represented in Table 1. Male patients were found to be more prevalent in both non-ICU (56.4%) and ICU (68.8%) hospitalizations than female patients. In terms of nationality, Saudis were found to be more (55.1% in non-ICU and 61.6% in ICU patients). In the age-group distribution, those older than 60 years were found to be more in both non-ICU (43.1%) and ICU (57.6%). The hospitalization of married people was found to be more (81.6% in non-ICU and 92.4% in ICU patients) than the unmarried population. The comparative data of employment status suggested that the unemployed population was found to be the most frequent hospitalized patients due to COVID-19 (59.6% in non-ICU and 63.2% in ICU) compared to employed people.

TABLE 2 Clinical characteristics of hospitalized COVID-19 patients.

Clinical characteristic	Non-ICU patients ($n = 369$)	ICU patients ($n = 250$)
Vaccine status		
Vaccinated	104 (28.2)	37 (14.8)
Unvaccinated	265 (71.8)	213 (85.2)
Symptoms		
Cough	133 (36.0)	160 (64)
Loss of smell/taste	209 (56.6)	179 (71.6)
Fever	287 (77.2)	202 (80.8)
Loss of appetite	149 (40.4)	182 (72.8)
Fatigue	226 (61.2)	229 (91.6)
Diarrhea	113 (30.6)	146 (58.4)
Vomiting	92 (24.9)	168 (67.2)
Dyspnoea	126 (34.3)	223 (89.2)
Complications		
Pneumonia	17 (4.6)	221 (88.4)
Septic shock	3 (0.8)	89 (35.6)
Multiorgan failure	0	146 (58.4)
Comorbidities		
Hypertension	173 (46.8)	197 (78.8)
Type-2 diabetes mellitus	136 (36.9)	156 (62.4)
Heart failure	11 (2.9)	71 (28.4)
Chronic pulmonary disease	104 (28.2)	163 (65.2)
Coronary artery disease	5 (1.3)	23 (9.2)
Cancer	2 (0.5)	15 (6.0)
Medications		
Prednisolone	223 (60.4)	217 (86.8)
Favipravir	21 (5.7)	66 (26.4)
Ivermectin	4 (1.1)	31 (12.4)
Hydroxychloroquine	6 (1.6)	42 (16.8)
Azithromycin	5 (1.3)	63 (25.2)
Remdesivir	3 (0.8)	20 (8.0)

Values are represented as total number (%).

Clinical characteristics of hospitalized COVID-19 patients

The clinical characteristics data of COVID-19 hospitalized patients indicated that the majority of them had not received vaccines (71.8% in non-ICU and 85.2% in ICU). The most frequent symptom recorded in non-ICU patients was fever (77.2%), followed by fatigue (61.2%) and loss of smell or taste (56.6%). Also in the ICU patients, the three common symptoms were fatigue (91.6%), dyspnea (89.2%), and fever (80.8%). In non-ICU patients, the most common complication

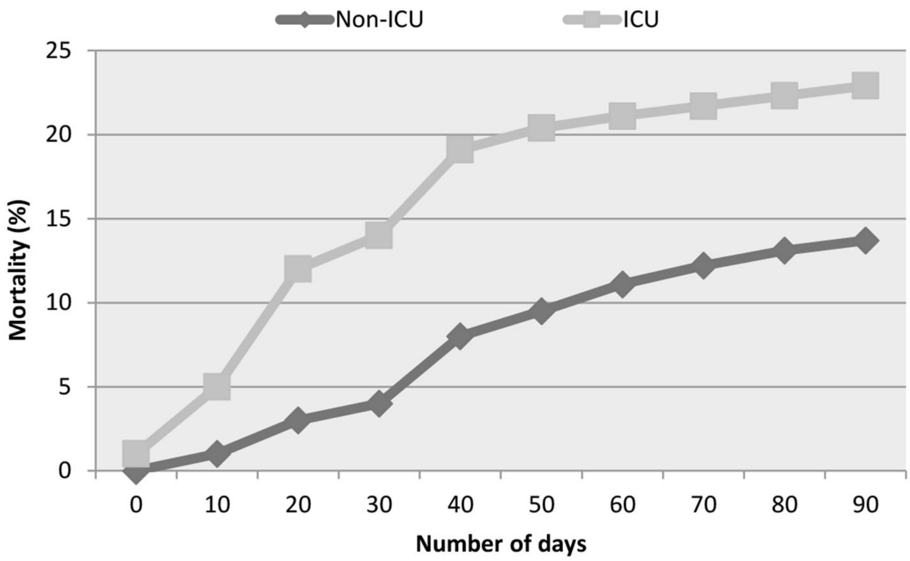

FIGURE 1
All-cause mortality recorded in COVID-19 patients.

was pneumonia (4.6%), while in the ICU, patients had pneumonia (88.4%), followed by multiorgan failure (58.4%) and septic shock (35.6%). Hypertension was the most common comorbidity among both non-ICU (46.8%) and ICU (78.8%) patients, followed by diabetes (36.9% in non-ICU) and chronic pulmonary disease (62.4% in ICU) patients. Prednisolone was the most frequently used medication to manage the complications of COVID-19 in both non-ICU (60.4%) and ICU (86.8%) patients, followed by favipiravir (5.7% in non-ICU and 26.4% in ICU) (Table 2).

The percentage of mortality recorded for COVID-19 patients at different intervals of days is represented in Figure 1. In non-ICU patients, the data indicated that 1% mortality was observed between 0 and 10 days of hospitalization, and this increased to 8% between 10 and 40 days. Thereafter, the percentage mostly remained steady and remained between 9.5% (50 days) and 13.7% (90 days). In the COVID-19 ICU patients, 1% of mortality was recorded on the day of hospitalization, which increased to 12% between 10 and 20 days and 19.1% between 30 and 40 days. After 50 days, the slope of the curve indicated a steady rate of mortality of 20.4% (50 days) and 22.9% (90 days).

Association between potential risk factors and COVID-19 based on demographic characteristics

The association between the demographic characteristics and hospitalization in COVID-19 patients is given in Table 3. The unadjusted odd ratio of non-ICU male patients was found to be 3.36, and the value increased significantly ($p = 0.03$) to 5.01 in ICU hospitalization. The adjusted odds ratio also showed a significant ($p = 0.02$) increase in the ICU male patients when compared with the non-ICU hospitalization. In the female patients, although the unadjusted odds ratio was above 3, non-significant variation was observed between non-ICU and ICU hospitalization. Similarly, the adjusted odds ratio showed non-significant variation between the non-ICU and ICU female patients.

The analysis of data depending on patients' nationality indicated a significant increase ($p = 0.01$) in the adjusted odds ratio of ICU patients when compared with non-ICU hospitalization. Other values in this domain did not show any significant variation when compared between them. In the age criteria, a significant ($p = 0.02$) higher adjusted odds ratio was observed for ICU patients aged 41–60 years when compared with non-ICU hospitalization. Furthermore, patients older than 60 years had a significantly higher odds ratio when comparing non-ICU and ICU hospitalization in both unadjusted ($p = 0.01$) and adjusted ($p = 0.03$) setups. The odds ratio showed a gradual increase as the age of the patients increased but was found to be non-significant when non-ICU and ICU data were compared.

The marital status parameter indicated a significant ($p = 0.04$) increase in the adjusted odds ratio for ICU patients when compared with non-ICU for the married patients. The comparison of data between non-ICU and ICU for both unadjusted and adjusted odds ratios of unmarried/single patients did not show significant variation. Furthermore, the employment status of the hospitalized patients showed

TABLE 3 Association between potential risk factors and COVID-19 hospitalization depending on demographic characteristics.

Demographic characteristic	Unadjusted Odds Ratio (95% CI)			Adjusted Odds Ratio (95% CI)		
	Non-ICU	ICU	*p*-value	Non-ICU	ICU	*p*-value
Gender						
Male	3.36 (2.74–4.69)	5.01 (3.14–6.68)	**0.03**	1.21 (0.91–1.97)	2.95 (2.05–3.32)	**0.02**
Female	3.02 (2.31–3.56)	3.26 (2.14–3.89)	1.06	1.26 (0.79–1.32)	1.92 (1.70–2.06)	0.11
Nationality						
Saudis	2.62 (1.88–2.95)	2.08 (2.01–2.24)	0.24	1.89 (0.98–2.29)	3.21 (2.62–3.74)	**0.01**
Non-Saudis	1.92 (1.65–2.20)	2.17 (1.21–2.92)	0.09	0.98 (0.62–1.02)	1.29 (0.71–1.78)	0.33
Age (Yrs)						
0–20	0.31 (0.28–0.44)	0.06 (0.01–0.09)	1.12	0.07 (0.03–1.02)	0.03 (0.01–0.05)	1.02
21–40	1.72 (1.25–1.96)	0.92 (0.61–1.16)	0.04	0.81 (0.46–0.98)	0.61 (0.21–0.88)	0.66
41–60	2.42 (1.72–2.36)	2.89 (2.44–3.48)	0.13	1.47 (0.82–1.86)	2.73 (1.88–2.52)	**0.02**
Above 60	3.26 (2.92–3.62)	5.16 (3.67–5.89)	**0.01**	2.18 (2.06–2.96)	4.06 (3.91–4.12)	**0.03**
Marital status						
Married	2.16 (1.82–2.41)	1.68 (1.34–1.81)	0.26	1.30 (0.96–1.88)	3.05 (2.96–4.48)	**0.04**
Single	1.77 (0.93–2.21)	1.65 (0.88–1.86)	1.33	0.85 (0.62–0.96)	1.09 (0.84–1.26)	0.63
Employment status						
Employed	1.91 (0.92–2.30)	1.32 (0.88–1.50)	0.16	1.10 (0.91–1.30)	0.85 (0.69–1.02)	0.56
Unemployed	2.21 (2.01–2.69)	1.89 (1.16–2.06)	0.39	1.80 (0.98–2.41)	2.52 (2.12–2.69)	0.96

Statistical analysis: Chi-square test. Bold values indicates the 'statistical significant values'.

non-significant variation between non-ICU and ICU odds ratios in both unadjusted and adjusted testing modules.

Clinical characteristics-based association between potential risk factors and COVID-19 hospitalization

The clinical analysis of vaccinated and unvaccinated patients indicated a significant ($p = 0.04$) increase in the unadjusted odds ratio for ICU hospitalization compared to non-ICU patients. A similar significant ($p = 0.03$) increase was observed for the adjusted odds ratio for ICU hospitalization when compared with non-ICU patients. In both unadjusted and adjusted odds ratios, the values for unvaccinated non-ICU and ICU patients were found to be above 3. The comparison of the non-ICU- and ICU-hospitalized unadjusted odds ratios indicated a significant ($p = 0.02$) increase, while in the adjusted odds ratio, no significant variation was observed. On the other hand, comparison of data for both unadjusted ($p = 0.04$) and adjusted ($p = 0.01$) odds ratios indicated a significant increase in ICU-hospitalized patients compared to non-ICU patients.

The three complications recorded in the hospitalized COVID-19 patients, such as pneumonia, septic shock, and multiorgan failure, indicated an odds ratio above 2 for non-ICU patients in both unadjusted and adjusted analyses. These values increased above 3 and were found to be significantly ($p < 0.05$) high for the ICU-hospitalized patients upon comparison with non-ICU patients for all the three complications. In the

TABLE 4 Association between potential risk factors and COVID-19 hospitalization depending on clinical characteristics.

Clinical characteristic	Unadjusted Odds Ratio (95% CI)			Adjusted Odds Ratio (95% CI)		
	Non-ICU	ICU	*p*-value	Non-ICU	ICU	*p*-value
Vaccine status						
Vaccinated	0.62 (0.38–0.74)	0.48 (0.46–0.96)	0.09	0.32 (0.28–0.59)	0.25 (0.19–0.42)	0.39
Unvaccinated	3.06 (2.98–3.12)	4.39 (2.41–4.87)	**0.04**	3.17 (2.66–3.41)	4.06 (2.99–4.62)	**0.03**
Symptoms						
Cough	0.74 (0.56–0.98)	0.88 (0.71–0.91)	0.09	0.81 (0.94–2.52)	0.96 (0.96–1.25)	0.11
Loss of smell/taste	2.69 (2.14–2.92)	2.03 (2.84–4.46)	1.03	2.11 (1.91–2.36)	1.86 (2.76–3.43)	0.84
Fever	0.72 (0.62–0.97)	1.14 (0.95–1.65)	0.46	1.05 (0.86–1.23)	1.15 (0.88–1.29)	0.09
Loss of appetite	0.86 (0.78–0.97)	0.78 (0.62–0.89)	0.96	1.14 (0.90–1.36)	0.96 (0.72–1.08)	0.61
Fatigue	1.22 (1.16–1.59)	2.96 (0.79–1.09)	**0.02**	1.89 (1.49–1.96)	1.20 (1.12–1.30)	0.07
Diarrhea	0.99 (0.81–1.32)	1.16 (0.74–1.69)	0.36	1.32 (0.72–1.53)	0.96 (0.88–1.21)	0.48
Vomiting	0.56 (0.41–0.79)	1.01 (0.89–1.23)	0.60	1.01 (0.89–1.14)	1.06 (0.82–1.28)	0.19
Dyspnoea	2.15 (2.02–2.46)	3.69 (3.15–3.96)	**0.04**	1.49 (1.16–1.40)	4.15 (3.92–4.41)	**0.01**
Complications						
Pneumonia	1.69 (1.14–2.63)	3.96 (2.96–4.23)	**0.03**	1.36 (1.11–1.59)	4.41 (2.72 –4.95)	**0.02**
Septic shock	1.29 (1.04–1.90)	4.06 (3.26–4.51)	**0.02**	1.12 (0.86–1.24)	3.97 (3.78–5.26)	**0.01**
Multiorgan failure	0.89 (0.44–1.02)	3.78 (2.66–3.95)	**0.04**	0.69 (0.42–1.16)	4.16 (2.99–4.46)	**0.03**
Comorbidities						
Hypertension	2.26 (1.92–2.58)	3.96 (2.89–4.28)	**0.04**	2.89 (2.79–3.16)	5.04 (3.32–5.26)	**0.01**
Type-2 diabetes	2.76 (2.14–2.86)	3.45 (2.36–3.12)	0.08	3.02 (2.91–3.21)	3.92 (3.06–4.09)	**0.03**
Heart failure	2.09 (0.92 –2.36)	2.25 (2.16–2.68)	0.06	2.16 (1.42–2.89)	3.23 (3.15–3.76)	**0.02**
Chronic pulmonary disease	2.62 (2.22–2.89)	3.88 (3.11–3.96)	**0.03**	2.82 (2.52–3.03)	3.74 (3.25–3.79)	**0.02**
Coronary artery disease	2.41 (2.10–2.78)	2.88 (2.52–3.23)	0.56	2.41 (2.16–2.88)	3.68 (3.39–3.86)	**0.04**
Cancer	1.81 (0.92–1.97)	1.21 (0.96–1.46)	0.82	1.15 (0.99–1.29)	1.07 (1.02–1.62)	0.41
Medications						
Prednisolone	1.66 (0.72–1.85)	1.84 (0.75–1.92)	0.07	1.44 (0.56–1.29)	0.71 (0.82–1.18)	**0.04**
Favipravir	1.41 (0.71–1.12)	1.27 (0.63–1.59)	0.08	0.99 (0.52–1.34)	1.01 (0.37–1.50)	0.14
Ivermectin	2.54 (2.32–2.74)	3.14 (2.81–3.69)	0.19	3.14 (2.62–3.79)	3.78 (3.39–4.68)	0.48

(Continued)

TABLE 4 Continued

Clinical characteristic	Unadjusted Odds Ratio (95% CI)			Adjusted Odds Ratio (95% CI)		
	Non-ICU	ICU	*p*-value	Non-ICU	ICU	*p*-value
Hydroxychloroquine	2.09 (0.66–2.81)	1.81 (1.29–3.54)	0.07	2.51 (2.39–2.68)	2.33 (2.19 –2.46)	0.19
Azithromycin	3.69 (3.47–3.80)	3.58 (3.02–3.66)	0.26	2.63 (2.44–2.79)	3.12 (2.96–3.56)	0.36
Remdesivir	0.72 (0.59–0.91)	0.41 (0.39–0.57)	**0.04**	0.56 (0.34–0.68)	0.30 (0.28–0.42)	**0.03**

Statistical analysis: Chi-square test. Bold values indicates the 'statistical significant values'.

comorbidity conditions, hypertension and chronic pulmonary disease, the unadjusted odds ratio of ICU hospitalization increased significantly ($p < 0.05$) compared to non-ICU patients. However, the adjusted analysis indicated a significant increase in the ICU odds ratio for hypertension ($p = 0.01$), type 2 diabetes ($p = 0.03$), heart failure ($p = 0.02$), chronic pulmonary disease ($p = 0.02$), and coronary artery disease ($p = 0.04$) compared with non-ICU patients.

The available data suggested that different medications, such as prednisolone, favipiravir, ivermectin, hydroxychloroquine, azithromycin, and remdesivir, were used to treat the symptoms and complications of COVID-19. Among them, the unadjusted analysis indicated a significant ($p = 0.04$) reduction in the odds ratio with remdesivir in ICU patients compared to non-ICU hospitalization. In addition to remdesivir ($p = 0.03$), the treatment of prednisolone also significantly reduced ($p = 0.04$) the odds ratio in ICU patients when compared to non-ICU hospitalization (Table 4).

Severity score of mortality in hospitalized COVID-19 patients

Figure 2 represents the percentage of severity scores due to COVID-19 in the hospitalized patients. Of the non-ICU patients, 62.3% were found to be at low risk, 28.9% at moderate risk, and 8.8% at high risk of mortality due to COVID-19. The analysis of ICU patients revealed that 56.8% of them are at high risk, 23.7% at moderate, and 19.5% are at low risk of COVID-19-induced mortality.

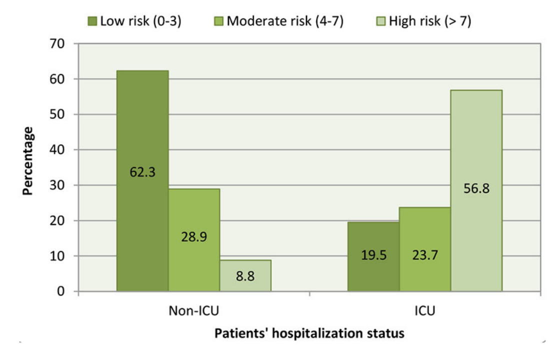

FIGURE 2
Severity score in hospitalized patients due to COVID-19.

Discussion

The present study assessed the potential risk factors of hospitalization due to COVID-19. The analysis of the data indicated that the hospitalization of male patients was found to be more in both non-ICU (56.4%) and ICU (68.6%) admissions than that of female patients (Table 1). The unadjusted odds ratio (OR) increased for male patients severalfold and was found to be 3.36 for non-ICU patients, which further increased to 5.01 for ICU admission. The comparison of these two values indicated a significant ($p = 0.03$) increase for ICU-hospitalized patients. In addition, the adjusted odds ratio of ICU admission was found to be significantly ($p = 0.02$) higher than that of non-ICU patients (Table 3). The observations suggested that male gender could be a risk factor for hospitalization, including ICU due to COVID-19. A similar observation was found in an earlier study where the male population was found to be at higher risk of not only the disease but also hospitalization due to complications (16). The Y-chromosome has been implicated as the risk factor for COVID-19-induced complications (17).

The risk of hospitalization was found to be higher among Saudi nationals than among non-Saudis in both non-ICU (55.1%) and ICU (61.6%) admissions (Table 1). The analysis to determine the potential risk indicated that Saudi nationals are slightly at a higher risk of hospitalization than other nationals, as observed in both the unadjusted and adjusted odds ratios. Their chances of complications due to COVID-19 and admission to ICU (OR = 3.21) were also found to be higher than those for non-Saudis (OR = 1.29). The comparative analysis revealed that the ICU admission of Saudi nationals showed a significantly (p = 0.01) higher odds ratio (3.21) than non-ICU (OR = 1.89) in the adjusted analysis (Table 3). Earlier studies indicated that a significant portion of the Saudi population (39.3%) suffers from several metabolic diseases, such as type 2 diabetes, hypertension, and obesity (18). Occurrences of metabolic diseases were found in the population in the early age. Obesity which was considered to be one of the risk factors of metabolic diseases was found to be prevalent among 18% of Saudi children and rises to 39.9% among adolescents (19). The incidences of metabolic diseases are increasing at an alarming rate in the Saudi population and are reported to be due to lack of physical activity, changing life style, and shift from traditional diet to those rich in carbohydrates, fats, and carbonated beverages (9). There are multiple pathways, such as altered immunological response, blood circulation, and inflammatory processes, reported for the COVID-19-induced complications in the patients suffering from metabolic diseases (20). Since these comorbidities act as potential risks of COVID-19-induced complications, a higher prevalence of hospitalization could be linked to this in the present study (21).

A higher prevalence of metabolic diseases and chronic disorders can also be observed in the clinical characteristics of hospitalized patients (Table 2). Except for cancer, these comorbidities showed an odds ratio above 2 for both non-ICU- and ICU-hospitalized patients. Moreover, a significantly ($p < 0.05$) higher OR was found for ICU patients than for non-ICU patients (Table 4). Furthermore, the association of advanced age, comorbidities, and an increased risk of COVID-19-induced complications is reported in the literature. The data from the present study suggest that the increase in OD is directly proportional to the age of the patients. The OR values for older adults were found to be more than 2, indicating the enhanced risk associated with COVID-19. A significantly ($p < 0.05$) higher OR (> 4) in ICU patients older than 60 years supports the association of age, comorbidities, and potential risk of hospitalization due to COVID-19 (18–22).

Comorbidities are known to complicate COVID-19 through multiple mechanisms, such as dysfunction of renin–angiotensin, coagulatory, circulatory, and immunological systems (23). Furthermore, the marital status and higher incidences of OR could indicate that elderly patients with multiple diseases are at risk of COVID-19-induced complications. In addition, marital status may increase the chance of viral transmission due to close contact among family members (24). Studies have indicated that marital status could play both positive and negative influence on the anxiety and stress that was experienced during the COVID-19 pandemic (25). Quarantine and self-isolation methods adopted to reduce the transmission of the infection was reported to affect the mental health adversely and increased the chances of COVID-19-associated complications (26). Furthermore, the non-significant increase in OD (>1.80) observed in unemployed patients can also be linked to patients older than 60 years (Table 3).

The vaccinated status of the COVID-19 patients indicated that most of the non-ICU (71.8%) and ICU (85.2%) admissions had not received the required dosages of approved vaccines (Table 1). A significantly higher odds ratio was observed for unvaccinated ICU (OR > 3) patients when unadjusted (p = 0.04) and adjusted (p = 0.03) analyses were carried out (Table 2). The findings suggest that the vaccinated status might protect the population from the complications of COVID-19. Saudi Arabia has approved major COVID-19 vaccines, such as AstraZeneca, Pfizer, Moderna, and Johnson (27). Currently, the vaccination status in the country has crossed 90% (28). Since the WHO has approved a few vaccines and prioritized the recipient groups, only limited numbers were vaccinated during the study period.

The most common symptoms of non-ICU- and ICU-hospitalized patients were found to be fever (77.2%) and fatigue (91.6%), respectively (Table 1). The unadjusted odds ratio analysis indicated a significantly (p = 0.02) higher value for ICU patients (OR = 2.96) than for non-ICU patients (OR = 1.22). In addition, dyspnea in both unadjusted (p = 0.04) and adjusted (p = 0.01) odds ratios was found to be higher for ICU (OR > 3.6) than for non-ICU (OR = 1.49–2.15) patients (Table 4). Fatigue could be due to desaturation of blood oxygen levels, and dyspnea is one of the frequent symptoms associated with respiratory distress (29). Both these symptoms are reported to occur when the body's immune system responds aggressively to COVID-19. The cytokine storm reported during this phase of immunological response causes pneumonia and interferes with respiratory function (30). The appearance of complications, such as pneumonia, septic shock, and multi-organ failure, could also be the consequence of the immunological reaction due to COVID-19 (Tables 2, 4). The significant ($p < 0.05$) elevation of the OR (>4) in ICU patients (Table 4) is in agreement with the previous studies where pneumonia, septic shock, and multi-organ failure were considered the major reasons for ICU hospitalization (31).

The medication analysis revealed that prednisolone was the most frequent intervention in both non-ICU-hospitalized (60.4%) and ICU-hospitalized (86.6%) patients (Table 2). Some of the other medications also reduced the odds ratio, but significant variation was observed only with prednisolone and remdesivir. Prednisolone in the adjusted analysis decreased significantly (p = 0.04) the odds ratio of ICU patients compared to non-ICU patients. In both unadjusted and adjusted analyses, remdesivir significantly reduced the ICU odds ratio significantly ($p < 0.05$) compared to non-ICU hospitalization (Table 4). Prednisolone is a corticosteroid reported to be effective in reducing the inflammatory process associated with COVID-19. The drug was approved by the WHO for treating mild to moderate complications of COVID-19. The intravenous administration of prednisolone was found to be effective in reducing the actions of pro-inflammatory mediators and the hyper-immunological responses during COVID-19 (32). The drug was first authorized for emergency use by the U.S. FDA to treat complicated COVID-19 cases. The drug exhibits its action by inhibiting SARS-CoV-2 RNA-dependent RNA polymerase, essential for viral replication (33). The findings of the present study are in line with those of the previous research where both prednisolone and remdesivir were found to be effective in reducing the complications associated with COVID-19 (32, 33). Favipiravir and azithromycin were also frequently used in the management of COVID-19-related complications, but these medications did not show significant variation in OR values in both non-ICU and ICU patients (Table 4).

The percentage of mortality recorded among the non-ICU patients indicated a progressive increase as the number of days in the hospital increased. The highest percentage of mortality in non-ICU patients was found to be between 30 and 50 days. On the other hand, the mortality percentage increased rapidly for ICU-admitted patients from the 10th to the 40th day (Figure 1). These findings support previous research, indicating that mortality due to COVID-19 in ICU hospitalization was highest between the 10th and the 40th day (3) of comorbidities. Advanced age, male gender, and unvaccinated status could all be the major factors for the observed hospitalized COVID-19 patients (34).

Analysis of severity score in the hospitalized patients due to COVID-19 indicated that 8.8% of non-ICU admissions are at higher risk of mortality, while 62.3% of them were found to be at lower risk. On the other hand, 56.8% of ICU-admitted patients were considered at higher risk of mortality due to the complications of COVID-19, and the lower risk in them was found to be 19.5% (Figure 2). As reported in the literature, advanced age and presence of several comorbidities along with lack of immunization could be the reasons for higher risk in patients admitted to the ICU (10).

The prevalence and mortality in the first wave of COVID-19 in Saudi Arabia were reported to be 6.1 and 2.0%, respectively. During this phase, where limited options were available for treating the COVID-19-induced complications, the healthcare professionals were reported to follow the latest guidelines of the World Health Organization. These include several therapeutic interventions listed in Table 2 and mechanism ventilation (invasive and non-invasive) as well as intubation. These options were attempted depending on the severity of COVID-19-induced complications. The research conducted on these patients suggested that mortality was associated with leukocytosis, anemia, thrombocytopenia, and higher levels of prothrombin time, troponin, and ferritin (35). In addition, the study indicated that such abnormal biomarker levels and higher incidences of mortality were frequent among the aged COVID-19 patients diagnosed with metabolic diseases (36).

The findings of the study on the group of COVID-19 patients represented an important analysis of factors responsible for the hospitalization. As per the available data, a significant proportion of Saudi population suffers from different types of metabolic syndrome, including type 2 diabetes, hypertension, and obesity (19). Several studies in the past have linked the presence of metabolic syndrome with COVID-19-induced complications (19). Obesity is considered to be important metabolic syndrome that has been linked to several diseases, such as hypertension, type 2 diabetes, and coronary artery disease. A study conducted in the past indicated that the risk of hypertension increased up to 70% in obese patients (37). The prevalence of type 2 diabetes in Saudi population was reported to increase to 38.9% in the obese population (38). The analysis of the data of the present study data suggested higher odd ratios for hypertension (OD = 5.04) and type 2 diabetes (OD = 3.92) for the ICU-hospitalized patients due to COVID-19 (Table 4). This information suggested that obesity, which is common in Saudi population, could be one of the major risk factors for the COVID-19-induced complications and hospitalization. The data from this study could be used by healthcare providers to target a specific group of the population in designing strategies to reduce the severity of any future diseases depending on the risk associated with them.

Limitation of study

The present study represents the analysis of COVID-19-hospitalized patients when the country experienced the first wave of infection. The study was conducted by retrieving the patients' data from a COVID-19-designated specialty hospital. Several advancements have occurred since then in medical interventions and the vaccinated status of the population, which is reported to have crossed over 90%. Hence, the findings will only represent the data from a select group of patients during the study period and may not reflect the whole population affected by COVID-19 in the region.

Conclusion

In the present study, the analysis of the data indicated several confounders for the hospitalization of COVID-19 patients. Gender, age, vaccinated status, dyspnea, comorbidities, and complications due to COVID-19 were found to be the major risk factors for hospitalization, including ICU admission. Obesity, which is common in Saudi population, could be one of the important risk factors for the COVID-19-induced complications and hospitalization. Since coronavirus mutates at regular intervals with increasing virulence, healthcare providers must investigate these factors and prioritize the preventive strategies to minimize the risk of hospitalization for any future outbreak of the disease.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by Regional Ethics Committee of Qassim province, H-04-Q-001. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

Under the supervision of SR, A-HA, AH, BA, NAld, AAlm, AAlh, and NAlh carried out the research methodology. AAla was responsible for formal analysis of the work, while WFA, A-HA, AH, and BA participated in writing the original draft of the manuscript. MA administered the project. SAs was instrumental in reviewing and editing the manuscript. All authors contributed to the article and approved the submitted version.

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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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EDITED BY
Katri Jalava,
University of Helsinki, Finland

REVIEWED BY
Diana C. Sanchez-Ramirez,
University of Manitoba, Canada
Jiandong Zhou,
University of Oxford, United Kingdom

*CORRESPONDENCE
Chuanhua Yu
yuchua@whu.edu.cn

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Non-pharmacological interventions of travel restrictions and cancelation of public events had a major reductive mortality affect during pre-vaccination coronavirus disease 2019 period

Haoyu Wen[1], Fang Shi[1], Yan Liu[1], Cong Xie[2], Guiyu Qin[1], Fang Wang[3], Xiaoxue Liu[1], Jianjun Bai[1], Qiumian Hong[1], Runxue Ma[1] and Chuanhua Yu[1,4]*

[1]Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University, Wuhan, China, [2]Hubei Provincial Center for Disease Control and Prevention, Institute of Preventive Medicine Information, Wuhan, China, [3]Department of Biostatistics, School of Public Health, Xuzhou Medical University, Xuzhou, China, [4]China Global Health Institute, Wuhan University, Wuhan, China

Background: The coronavirus disease 2019 (COVID-19) is a severe acute respiratory disease that poses a continuous threat to global public health. Many non-pharmacological interventions (NPIs) have been implemented to control the COVID-19 pandemic since the beginning. The aim of this study was to assess the impact of various NPIs on COVID-19 mortality during pre-vaccination and vaccination periods.

Methods: The COVID-19 data used in this study comes from Our World in Data, we used the Oxford Strict Index (OSI) and its five combination interventions as independent variables. The COVID-19 mortality date (MRT) was defined as a date when daily rate of 0.02 COVID-19 deaths per 100,000 population in a country was reached, and the COVID-19 vaccination date (VRT) was defined as people vaccinated reaching 70%. Linear regression and random forest models were used to estimate the impact of various NPI implementation interventions during pre-vaccination and vaccination periods. The performance of models was assessed among others with Shapley Additive Explanations (SHAP) explaining the prediction capability of the model.

Results: During the pre-vaccination period, the various NPIs had strong protective effect. When the COVID-19 MRT was reached, for every unit increase in OSI, the cumulative mortality as of June 30, 2020 decreased by 0.71 deaths per 100,000 people. Restrictions in travel (SHAP 1.68) and cancelation of public events and gatherings (1.37) had major reducing effect on COVID-19 mortality, while staying at home (0.26) and school and workplace closure (0.26) had less effect. Post vaccination period, the effects of NPI reduced significantly: cancelation of public events and gatherings (0.25), staying at home (0.22), restrictions in travel (0.14), and school and workplace closure (0.06).

Conclusion: Continued efforts are still needed to promote vaccination to build sufficient immunity to COVID-19 in the population. Until herd immunity is achieved, NPI is still important for COVID-19 prevention and control. At the beginning of the COVID-19 pandemic, the stringency of NPI implementation had a significant negative association with COVID-19 mortality; however, this association was no longer significant after the vaccination rate reached 70%. As vaccination progresses, "cancelation of public events and gatherings" become more important for COVID-19 mortality.

KEYWORDS

COVID-19, vaccines, public health interventions, random forest, mortality

Introduction

Corona virus disease 2019 (COVID-19) is a highly concealed and highly transmissible severe acute respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The World Health Organization (WHO) announced that COVID-19 has developed into a "pandemic" on March 11, 2020 (2). COVID-19 is a continuous threat to global public health. According to WHO statistics, as of December 31, 2021, a total of 285,581,643 COVID-19 cases and 5,428,033 deaths from COVID-19 have been reported worldwide (3). The number of COVID-19 cases and deaths continues to grow rapidly.

Before the COVID-19 vaccine was invented and widely used, various non-pharmacological interventions (NPIs) had been implemented in most countries around the world to cope with the sharp increase in the COVID-19 cases and deaths and to maintain the normal operation of the healthcare system. In Wuhan, China, a series of multifaceted interventions resulted in significant mitigation of the COVID-19 outbreak (4). Italy was the first European country to carry out interventions to deal with COVID-19, and other countries followed suit (5). The interventions, largely successful in curbing the spread of COVID-19, incurred economic and social costs, including increased unemployment (6), declined income, education interruption, social isolation and related socio-psychological consequences (7). Gaining a better understanding of when and how these interventions can effectively control COVID-19 is critical for health prevention and control experts to implement a specific sequence of key countermeasures judiciously and timely.

On November 18, 2020, Pfizer/BioNTech became the first in the world to release full late-stage trial data for the COVID-19 vaccine. Shortly after, on December 8, 2020, the United Kingdom became the first of all countries to vaccinate the public with COVID-19 (8). According to the WHO, as of December 31, 2021, the countries with largest proportion of population vaccinated are Gibraltar, Pitcairn Islands, United Arab Emirates, all with a proportion of more than 90% (3). In this case, an important issue is how should we better implement NPI as vaccination progresses? Previous studies have focused on the early stages of the COVID-19 outbreak, exploring the association between NPI and COVID-19 mortality (9–14). However, there is a lack of research on changes in this association after vaccination, and a lack of exploration of the effectiveness of NPI after vaccination as well.

Hence, to address these limitations, this study aimed to assess the impact of various NPIs on COVID-19 mortality during pre-vaccination and vaccination periods. This study uses the linear regression to find out the association between NPI and COVID-19 mortality, and investigate the priority of NPI by random forest model.

Materials and methods

Data source

The data used in this study comes from Our World in Data (OWID) (15). OWID provides statistics on the coronavirus pandemic in 207 countries/regions around the world. Data on COVID-19 deaths comes from the European Center for Disease Control and Prevention and Johns Hopkins University, and the vaccination dataset is the most recent official numbers from governments and health ministry's worldwide (16). The population estimates for per capita indicators are based on the United Nations World Population Prospects (17).

Methods

In this study, the COVID-19 mortality rate was the outcome variable, the Oxford Strict Index (OSI) and the interventions included were independent variables. The reason why this study chose COVID-19 mortality rather than COVID-19 incidence as the outcome variable is that the former is more reliable. The incidence data of COVID-19 depends largely on the testing capacity, which could cause great data inaccuracy (18). The Oxford Stringency Index (19) records the strictness of the intervention that primarily restricts people's behavior, which is a composite index based on nine interventions: school closures, workplace closures, cancelation of public events, restrictions on public gatherings, closures of public transport, stay-at-home requirements, public information campaigns, restrictions on internal movements, international travel controls (the definitions of these nine NPIs are provided in **Supplementary Table 1**). According to the classification principles of OWID, we further transformed these nine interventions into five intervention combinations: "school and workplace closures," "cancelation of public events and gatherings," "stay-at-home restrictions," "public information campaigns," "restrictions in international and domestic travel." NPI combination "school and workplace closures" contains NPI "schools closures" and "workplaces closures"; NPI combination "cancelation of public events and gatherings" contains "cancelation of public events" and "restrictions on public gatherings"; NPI combination "restrictions in international and domestic travel" contains "closures of public transport," "restrictions on internal movement," "international travel controls." The stringency of an NPI combination is calculated as the average of the stringency of the NPIs it contains.

In this study, we set two thresholds: the COVID-19 mortality rate threshold (MRT) and the COVID-19 vaccination rate threshold (VRT). The COVID-19 MRT is defined as a daily rate of 0.02 new COVID-19 deaths per 100,000 people (based on a 7-day moving average), and the COVID-19 VRT is defined as people vaccinated (one dose or two doses) per hundred reaching 70%. Since vaccination is ongoing, the number of countries reaching the COVID-19 VRT is increasing. In order to maintain the certainty of the countries chosen in this study, we only selected countries reaching the COVID-19 VRT (the proportion of population vaccinated greater than 70%) on or before October 31, 2021. Finally, based on the above two thresholds, 34 countries with more than 250,000 inhabitants and for which relevant data were available were included (Specific country names are shown in Supplementary Documents).

Linear regression

In this study, we established two linear regression models, "Lm1" and "Lm2." "Lm1" used the OSI on the day a country reached the COVID-19 MRT as the independent variable, and used the cumulative COVID-19 death rate per 100,000 people on June 30, 2020 as the dependent variable; "Lm2" used the OSI on the day a country reached the COVID-19 VRT as the independent variable, and the cumulative death rate per 100,000 people between the day the COVID-19 VRT was reached and December 31, 2021 was used as the dependent variable. June 30, 2020 was chosen in "Lm1" because on that day the new COVID-19 death rate fell to relatively low level in almost all 34 countries; and December 31, 2021 was chosen in "Lm2" as the data was the latest available to date.

In addition, the regression models "Lm1" and "Lm2" control for the same 11 health-related indicators as covariates: the date the threshold was reached, because the effect of NPI is closely related to time; the number of hospital beds per 1,000 people is taken as a measure of baseline health care capacity; proportion of people aged 65 older, because age is an important risk factor for COVID-19 death; female smoking prevalence, male smoking prevalence and diabetes prevalence reflect the basic health status of the population, population density, because higher population density leads to higher exposure rates; per capita GDP and the share of people living in extreme poverty to explain the wealth difference; the human development index and life expectancy reflect the comprehensive health level of a country. Health-related covariate data for the 34 countries included in the study are presented in **Supplementary Table 2**.

Random forest

The decision tree model is a tree structure composed of root nodes, branch nodes and leaf nodes, reflecting the mapping relationship between features and tags. Random forest (RF) is an ensemble learning method based on decision trees (20). The RF model can be briefly understood as the following 4 steps (21): (1) randomly select k samples from the given dataset (k is usually equal to 2/3 of the dataset) for training the model, and the remaining samples are used to estimate the RF's goodness of fit; (2) from each sample with m variables, randomly select a subset with n variables ($n < m$) and create a decision tree; (3) each tree grows at a constant n over a maximum extent, without pruning, until it cannot split.; (4) calculate the prediction result for each tree, and the average prediction of all trees is used to create the final output.

The RF model in this study is generated based on 500 decision trees. We use 70% of the dataset as the training set and the remaining 30% as the test set. RMSE (root mean square error), MAE (mean absolute error), MSE (mean square error), and MAPE (mean absolute percentage error) were used to assess the performance of the random forest model. In this study, we generated two random forest regression models: "RF1"and "RF2." "RF1" used the stringency of the five NPI combinations on the day a country reached the COVID-19 MRT as the independent variable and uses the same dependent variable as "Lm1"; "RF2" used the stringency of the five NPI combinations on the day a country reached the COVID-19 VRT as the independent variable and uses the same dependent variable as "Lm2." These two random forest models included the same covariates as in the previous linear regression.

We ranked NPIs by three importance measures: (a) permutation based feature importance, (b) Gini-based importance, and (c) feature importance computed with Shapley Additive Explanations (SHAP) Values. The permutation based feature importance is measured using mean decrease in accuracy (MDA). MDA is a method of computing the feature importance on permuted out-of-bag (OOB) samples based on mean decrease in the accuracy (22). The Gini-based importance is measured using mean decrease in Gini (MDG). MDG is a measure of the contribution of individual variables to the homogeneity of the nodes in a random forest model. Each node split is compared to the original model Gini coefficient, which is a measure of the statistical dispersion of node homogeneity across all runs (23). The changes in Gini are summed for each variable and normalized, variables with higher node purity have a higher decrease in Gini coefficient. And for feature importance computed with SHAP Values, which were based on "Shapley values" developed by Shapley in the cooperative game theory (24). The goal of SHAP is to explain the prediction of an instance x by computing the contribution of each feature to the prediction. The SHAP explanation method computes Shapley values from coalitional game theory, where the feature values of a data instance act as players in a coalition (25). We also explored the correlation of the NPIs importance rankings obtained by the three importance measures through the Spearman correlation coefficient.

Results

Linear regression

Among the 34 countries included in the study, the date of reaching the COVID-19 MRT ranges from February 2, 2020 in China to April 10, 2020 in New Zealand, and the OSI on the date of reaching the COVID-19 MRT ranges from 11.11 in Spain and Iceland to 100 in Argentina and Sri Lanka (**Supplementary Table 3**). Countries with higher OSI when reaching COVID-19 MRT have a lower cumulative COVID-19 mortality on June 30, 2020 (**Figure 1**). This association persisted after controlling for the aforementioned 11 health-related covariates (**Supplementary Table 4**). When the COVID-19 MRT is reached, for every unit increase in OSI, the cumulative mortality rate as of June 30, 2020 will decrease by 0.71 deaths per 100,000 people (95% CI = −1.08 to −0.34 per 100,000 people).

Among the 34 countries included in the study, the date the country reached the COVID-19 VRT ranges from June 23, 2021 in Iceland to October 28, 2021 in Ecuador, and the OSI on the date of reaching the COVID-19 VRT ranges from 32.41 in Mauritius to 84.72 in Chile. However, the OSI on the day of reaching the COVID-19 VRT and the cumulative COVID-19 death rate per 100,000 people between the day the COVID-19 VRT was reached and December 31, 2021 did not show a significant association (**Figure 1**). After adjusting for the aforementioned covariates, the *P*-value of the "Lm2" is greater than the significance level ($\alpha = 0.05$).

Random forest model

The most common NPI combinations these countries implemented when they reached the COVID-19 MRT was "public information campaigns" (33 out of 34 countries), while the NPI combinations implemented by the fewest countries was "stay-at-home requirements" (20 out of 34 countries) (see **Table 1**). For a country, in addition to the number of NPIs implemented, the strictness of the implementation of NPIs is also important. Among the 34 countries included in this study, NPI combinations "public information campaigns" (33/34) was implemented with the strictest standards by the most countries, and followed by "school and workplace closures" (10/34) and "cancelation of public events and gatherings" (10/34). According to the RF model, the most important NPI combination for COVID-19 mortality is "restrictions in international and domestic travel" and "cancelation of public events and gatherings" (see in **Figure 2**). All three importance measures indicated that "restrictions in international and domestic travel" (SHAP 1.68) and "cancelation of public events and gatherings" (1.37) had major reducing effect on COVID-19 mortality, while "stay-at-home requirements" (0.26) and "school and workplace closure" (0.26) had less effect. Based on MAE, MSE, RMSE, MAPE, we can see that the random forest model performs well (see in **Supplementary Table 5**).

For countries reaching the COVID-19 VRT, the most common implemented NPI combinations were "public information campaigns," "cancelation of public events and gatherings" and "restrictions in international and domestic travel" (34 out of 34 countries); while the NPI combination with the fewest implementing countries is "stay-at-home requirements" (22 of 34) (see in **Table 2**). The NPI combination "public information campaigns" with strictest standard were still enforced in the most countries (34/34), followed by "cancelation of public events and gatherings" (12/34). When reaching the COVID-19 VRT, all three importance measures indicated that "cancelation of public events and gatherings" had the greatest impact on COVID-19 mortality, followed by "stay-at-home requirements." However, after reaching the COVID-19 VRT, the effects of all NPIs on COVID-19 mortality were

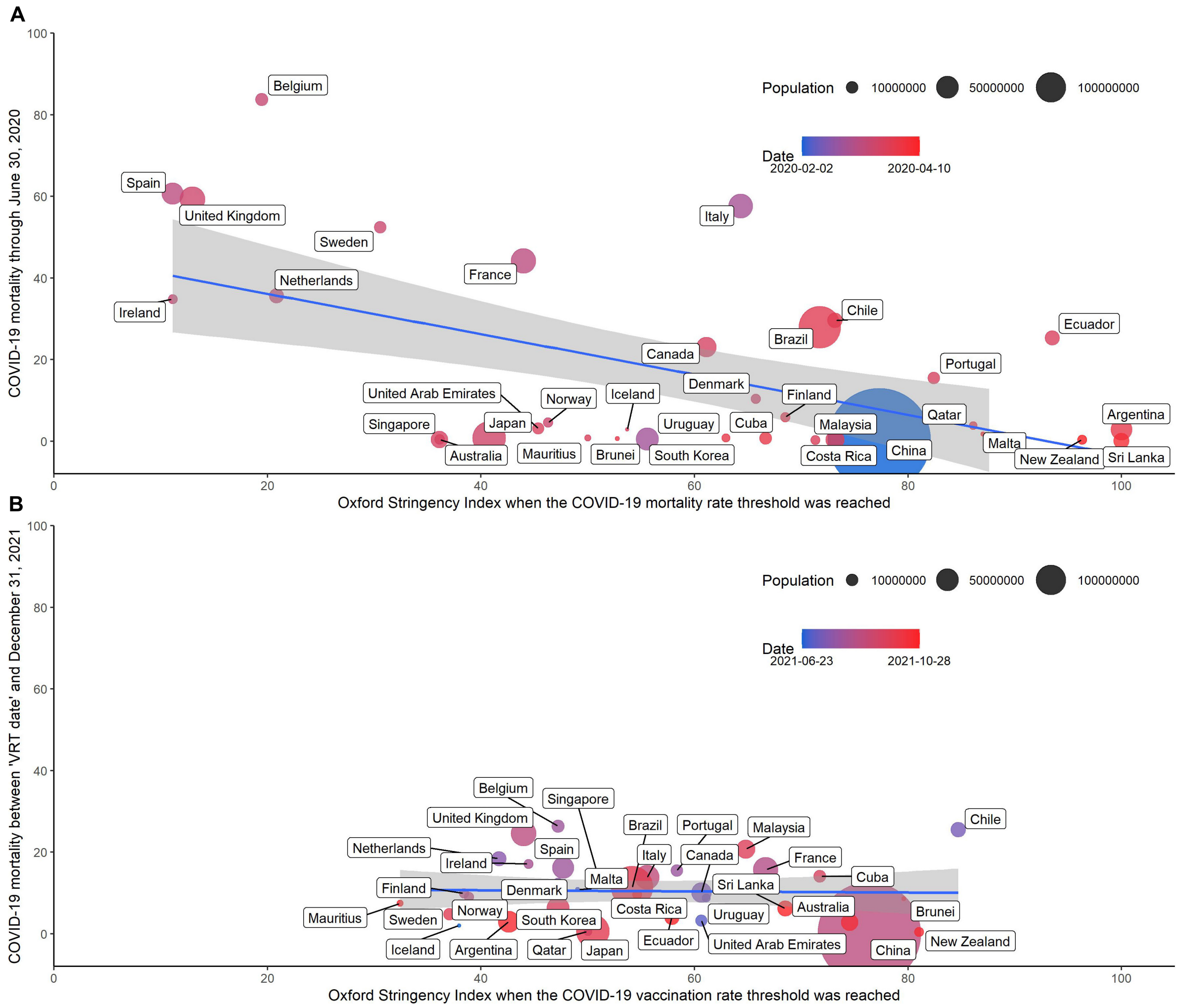

FIGURE 1
(A) The OSI on the day of reaching the COVID-19 mortality rate threshold and cumulative COVID-19 mortality through June 30, 2020. **(B)** The OSI on the day of reaching the COVID-19 vaccination rate threshold and cumulative COVID-19 mortality between the day of reaching the COVID-19 vaccination rate threshold and December 31, 2021.

significantly lower than before: "cancelation of public events and gatherings" (SHAP 0.25), "stay-at-home requirements" (0.22), "restrictions in international and domestic travel" (0.14) and "school and workplace closure" (0.06). The Gini-based importance ranking and SHAP importance ranking hold strong correlations, and the correlation was significant ($p < 0.05$). Permutation based importance correlates weakly with both above (see in **Supplementary Tables 6, 7**).

Discussion

This study found that the stringency of NPI implementation was strongly negatively associated with COVID-19 mortality in the early stage of COVID-19 pandemic, and this association was no longer significant after COVID-19 vaccination rate reached 70%. As vaccination progressed, the most important NPI combinations changed from "restrictions in international and domestic travel," "cancelation of public events and gatherings" to "cancelation of public events and gatherings."

Since the emergence of COVID-19 at the end of 2019, it has been raging around the world for about 2.5 years. Until COVID-19 vaccines were invented, NPIs were the most effective way for countries to fight against COVID-19. Large-scale social distance intervention saved time for health services to treat cases and increase treatment capacity. Many studies have proved the effectiveness of interventions (9–11), however, the implementation of many interventions came with great social and economic costs. For example, the closure of educational facilities would interrupt learning and could lead to malnutrition,

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TABLE 1 Implementation of non-pharmacological intervention combinations at the date the COVID-19 mortality rate threshold was reached in 34 countries.

Location	MRT date	School and workplace closures	Cancelation of public events and gatherings	Restrictions in international and domestic travel	Stay-at-home requirements	Public information campaigns
Argentina	2020/3/8	2.0	2.5	1.0	0.0	2.0
Australia	2020/3/1	2.5	3.0	2.3	2.0	2.0
Belgium	2020/3/11	2.0	1.0	1.0	1.0	2.0
Brazil	2020/3/20	0.0	2.0	1.0	0.0	2.0
Brunei	2020/3/28	2.5	2.5	1.7	2.0	2.0
Canada	2020/3/9	2.0	1.0	2.0	1.0	2.0
Chile	2020/3/22	3.0	2.5	1.3	1.0	2.0
China	2020/1/28	0.0	1.5	0.0	0.0	2.0
Costa Rica	2020/3/19	2.0	2.0	2.0	1.0	2.0
Cuba	2020/3/18	2.5	3.0	2.7	1.0	2.0
Denmark	2020/3/14	3.0	3.0	1.7	2.0	2.0
Finland	2020/3/21	0.0	0.5	0.3	0.0	2.0
France	2020/3/5	0.0	0.0	0.0	0.0	2.0
Iceland	2020/3/21	0.0	0.0	0.0	0.0	2.0
Ireland	2020/3/11	1.5	3.0	0.3	0.0	2.0
Israel	2020/3/20	2.0	3.0	1.7	1.0	2.0
Italy	2020/2/24	2.5	1.0	1.0	0.0	2.0
Japan	2020/3/10	0.0	0.0	0.0	1.0	2.0
Malaysia	2020/3/17	3.0	3.0	1.3	3.0	2.0
Malta	2020/4/8	3.0	3.0	1.3	2.0	2.0
Mauritius	2020/3/21	2.0	2.0	1.3	1.0	2.0
Netherlands	2020/3/6	1.5	1.0	2.3	2.0	2.0
New Zealand	2020/3/29	3.0	2.0	1.7	1.0	2.0
Norway	2020/3/14	0.0	1.5	1.0	0.0	2.0
Portugal	2020/3/17	3.0	2.5	2.3	1.0	2.0
Qatar	2020/3/28	2.0	0.5	1.0	0.0	2.0
Singapore	2020/3/21	1.5	2.5	1.3	0.0	2.0
South Korea	2020/2/23	0.0	2.0	1.0	0.0	2.0
Spain	2020/3/3	2.5	1.0	2.7	0.0	2.0
Sri Lanka	2020/3/28	3.0	3.0	2.7	2.0	2.0
Sweden	2020/3/10	3.0	3.0	2.7	3.0	2.0
United Arab Emirates	2020/3/20	3.0	1.0	1.7	0.0	0.0
United Kingdom	2020/3/10	3.0	3.0	2.7	3.0	2.0
Uruguay	2020/3/28	3.0	2.5	2.7	2.0	2.0

The numbers in the table represent the strictness of NPI combination implementation. The stringency of an NPI combination is calculated as the average of the stringency of the NPIs it contains. For the specific meaning of the strictness of the single NPI, see in **Supplementary Table 1**. MRT date, the date the COVID-19 mortality rate threshold was reached.

stress, and social isolation among children (26–28). The intervention "stay-at-home requirements" has significantly increased the incidence of domestic violence in many countries, with a huge impact on women and children (27). It also limits access to long-term care (such as chemotherapy), with a substantial impact on the health and survival chances of patients, especially for critically ill patients (29, 30). Therefore, the government must strike an acceptable balance between benefits and drawbacks when implementing interventions.

The ultimate goal of COVID-19 prevention and control is to reduce the mortality rate of COVID-19 to an extremely low and acceptable level, and to turn the epidemic into a more benign, endemic and cold-causing disease, on the premise that people are not restricted by large-scale interventions (31). Vaccination is considered the most likely way to achieve this. Existing studies have shown that most currently used COVID-19 vaccines are highly effective (>90%) against SARS-CoV-2 infection, symbolic COVID-19 disease, severe COVID-19 disease, and COVID-19 death at 2 months or less after vaccination (32–34).

TABLE 2 Implementation of non-pharmacological intervention combinations at the date the COVID-19 vaccination rate threshold was reached in 34 countries.

Location	VRT date	School and workplace closures	Cancelation of public events and gatherings	Restrictions in international and domestic travel	Stay-at-home requirements	Public information campaigns
Argentina	2021/10/21	1.0	1.0	1.3	1.0	2.0
Australia	2021/10/14	2.5	3.0	2.3	2.0	2.0
Belgium	2021/8/4	1.5	2.5	1.0	0.0	2.0
Brazil	2021/9/27	2.0	1.5	2.0	2.0	2.0
Brunei	2021/10/4	3.0	3.0	1.7	2.0	2.0
Canada	2021/7/20	2.0	2.5	2.3	1.0	2.0
Chile	2021/7/15	3.0	3.0	2.7	3.0	2.0
China	2021/8/26	3.0	3.0	1.7	3.0	2.0
Costa Rica	2021/10/18	2.0	2.0	0.7	1.0	2.0
Cuba	2021/9/18	2.5	3.0	2.0	2.0	2.0
Denmark	2021/7/24	1.5	2.0	1.0	0.0	2.0
Finland	2021/8/19	1.5	2.5	1.7	1.0	2.0
France	2021/8/20	1.0	2.5	0.7	1.0	2.0
Iceland	2021/6/23	1.5	2.5	2.0	0.0	2.0
Ireland	2021/8/12	1.0	1.5	1.0	0.0	2.0
Israel	2021/10/4	1.5	2.0	1.0	0.0	2.0
Italy	2021/8/28	1.5	1.5	2.0	2.0	2.0
Japan	2021/9/29	1.5	1.5	1.7	1.0	2.0
Malaysia	2021/9/24	2.5	0.5	2.0	2.0	2.0
Malta	2021/7/1	1.0	3.0	1.0	0.0	2.0
Mauritius	2021/10/21	1.0	1.5	0.7	0.0	2.0
Netherlands	2021/7/25	1.5	0.5	1.3	0.0	2.0
New Zealand	2021/10/7	3.0	3.0	2.7	2.0	2.0
Norway	2021/8/25	1.0	0.5	1.0	1.0	2.0
Portugal	2021/8/2	1.5	3.0	1.3	0.0	2.0
Qatar	2021/7/31	1.0	2.5	1.0	1.0	2.0
Singapore	2021/7/17	1.5	2.5	1.0	1.0	2.0
South Korea	2021/9/17	2.0	3.0	0.7	0.0	2.0
Spain	2021/8/4	1.0	3.0	0.7	2.0	2.0
Sri Lanka	2021/10/26	0.5	3.0	2.0	1.0	2.0
Sweden	2021/9/26	0.0	2.0	1.0	1.0	2.0
United Arab Emirates	2021/7/5	1.5	3.0	2.0	0.0	2.0
United Kingdom	2021/8/24	1.5	2.5	1.3	0.0	2.0
Uruguay	2021/7/15	2.0	2.0	2.0	1.0	2.0

The numbers in the table represent the strictness of NPI combination implementation. The stringency of an NPI combination is calculated as the average of the stringency of the NPIs it contains. For the specific meaning of the strictness of the single NPI, see in **Supplementary Table 1**. VRT date, the date the COVID-19 vaccination rate threshold was reached.

The negative association between OSI and COVID-19 mortality was not significant under COVID-19 VRT, which does not mean that NPI is no longer important for COVID-19 prevention and control at 70% COVID-19 vaccination rate, nor does it mean that a 70% vaccination rate is equivalent to the herd immunity threshold. Early relaxation of NPIs, before sufficient immunity has been established, could trigger a wave of infections that lead to hospitalizations and deaths (35). To build adequate immunity in the population, we need to consider not only about vaccinating the general population, but also about vaccinating the most vulnerable populations who need protection against disease. The lack of vaccination in highly susceptible pockets in the population could trigger small outbreaks and reduce the effect of population immunity (35). In addition, it is crucial to understand the drivers of vaccine hesitancy (36–38) and solve the inequality of vaccination opportunities (39).

On longer timescales, the possibilities of waning immunity and SARS-CoV-2 variants could lead to reduced immunity in the population. Six months after vaccination, the effectiveness of the COVID-19 vaccine against SARS-CoV-2 infection,

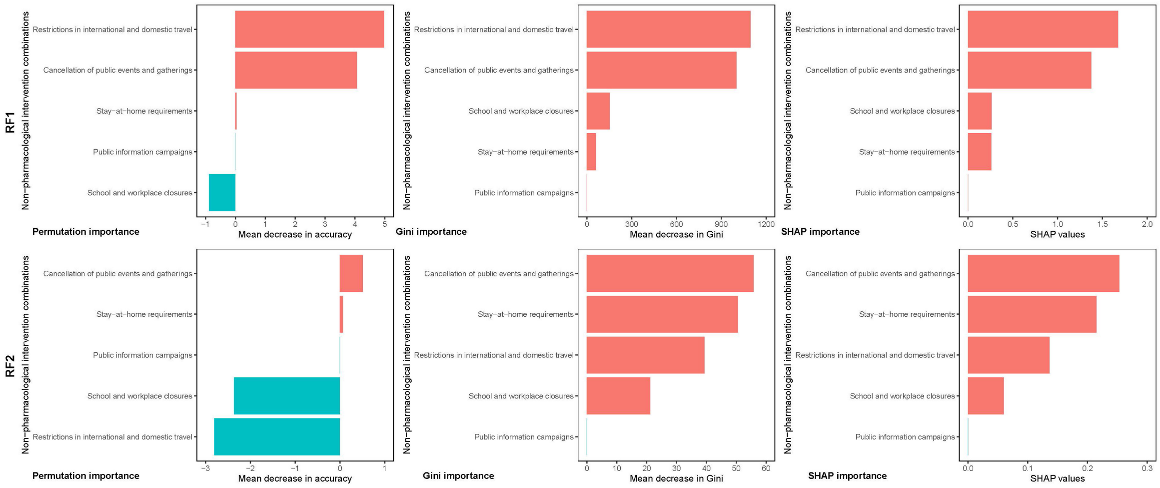

FIGURE 2
Ranking of the importance of NPI combinations to COVID-19 mortality.

symbolic COVID-19 disease decreased by more than 20 percentage points, but the effectiveness against severe COVID-19 disease and COVID-19 death waned limited, still around 80% (32–34, 40). Given that preventing of severe disease and death remains the primary goal of COVID-19 vaccination, this limited decline in vaccine efficacy or effectiveness for severe disease and death is acceptable. A seasonal vaccination program against SARS-CoV-2 similar to seasonal influenza vaccinations may be implemented in the future to counteract declining immunity (41). In addition, the booster dose of COVID-19 vaccine is also considered a way to combat declining immunity (32, 42). The SARS-CoV-2 variants are rapidly developing, currently including Alpha variant (B.1.1.7), Beta variant (B.1.351), Gamma variant (P.1), Delta variant (B.1.617.2), Omicron variant (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5) and so on (43). Compared with the previous variants, the Delta variant is more than twice as contagious, and may cause more severe illness in unvaccinated people (44–46). And the Delta and Omicron variants may be immune escape, leading a breakthrough infection of COVID-19 (47, 48). The emergence of the variants of SARS-CoV-2 further emphasizes the importance of vaccination and booster.

At a time when COVID-19 herd immunity has not yet been achieved, and we still need NPIs to fight the COVID-19 epidemic, so it is important to understand NPI priorities. The priority of NPI during the early stage of the COVID-19 pandemic in this study is consistent with previous studies (27). Restrictions in international and domestic travel make sense in preventing infection introduction (49, 50), especially given that travel has played a central role in the global spread of previous SARS epidemic (51). Cancelation of public events and gatherings are beneficial in reducing COVID-19 mortality and reproductive numbers, which have been shown in several studies (12, 28, 52). The strong impact of above NPI combinations on COVID-19 mortality may result from the fact that they are both mandatory policies and public facility closures which are easier to implement (53). The study found that "cancelation of public events and gatherings" have a greatest impact on COVID-19 mortality among the five common NPI combinations after vaccination rate reaching 70%. The prominent importance of "cancelation of public events and gatherings" to COVID-19 mortality has also been examined in previous studies (27, 54, 55). This NPI combination contributed to curb the spread of COVID-19 by preventing exposure to numerous and dense locations, where social distancing rules are more likely to be violated and contact tracing is difficult (55). In addition, there are studies demonstrating that the stricter implementation of "cancelation of public events and gatherings" will bring about a better suppression effect on the incidence and time-varying reproduction number of COVID-19 (52, 54). Perhaps COVID-19 public health experts can take this into account in the future to formulate more reasonable COVID-19 mitigation policies.

There are three limitations to this study. First, the intervention variable encoding of the Oxford COVID-19 Government Response Tracker relied on government announcements. However, the announcement did not guarantee effective policy implementation. Second, this research does not cover all mitigation policies that countries might apply (such as requirements for masks, hand hygiene, increased healthcare funding, ventilators, and protective equipment). Finally, many interventions were implemented simultaneously, making it difficult to completely isolate the effect of each other.

Conclusion

Continued efforts are still needed to promote vaccination to build sufficient immunity to COVID-19 in the population. Until herd immunity is achieved, NPI is still important for COVID-19 prevention and control. At the beginning of the COVID-19 pandemic, the stringency of NPI implementation had a significant negative association with COVID-19 mortality; however, this association was no longer significant after the vaccination rate reached 70%. As vaccination progresses, "cancelation of public events and gatherings" become more important for COVID-19 mortality.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The datasets analyzed during the current study are available in the (Our World in Data) repository (https://ourworldindata.org/coronavirus).

Author contributions

CY and HW contributed to conception and design of the study. HW organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. CY, HW, CX, FS, YL, FW, XL, GQ, JB, QH, and RM revised the final manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.914732/full#supplementary-material

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Zisis Kozlakidis,
International Agency for Research on Cancer (IARC), France

REVIEWED BY
Sumona Mondal,
Clarkson University, United States
Djavad Ghoddoosi-Nejad,
Birjand University of Medical Sciences, Iran

*CORRESPONDENCE
Huakun Lv
hklv@cdc.zj.cn

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Knowledge, attitudes, and practices toward COVID-19: A cross-sectional study during normal management of the epidemic in China

Juan Yang[1], Yuting Liao[1], Qianhui Hua[2], Chang Sun[3] and Huakun Lv[4]*

[1]State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, National Institute of Diagnostics and Vaccine Development in Infectious Diseases, School of Public Health, Xiamen University, Xiamen, China, [2]School of Medicine, Ningbo University, Ningbo, China, [3]School of Journalism and Communication, Peking University, Beijing, China, [4]The Center for Disease Control and Prevention of Zhejiang Province, Hangzhou, China

Background: The COVID-19 pandemic is striking the world with serious public health and economic losses. Complying with precautionary measures is affected by knowledge, attitudes, and practices (KAP) toward COVID-19 among the general public, so it is urgent to know the public's awareness of COVID-19 as to promote the epidemic management of COVID-19 in China.

Methods: An online sample of Chinese residents was recruited. We administered a self-developed online KAP survey comprising 39 questions regarding awareness of COVID-19, transmission mode, symptoms, preventive measures, and respondents' attitudes and practices with respect to COVID-19. The total score of each item (knowledge, attitudes, and practices) adopts the ten points system, score of KAP is 30 points. Descriptive statistics, analysis of variance, and binomial logistic regression were used in the statistical analysis.

Results: Among respondents, average scores for COVID-19-related knowledge, attitudes, and practice were 8.94 ± 0.79, 5.97 ± 1.58, and 7.03 ± 3.14, respectively. 91.2% were aware that COVID-19 is an acute viral infection and 99.95% knew that wearing a mask is one way to prevent COVID-19 infection. Participants correctly identified the symptoms of COVID-19 with a high accuracy rate of over 85%.

Conclusion: Many adults in the present study had adequate knowledge, a positive attitude and engaged in correct practices against COVID-19. People in China have a high awareness of epidemic prevention and control. However, conducting KAP surveys among people with different demographic characteristics at different stages of the epidemic is important to improve public health education and implement proper COVID-19 prevention and control measures.

KEYWORDS

COVID-19 vaccine, online survey, knowledge, attitude, practices

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the respiratory illness known as coronavirus disease 2019 (COVID-19). COVID-19 could lead to serious respiratory conditions, the main clinical signs and symptoms include fatigue, high fever, dry cough, dyspnea, fatigue and myalgia. It could lead to severe pneumonia, acute respiratory syndrome, and even death in some severe cases (1, 2). Since emerging in December 2019, the outbreak of COVID-19 has spread to nearly every country worldwide (3). On 11 March 2020, the World Health Organization declared the COVID-19 epidemic to be a pandemic (4). As of 4 April 2022, there have been more than 489 million cumulative COVID-19 cases and 6 million deaths worldwide (5). The COVID-19 pandemic in China is largely under control, but local outbreaks of COVID-19 have occurred in parts of the country including Beijing, Wuhan, and Hebei (6–8), indicating that disease prevention and control measures must continue to be followed in the country. The public is one of the key actors in Public Health Emergency Preparedness, responding to Public Health Emergency by heightened risk perceptions (9, 10), increased knowledge and awareness about specific threats (11), and the implementation of precautionary measures (12, 13). Morever, recent studies on COVID-19 revealed knowledge perceived controllability, optimistic beliefs, emotion, and risk perception might all interpret precautionary actions of the public (14–17).

In addition, the knowledge, attitudes, practices (KAP) model is commonly used to explain how individual knowledge and attitudes affect health behavior changes, which is a behavioral intervention theory. It was proposed in the 1960s by Mayo, a professor at Harvard University (18). The improvement of personal knowledge, attitudes, and practices can help improve health-related behavior as well as disease prevention and control (19). Therefore, understanding people's knowledge, attitudes, and behaviors toward COVID-19 can provide a reference for the development of health education plans. One study revealed that adherence to prevention and control measures is an essential strategy to halt the spread of an infectious disease outbreak (14), which is directly linked to the knowledge, attitudes, and practices (KAP) level of the population toward COVID-19. According to Khattak et al., sex, marital status, education, and residential area have a significant association with COVID-19-related knowledge scores (20). A study among adolescents in Spain showed that COVID-19-related knowledge was influenced by sex, place of residence, level of education, and financial aid; attitudes and risk perceptions were influenced by age and financial aid (21). A study conducted by Kebede et al. showed that COVID-19 risk communication and public education efforts should focus on building an appropriate level of knowledge while enhancing the adoption of recommended self-care practices, with special emphasis on high-risk audiences segments (22). A study in Sierra Leone shows that in the context of COVID-19, there is a strong association between knowledge and practices (23). People's knowledge, attitude and practices (KAP) toward COVID-19 may play a critical role in their acceptance of measures to curb its spread and their willingness to seek and adhere to treatment (24). Research in Uganda has shown that there are differences in perceptions of COVID-19 across occupations and the need to mobilize the entire population to the same level of knowledge will have an impact on attitudes and practices to prevent the spread of COVID-19 disease (25).

Our research was carried out at a time when COVID-19 had been brought under control in China and regular work and production had returned to normal levels, but there was still a risk of sporadic and imported cases. With recovery of the economy, population mobility increases and the task of epidemic prevention and control becomes challenging. Thus, the aim of this study was to evaluate the KAP regarding COVID-19 among residents of China and factors affecting KAP and provide a basis for relevant authorities to formulate effective prevention and control strategies, so as to promote correct information regarding COVID-19 control among the general public and improve their capacity toward COVID-19 prevention, to facilitate COVID-19 outbreak management.

Materials and methods

Study design, participants, and sampling

We conducted a cross-sectional survey using convenience and snowball sampling from September to October 2020 in Zhejiang Province, participants aged over 18 could fill in the questionnaire anonymously. The survey conducted through the largest online survey platform in China, Wen Juan Xing (https://www.wjx.cn/ accessed 4 April 2022). We consulted the relevant domestic and foreign literature on vaccination willingness and referred to relevant questionnaires with high reliability and validity; together with information related to COVID-19 infection, COVID-19 vaccination, and China's social and cultural background, we designed the questionnaire used in this investigation. The online survey link was disseminated *via* QQ (https://im.qq.com/index accessed 4 April 2022) and WeChat (https://weixin.qq.com/ accessed 4 April 2022), on which personal information and public websites can be shared with family members, friends and colleagues and forwarded to others by participants. To identify possible problems with our self-developed questionnaire, we conducted a preliminary survey among a small group of people before formally administering the survey. The results of returned survey and deficiencies described in feedback regarding survey items were revised, and the questionnaire was improved on this basis. We used a formula $n = \left(\frac{Z_{(1-\frac{\alpha}{2})}}{d}\right)^2 p(1-p) \times \text{Deff}$ of sample size required for cross-sectional investigation, the willingness rate of COVID-19 vaccination is 80%, significance level α =0.05, and absolute allowable error $d = 2.5\%$. As the research was non-random sampling, Deff =2 was taken as the design effect. Considering the sample loss caused by unpredictable factors, we increased by about 10% on the basis of the estimated sample size, and the minimum was calculated as $n = 2164$. To ensure validity of the online survey, we applied the following exclusion criteria: incomplete answers, inconsistent answers, and obvious logic errors responses. At last, 12 invalid questionnaires that did not meet the requirements were excluded, leaving a total of 2,171 valid questionnaires.

Data collection instrument

The questionnaire included basic demographic characteristics and information regarding knowledge, attitude, and practice levels. The knowledge section comprised four parts: awareness about COVID-19, a total of 10 items; transmission mode of COVID-19, seven items in total; symptoms of COVID-19 infection, 8 items in total; and preventive measures against COVID-19 infection, nine entries in total. Respondents rated the statements as "true," "false" and "unclear." The total score in each of the four dimensions was 10 points. The total score for the knowledge section was also 10 points, which was the average of the total scores in the four dimensions. The attitude section comprised four questions: "Do you think the domestic COVID-19 epidemic will worsen again in autumn and winter this year?" "Do you think you will be infected with COVID-19 this autumn and winter?", "What is your opinion regarding the safety of the COVID-19 vaccines currently entering phase III clinical trials in China?", "What is your opinion regarding the effect of the COVID-19 vaccines that has entered phase III clinical trials in China?" The practice section included one question: "Would you be vaccinated once the COVID-19 vaccines receive an Emergency Use Administration authorization?" For questions related to knowledge, correct responses were scored as one point; incorrect and unclear responses were scored as zero point. In the attitude and practice segments, each question was assigned a score from 0 to 10, with zero being the least likely/strongly disagree and 10 being the most likely/strongly agree.

Statistical analysis

Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) was used to sort the data, and IBM SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Classification variables are expressed as frequency and percentage, and continuous variables are expressed as mean and standard deviation. Single factor analysis was performed using F or *t-tests*. The variables age, sex, education level, average monthly income, and occupation were included in the multivariate binary or ordered multiple logistic regression analysis model (forward logistic regression). A two-sided test was performed with test level $\alpha = 0.05$. "Wald test" was used to test the regression coefficient of the Logistic regression model, we conducted "Hosmer and lemeshow Tests" on logistic regression models. The four models (knowledge, attitude, practice, KAP) worked well ($p > 0.1$).

Results

In total, 2171 valid questionnaires were finally included in the analysis, our participants came from all prefecture-level cities in the province, covering a wide range. Most respondents were women (60.5%). Respondents aged 18–30, 31–40, 41–50, and ≥51 years accounted for 29.4, 32.2, 24.3, and 14.1% of the sample, respectively. Among respondents, 71.8% had a junior college/university degree, 11.7% had a technical secondary school degree or below, and 16.5% had a master's degree or above. Among respondents, 38.7% were students; those engaged in mental labor, other occupations, and physical labor accounted for 23.8, 24.1 and 13.4% of the sample, respectively. Respondents with monthly income between 5001 and 10,000 RMB accounted for the largest proportion (38.7%).

In the knowledge section of the survey, 42.6% of respondents correctly answered all 10 items in the first part, awareness about COVID-19. The correct response rate of items "COVID-19 is an acute viral infection," "COVID-19 is spreading worldwide and can infect anyone in any age," "COVID-19 is a serious disease that can cause death," "COVID-19 infection is more serious and has a higher mortality rate in older people," and "Contracting COVID-19 is more severe for people with chronic diseases, with higher mortality rates" were above 90%. The correct response rate for "COVID-19 cannot spread among people easily," "COVID-19 is not a serious public health problem," and "There are specific drugs for the treatment of COVID-19" were very low, with 1.38, 3.59, and 7.55%, respectively. The correct response rate for "COVID-19 affects the economy by reducing labor productivity and increasing the burden of healthcare costs," and "Vaccination is the most effective way to prevent COVID-19 and its complications" were 81.85% (Table 1).

In the second part, mode of COVID-19 transmission, only 330 respondents (15.20%) correctly responded to all seven items. "transmission by droplets from an infected person" item had the highest correct response rate (99.59%), and "contacting pets" item had the lowest rate (51.08%). The correct response rates for "touching elevators, tables, door handles, handrails, coins or paper money," "exposure to fecal contaminants," "frozen food imported from abroad," and "aerosols" were more than 85%, and that of "shaking hands with an infected person" was slightly lower (79.92%) (Table 2).

TABLE 1 Cognition of COVID-19.

Items	Accuracy (%)
K1: COVID-19 is an acute viral infection	91.20
K2: COVID-19 is spreading worldwide and can infect anyone in any age	99.12
K3: COVID-19 cannot spread among people easily	1.38
K4: COVID-19 is a serious disease that can cause death	94.10
K5: COVID-19 is not a serious public health problem	3.59
K6: COVID-19 affects the economy by reducing labor productivity and increasing the burden of healthcare costs	81.85
K7: COVID-19 infection is more serious and has a higher mortality rate in older people	92.95
K8: Contracting COVID-19 is more severe for people with chronic diseases, with higher mortality rates	92.03
K9: There are specific drugs for the treatment of COVID-19	7.55
K10: Vaccination is the most effective way to prevent COVID-19 and its complications	81.85

TABLE 2 Transmission mode of COVID-19.

Propagation mode of COVID-19	Accuracy (%)
K11: Transmission by droplets from an infected person (talking, coughing, sneezing)	99.59
K12: Shaking hands with an Infected person	79.92
K13: Touch elevators, tables, door handles, handrails, coins or paper money	88.95
K14: Contact pets	51.08
K15: Exposure to faecal contaminants (public toilets)	87.47
K16: Frozen food imported from abroad (seafood, meat)	86.27
K17: Aerosols (aerosols formed when droplets are mixed in the air and can cause infection when inhaled)	95.49

In the third part of the knowledge section, symptoms and manifestations of COVID-19 infection, 77.34% of respondents correctly responded to all eight items. The correct response rate for "fever," "cough," "fatigue," "pharyngalgia," "myalgia," and "dyspnea" were over 90%. "rhinobyon" item had the lowest rate of correct responses (85.17%) (Table 3).

In the last part of this section, preventive measures against SARS-CoV-2 infection, 55.69% of respondents answered all nine questions correctly. The correct response rate of "taking antibiotics," and "eating garlic" were only 14.37 and 17.55%, respectively. Some respondents had the misperception that eating garlic and taking antibiotics could prevent COVID-19. The correct response rate for the remaining seven items exceeded 95% (Table 4).

TABLE 3 Symptoms and manifestations of COVID-19 infection.

COVID-19 infection symptoms or manifestations	Accuracy (%)
K18: Fever	98.85
K19: Cough	97.60
K20: Fatigue	98.11
K21: Rhinobyon/running nose	85.17
K22: Pharyngalgia	92.49
K23: Myalgia	92.40
K24: Vomiting/diarrhea	87.98
K25: Dyspnea	97.47

TABLE 4 Preventive measures for SARS-CoV-2 infection.

Preventive measures for SARS-CoV-2 infection	Accuracy (%)
K26: Frequent hand-washing	99.77
K27: Keep a distance from people	99.72
K28: Avoid rubbing eyes, mouth and nose	98.89
K29: Wear a mask in public	99.95
K30: Try not to touch elevator buttons, door handles and other public facilities directly	99.12
K31: Ventilate the room	99.36
K32: Take antibiotics	14.37
K33: Eat garlic	17.55
K34: COVID-19 vaccination	95.12

Univariate analysis of COVID-19-related KAP scores

For COVID-19 knowledge scores, the average score was 8.94 ± 0.79. The mean ± standard deviation for COVID-19 knowledge scores was 8.88 ± 0.87 in men and 8.97 ± 0.74 in women ($P = 0.014$). Knowledge scores among respondents aged 31–50 years were higher than those among respondents between age 18–30 years and those over 50 years of age ($P < 0.001$). Respondents with higher education levels had higher COVID-19 knowledge scores, with the highest mean score among those with a master's degree or above (9.03 ± 0.76, $P < 0.001$). Participants with higher monthly income also had higher scores, with the highest mean score among those with monthly income more than 10,000 RMB (8.98 ± 0.78, $P = 0.007$). Mental laborers had the highest mean score (9.06 ± 0.74) for COVID-19 knowledge; those with other occupations and physical workers had lower scores (8.78 ± 0.82 and 8.81 ± 0.87, respectively; $P < 0.001$). Thus, sex, age, education, monthly income, and occupation were factors significantly associated with COVID-19 knowledge score.

For attitudes regarding COVID-19, the average score was 5.97 ± 1.58; this score was higher among men (6.16 ± 1.61) than among women ($P < 0.001$). Older respondents had higher attitude scores, with the highest scores among respondents aged more than 50 years ($P < 0.001$). Respondents with a technical secondary school education and below had the highest attitude scores. Interestingly, the higher the level of education, the lower the COVID-19 attitude score ($P < 0.001$). Physical laborers had the highest mean attitude score (6.08 ± 1.51); mean scores among mental laborers and students were 6.00 ± 1.58 and 5.60 ± 1.31, respectively (P=0.008). Sex, age, education level, and occupation were factors significantly associated with COVID-19 attitude scores.

Regarding practices related to COVID-19, the average score was 7.03 ± 3.14, and mean scores were higher among men (7.50 ± 3.01) than women ($P < 0.001$), Respondents aged between 41 and 50 years had the highest practice scores whereas those aged 18–30 years had the lowest scores. Scores were similar among respondents over 50 years old and those aged 41–50 years ($P < 0.001$). Mean practice scores among respondents living in urban and rural areas were 6.91 ± 3.18 and 7.38 ± 3.00, respectively, with higher scores among rural residents (P=0.003). Respondents with a technical secondary school degree and below had the highest practice scores (8.45 ± 2.63). Similar to COVID-19-related attitude scores, the higher the level of education, the lower the COVID-19-related practice score ($P < 0.001$). Respondents with monthly income 3,001–5,000 RMB and 5,001–10,000 RMB had mean practice scores 7.27 ± 2.98 and 7.18 ± 3.10, respectively ($P = 0.003$). Physical laborers had the highest mean COVID-19 practice score (7.34 ± 3.08) and students had the lowest mean score (6.47 ± 3.04). Sex, age, residential area, education, monthly income, and occupation were factors significantly associated with COVID-19 practice score.

As for total KAP score, the average score was 21.93 ± 4.18, with men scoring higher (22.55 ± 4.06) than women ($P < 0.001$). Older respondents had a higher mean total score, with the highest among those over 50 years old (22.59 ± 4.29). Respondents living in rural areas had higher mean total scores (22.28 ± 3.90) than urban residents ($P = 0.027$). Respondents with higher education levels had lower total KAP scores, with the lowest among respondents with a master's degree or above (21.21 ± 4.36, $P < 0.001$). Respondents with monthly income 3,001–5,000 and 5,001–10,000 RMB had similar mean scores, which were higher than scores among respondents with monthly income 3,000 RMB and below and 10,000 RMB and above ($P = 0.002$). Physical laborers had the highest mean total KAP score (22.23 ± 4.00) and students had the lowest (20.91 ± 3.82) ($P = 0.002$). Sex, age, residential area, education level, monthly income, and occupation were factors significantly associated with COVID-19 total KAP score (Table 5).

Binary logistic regression analysis of factors associated with COVID-19-related KAP scores

In Logistic Regression Analysis, Compared With Women, men Had Higher KAP Scores (Odds Ratio [OR]: 1.59; 95% Confidence Interval, [95% CI]: 1.31–1.92; $P < 0.001$). Older Respondents Also Had Higher Scores (OR: 2.00; 95% CI:1.43–2.80; $P < 0.001$). Respondents With Higher Education Levels Had Lower KAP Scores (OR: 0.45; 95% CI:0.29–0.68; $P < 0.001$). Binomial Logistic Regression Analysis Showed That sex, age, and Education Level Were Significantly Associated With Total KAP Toward COVID-19 (Table 6).

Discussion

Public health education is an effective measure to prepare the population for a catastrophic health emergency so that individuals can take preventive measures to reduce the likelihood of contracting a deadly disease (26). In our study, the average correct response rate for knowledge related to COVID-19 was close to 90%. This may be related to health education and dissemination of information to the Chinese public, consistent with the results of two previous studies in China (14, 27). Our study results indicated that 91.2% of respondents were aware that COVID-19 is an acute viral infection, which was slightly lower than the rate (97%) reported by Raza et al. (28). However, most respondents were unaware of the severity of COVID-19 and that there was still no specific treatment available at the time of the survey. However, 99.95% of respondents knew that wearing a mask was one way to prevent COVID-19 infection, which was consistent with the findings of Salman et al. (29). Most participants (99.72%) believed that keeping a physical distance from other people was a good way to avoid COVID-19 infection, which was similar to previous KAP studies conducted in China, the United Kingdom, South Korea, Indonesia, and the United Arab Emirates during infectious disease outbreaks (16, 26, 30, 31). Participants correctly identified the symptoms of COVID-19 with a high accuracy rate of over 85%, indicating a good understanding of this information. However, most participants mistakenly believed that eating garlic and taking antibiotics could prevent SARS-CoV-2 infection. These findings highlight that the responsible authorities should improve the dissemination of correct COVID-19-related information to improve knowledge and practices and help people prevent COVID-19 infection.

In logistic regression analysis, sex, age, and education level were significantly associated with the total KAP toward COVID-19. The relationship between sex, age, education, and KAP was consistent with attitudes and practices. The ORs indicated that male sex and age were predictors of high total

TABLE 5 Comparison of COVID-19 related KAP scores between different characteristics.

Characteristics		Number of participants (%)	Knowledge			Attitude			Practice			Total KAP		
			$\bar{x} \pm s$	t/F	*P*	$\bar{x} \pm s$	t/F	*P*	$\bar{x} \pm s$	t/F	*P*	$\bar{x} \pm s$	t/F	*P*
Gender	Male	857(39.5)	8.88 ± 0.87			6.16 ± 1.61			7.50 ± 3.01			22.55 ± 4.06		
	Female	1,314(60.5)	8.97 ± 0.74	6.027	0.014	5.84 ± 1.54	22.46	<0.001	6.72 ± 3.19	32.483	<0.001	21.53 ± 4.21	31.462	<0.001
Age-group (years)	18–30	639(29.4)	8.89 ± 0.76			5.67 ± 1.44			6.60 ± 3.08			21.16 ± 4.00		
	31–40	698(32.2)	9.04 ± 0.69			6.00 ± 1.56			6.98 ± 3.18			22.03 ± 4.25		
	41–50	528(24.3)	8.99 ± 0.78			6.14 ± 1.61			7.24 ± 3.10			22.37 ± 4.10		
	≥51	306(14.1)	8.69 ± 1.00	15.619	<0.001	6.21 ± 1.72	12.624	<0.001	7.70 ± 3.13	9.576	<0.001	22.59 ± 4.29	12.115	<0.001
Region	Urban	1,632(75.2)	8.95 ± 0.79			5.95 ± 1.57			6.91 ± 3.18			21.82 ± 4.26		
	Rural	539(24.8)	8.88 ± 0.81	3.244	0.072	6.01 ± 1.59	0.598	0.44	7.38 ± 3.00	9.059	0.003	22.28 ± 3.90	4.892	0.027
Education	Technical secondary school and below	253(11.7)	8.52 ± 0.97			6.46 ± 1.79			8.45 ± 2.63			23.42 ± 3.77		
	Junior College/University	1,559(71.8)	8.98 ± 0.74			5.91 ± 1.55			6.97 ± 3.12			21.86 ± 4.14		
	Master degree or above	359(16.5)	9.03 ± 0.76	42.169	<0.001	5.88 ± 1.45	14.206	<0.001	6.30 ± 3.29	36.802	<0.001	21.21 ± 4.36	22.057	<0.001
Monthly income/ China Yuan	≤3,000	290(13.4)	8.80 ± 0.77			5.82 ± 1.55			6.88 ± 3.10			21.49 ± 3.99		
	3,001–5,000	524(24.1)	8.92 ± 0.87			6.05 ± 1.67			7.27 ± 2.98			22.24 ± 4.06		
	5,001–10,000	840(38.7)	8.97 ± 0.75			6.03 ± 1.57			7.18 ± 3.10			22.18 ± 4.14		
	>10,000	517(23.8)	8.98 ± 0.78	4.026	0.007	5.86 ± 1.50	2.59	0.051	6.63 ± 3.36	4.628	0.003	21.47 ± 4.41	5.14	0.002
Occupation	Physical labor	290(13.4)	8.81 ± 0.87			6.08 ± 1.51			7.34 ± 3.08			22.23 ± 4.00		
	Other	524(24.1)	8.78 ± 0.82			5.94 ± 1.66			7.04 ± 3.30			21.76 ± 4.31		
	Students	840(38.7)	8.84 ± 0.76			5.60 ± 1.31			6.47 ± 3.04			20.91 ± 3.82		
	Mental labor	517(23.8)	9.06 ± 0.74	20.32	<0.001	6.00 ± 1.58	3.921	0.008	7.03 ± 3.09	2.797	<0.039	22.09 ± 4.20	4.91	0.002

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TABLE 6 Comparison of different COVID-19-related knowledge, attitude, and practice scores according to different participant characteristics.

Characteristics		Score of knowledge (≥7)	OR (95% CI)	P	Score of attitude (≥7)	OR (95% CI)	P	Score of practice (≥7)	OR (95% CI)	P	Score of total KAP (≥21)	OR (95% CI)	P
Gender	Female (Ref)	1,287(97.9%)			283(21.5%)	1		755(57.5%)	1		785(59.7%)	1	
	Male	824(96.1%)			256(29.9%)	1.51(1.23–1.84)	<0.001	602(70.2%)	1.77(1.46–2.14)	<0.001	599(69.9%)	1.59(1.31–1.92)	<0.001
Age-group (years)	18–30 (Ref)	624(97.7%)	1		103(16.1%)	1		358(56.0%)	1		349(54.6%)	1	
	31–40	690(98.9%)	2.30(0.96–5.50)	0.061	187(26.8%)	1.67(1.24–2.24)	0.001	432(61.9%)	1.27(0.99–1.62)	0.058	460(65.9%)	1.56(1.21–2.00)	0.001
	41–50	514(97.3%)	1.11(0.52–2.37)	0.786	150(28.4%)	1.71(1.26–2.34)	0.001	342(64.8%)	1.40(1.07–1.83)	0.014	349(66.1%)	1.53(1.17–2.02)	0.002
	≥51	283(92.5%)	0.44(0.22–0.90)	0.024	99(32.4%)	1.92(1.35–2.72)	<0.001	225(73.5%)	1.85(1.33–2.58)	<0.001	226(73.9%)	2.00(1.43–2.80)	<0.001
Education	Technical secondary school and below (Ref)	233(92.1%)	1		94(37.2%)	1		203(80.2%)	1		199(78.7%)	1	
	Junior College/University	1,523(97.7%)	2.91(1.60–5.29)	<0.001	364(23.3%)	0.54(0.39–0.73)	<0.001	953(61.1%)	0.49(0.35–0.69)	<0.001	977(62.7%)	0.52(0.37–0.74)	<0.001
	Master degree or above	355(98.9%)	5.07(1.64–15.69)	0.005	81(22.6%)	0.52(0.35–0.76)	0.001	201(56.0%)	0.43(0.29–0.65)	<0.001	208(57.9%)	0.45(0.29–0.68)	<0.001
Occupation	Physical labor (Ref)	281(94.9%)			73(24.7%)	1		198(66.9%)			199(67.2%)		
	Other	515(96.4%)			131(24.5%)	1.07(0.77–1.51)	0.681	330(61.8%)			327(61.2%)		
	Students	175(98.9%)			23(13.0%)	0.90(0.51–1.59)	0.723	93(52.5%)			92(52.0%)		
	Mental labor	1,140(97.9%)			312(26.8%)	1.47(1.07–2.02)	0.017	736(63.2%)			766(65.8%)		

KAP, and education level was negatively associated with high total KAP. Women scored higher than men for COVID-19-related knowledge, which was consistent with past studies (17, 26, 32). Highly educated respondents with a master's degree or above had better knowledge levels than respondents with lower education levels. A study conducted in China and Iran had a similar result (14, 17). More highly educated individuals may have more comprehensive knowledge of COVID-19 obtained from multiple sources. Mental laborers had the highest COVID-19 knowledge scores among all occupations. More highly educated people usually work in professions requiring more rigorous training and qualifications, which might explain the higher levels of COVID-19 knowledge in this group. Lower knowledge levels may be the result of relying on less credible information sources, which should be addressed in a timely manner. We propose that health ministries and government agencies arrange awareness and educational campaigns to promote COVID-19 prevention and control.

Univariate analysis showed that men had higher COVID-19 attitude and practice scores than women. Men were more willing to be vaccinated than women, a finding supported by other evidence reported in the literature (33, 34). This may be owing to concerns among women about the safety and effectiveness of COVID-19 vaccines, which is consistent with research conducted in China on COVID-19 vaccination willingness, where men were more likely to be vaccinated against COVID-19 (35). Older respondents had higher practice and attitude scores than younger ones, possibly because older people feel that they are at higher risk of contracting COVID-19. This group also has more limited sources of knowledge about COVID-19 and vaccines, mostly official media, and little exposure to false information and rumors. This is consistent with findings reported by Lazarus et al. (36) and Nguyen et al. (37). Respondents with lower education levels and physical laborers had higher COVID-19 practice and attitude scores than those with higher education levels and mental workers. This finding was consistent with those of a survey by Al-Marshoudi et al. (38) showing that people with low literacy levels were more willing to be vaccinated than those with post-secondary school or higher education levels, and a previous study of influenza vaccination reported similar results (39). This may be because individuals with higher education levels or professional occupations are concerned about the safety and effectiveness of COVID-19 vaccines. These groups may also have greater access to misinformation about COVID-19 and may be more influenced by rumors. A similar effect was recognized in a study showing that misinformation regarding COVID-19 directly affects health care workers (40). This indicates that even educated people can be affected by rumors. Reuben et al. (41) stated that unclear information and negative attitudes may lead to suffering and panic during an epidemic (40, 42). The Health Committee and Centers for Disease Control should disseminate correct information about COVID-19 in a timely and effective manner and find ways to address the fabrication and spread of rumors. COVID-19 practice scores among people living in rural areas were higher than those of their urban counterparts. People in rural areas have relatively low education levels, and most are engaged in physical labor. Most rural residents receive COVID-19-related information through official channels and are less affected by rumors. By knowing people's awareness of COVID-19 and their views on COVID-19 vaccine, and adopting epidemic prevention and control measures, we can spread correct knowledge and formulate appropriate prevention strategies, which play a crucial role in the management of COVID-19.

To control the COVID-19 pandemic, government agencies must launch effective public health campaigns. There is an urgent need to implement awareness-raising interventions at community level to educate the public regarding precautionary measures like wearing masks, correct hand hygiene, and the importance of social distancing. Mass media campaigns, talks held at educational institutions, and health promotion programs to provide health-related recommendations in rural and urban areas and eliminate misinformation and rumors are an important way forward.

This study had several limitations. We conducted online convenient sampling, which is inferior to random sampling; thus, the sample may not well represent the general public in China. We administered a cross-sectional survey and confounding factors could not be controlled to determine a causal relationship. Cohort studies are needed in the future to obtain additional information regarding KAP among the public and factors affecting KAP with respect to COVID-19. Online data collection will miss individuals who cannot access the Internet, such as older people and residents of remote areas. Because participants in our study were from some areas that were not severely affected by COVID-19, our study findings are not generalizable to residents living in other areas of China. Future studies should recruit a more representative and larger participant pool. Our questionnaire was conducted from September to October 2020; at that time, the epidemic situation was relatively stable, but the vaccination situation in China has changed since then. Nearly the entire Chinese population has now been vaccinated; therefore, our study findings cannot well represent the current situation. It is necessary to investigate KAP with regard to COVID-19 at different periods during the ongoing pandemic.

Conclusion

The findings of this study suggest that the general public in China has high levels of KAP regarding COVID-19 under the present conditions of regular prevention and control of COVID-19. Male sex and older age were predictors of high total KAP whereas education level was negatively associated with high total KAP. To improve public awareness regarding prevention and control of COVID-19, official and public social media platforms that are popular among Chinese people should be used to disseminate accurate information regarding COVID-19 prevention and control.

Data availability statement

The datasets generated and analyzed during this study are not publicly available due to the institute's data security and sharing policy, but are available from the corresponding author on reasonable request.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the Local Legislation and Institutional requirements. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional requirements.

Author contributions

Conceptualization: HL. Methodology, formal analysis, and investigation: HL and JY. Writing—original draft preparation: JY. Writing—review and editing: HL, JY, YL, QH, and CS. All authors contributed to the article and approved the submitted version.

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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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EDITED BY
José Tuells,
University of Alicante, Spain

REVIEWED BY
Alexander Chern,
NewYork Presbyterian Hospital,
United States
Santosh Kumar Swain,
Siksha O Anusandhan University, India

*CORRESPONDENCE
Ying Yang
yangying@bzmc.edu.cn
Chengyi Qu
qu430426@sxmu.edu.cn
Philip H.-S. Jen
jenp@missouri.edu

†These authors have contributed equally to this work and share first authorship

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Behavioral compliance with preventive health measures for students with and without hearing disability during COVID-19 pandemic: A cross-sectional study

Ying Yang[1*†], Yulu Liu[1†], Yanan Xiao[1], Chengyi Qu[1,2*] and Philip H.-S. Jen[1,3*]

[1]Department of Hearing and Speech Rehabilitation, Binzhou Medical University, Yantai, China, [2]Department of Epidemiology, Shanxi Medical University, Taiyuan, China, [3]Division of Biological Sciences and Interdisciplinary Neuroscience Program, University of Missouri-Columbia, Columbia, MO, United States

Background: Hearing loss affects over 1.5 billion individuals worldwide. Their disability and limited access to the coronavirus (COVID-19) pandemic information make them suffer a greater degree than ordinary people. However, the quantitative studies on the implementation of behavior compliance with preventive health measures for vulnerable groups such as people with hearing disability were limited. The purpose of this study was to explore the compliance with pandemic-related protective health measures among people with hearing disability.

Design: A cross-sectional survey, population-based cohort study of students aged 12–26 years with and without hearing disability was conducted. Behavioral compliance with preventive health measures was collected from the general education institutions and special education schools using an online questionnaire. Logistic regression and structural equation model were used to determine the associations among the demographic variables, different degrees of mental health status and psychological impacts, and preventive health behaviors.

Results: Among 1,589 participants, 485 (30.5%) students are with hearing disability (SHD), and 1,104 (69.5%) students with normal hearing (SNH). The SHD has a significantly lower degree of behavioral compliance with the preventive health measures than SNH has. Hearing disability and anxiety [odds ratio (OR) = 1.54–1.76, $p < 0.05$] are risk factors for avoiding sharing of utensils during mealtime. Hearing disability, male sex, father's education level, mother's profession, bedtime after 11:00 p.m., anxiety, and depression (OR = 1.45–2.95, $p < 0.05$) are risk factors for hand hygiene. Male sex (OR = 2.13, $p < 0.001$) is risk factor and being aged below 18 years old (OR = 0.62, $p = 0.03$) is protective factor for wearing masks. Exercise (OR = 0.32–0.70, $p < 0.01$) is the most protective factor for preventive health behaviors. Mediating effect of mental health status and psychological impacts between hearing level and the compliance with the preventive health measures was −0.044 (95% CI: −0.068 to −0.027).

Conclusions: To reduce the risk of contraction, update pandemic information, essential communication services, extra assistance, and support should be provided to these disabled persons who are more susceptible to a public health emergency.

KEYWORDS

preventive health measures, COVID-19, health behaviors, risk factors, hearing disability

Introduction

Since the identification of several novel coronavirus (COVID-19) infection cases in December 2019 in Wuhan, Hubei Province, the worldwide spread of the pandemic has created a global health crisis (1). According to the World Health Organization (WHO), as of 12 March 2022, there have been 460,280,168 infected patients and 6,050,018 deaths caused by the COVID-19 pandemic (2).

This fatal COVID-19 is caused by the SARS-CoV-2 virus which transmits through respiratory droplets and close contact with people of all ages (3). The virus has an incubation period between 2 days and 2 weeks and its transmission can be asymptomatic (4).

Since the outbreak of the pandemic, the Chinese government has immediately implemented strict preventive health measures across the country (5). The WHO has also announced several preventive health measures including washing hands with soap and water, using an alcohol-based hand rub, covering the nose and mouth during coughing or sneezing, using utensils separately, and wearing a mask during social contact (6).

It has been shown that adequate preventive health measures aimed at vulnerable populations can effectively block the spread of respiratory diseases (7). In addition to preventing the pandemic spread, medical-grade masks can effectively filter out pathogens (8). Further study has also shown that mass masking and general hygiene at the early stage of the COVID-19 pandemic produces a 50% decline in infectious respiratory diseases (9). The spread of the pandemic, strict lockdown measures, and heavy economic burdens have produced the risk of death and enormous psychological impacts on the mental health of the population (10). However, the challenges faced by vulnerable groups are even more acute. Specifically, people with disabilities have the same healthcare needs as those without disabilities such as access to vaccinations or personal protection (11, 12). In addition, people with disabilities may require access to specific specialist services such as rehabilitation and assistive devices (12). Therefore, the need for healthcare services may be higher among people with disabilities, but their access to these services is poorer than for people without disabilities (13). Compared to the general population, individuals with disabilities have less access to healthcare services and more barriers to communication and are thus more likely to have a higher risk of depression, lower life satisfaction, and enhanced loneliness (14, 15).

The COVID-19 pandemic and its associated restrictions have posed challenges, especially to individuals with disabilities. Indeed they face barriers to implementing basic health measures and may have a higher risk of contracting COVID-19 (16). Individuals with disabilities make up about 15% of the global population, and it is important to include information on disabilities in the assessment of pandemic effects (17). The WHO has stated that additional considerations from governments, healthcare systems, disability service providers, institutional settings, and the disability community are needed for people with disabilities during the COVID-19 (18).

In particular, individuals with a hearing disability have poorer mental health than the general population and are highly vulnerable to major emergencies in terms of preparing for, responding to, and recovering from emergencies (19, 20). People with hearing disability often use gestures, while relying on visual information to enhance the comprehension of spoken messages to achieve communication (21). Measures against COVID-19 have significantly changed communication strategies, most people with hearing disability had difficulty in auditory communication with people wearing masks, especially in noisy surroundings or with physical distancing (22). Furthermore, a study has shown that hearing devices (i.e., hearing aids and cochlear implants) and speech services for students with hearing disability (SHD) that are essential for recovering or restoring patients' communication skills have

Abbreviations: SHD, students with hearing disability; SNH, students with normal hearing; DASS-21, Depression Anxiety and Stress 21; IES-R, Impact of Events Scale-Revised.

not been consistently accessible during COVID-19 (23). The psychological distress of these vulnerable persons has been further accentuated because of limitations in communication, delayed access, and comprehension of the updated pandemic situation (23). Indeed, our previous study has shown that SHD suffers from a higher degree of mental stress and psychological distress than peer health groups during the COVID-19 pandemic (24).

On the other hand, a recent study has shown that the psychological status of persons is significantly associated with the preventive health measures taken during the pandemic (25). This is substantiated by the report that measures taken to prevent COVID-19 transmission have a protective psychological effect in the early stages of the pandemic outbreak (26). Furthermore, individual and social variables can influence compliance behavior with the preventive health measures during the COVID-19 pandemic (27).

All these studies prompt us to hypothesize that behavioral compliance with the preventive health measures during the COVID-19 pandemic would be different between ordinary and disabled persons. To test our hypothesis, we conducted a cross-sectional study of the behavioral compliance with the preventive measures between SHD and students with normal hearing (SNH) in multiple Chinese cities affected by the COVID-19 pandemic. Specifically, we statistically compared their degree of compliance with the preventive health measures to multiple demographic variables, mental health status and psychological impacts induced during the COVID-19 pandemic. Furthermore, we explore the relationship between hearing level, mental health status and psychological impacts, and preventive health behaviors.

Materials and methods

Study design and study population

The survey was conducted from 15 June 2020 to 23 November during the COVID-19 pandemic recurrence in 21 provinces (Liaoning, Henan, Heilongjiang, etc.) and 1 municipality (Beijing) in China. All data were collected using the cross-sectional survey design and snowball sampling method through Questionnaire Star (https://www.wjx.cn/) survey platform. Specifically, these participants were from middle schools, high schools, and universities (Binzhou Medical University; Liaoning Special Education Teachers College; Harbin Institute of Special Education, China, etc.) and special education schools (Yantai, Shenyang, Harbin, etc.). The study was approved by the Institutional Review Board of Binzhou Medical University (BMU-IRB-2020-54).

Study tool

The information contained in the questionnaire includes the following categories.

(1) Demographic data including gender, age, educational background, parents' profession and education level, family living status, communication strategies, satisfaction with current communication mode, bedtime, physical activity, and information on hearing loss based on their previous diagnosis in otolaryngology;
(2) Data on compliance with four preventive health measures including avoiding sharing of utensils (e.g., chopsticks) during mealtime, washing hands with soap and water, washing hands immediately after coughing or sneezing, rubbing the nose, and wearing a mask with or without the pandemic symptoms. Participants rated on each item using a 5-point Likert scale (0 = "never"; 4 = "always");
(3) The mental health status and psychological impacts of the participants were assessed using the Chinese version of the Depression Anxiety and Stress 21 (DASS-21) scale and the Impact of Events Scale-Revised (IES-R) (24). The suggested cut-off scores for detecting symptoms of major stress, anxiety, depression, and IES-R are 14, 7, 9, and 23, respectively.

Statistical analysis

The prevention scores for these four basic health measures derived from SHD and SNH were compared using the following tests for statistical significance. We defined a prevention score of >2 as a low-risk score and ≤ 2 as a high-risk score. We first calculated the proportion of high-risk and low-risk students in each group. We then used univariate analysis to statistically compare the distribution of students with high-risk scores to students with low-risk scores between SHD and SNH in demographic variables, different degrees of mental health status and psychological impacts. All the variables were subsequently analyzed by a multivariable regression model using SPSS Statistic 21.0 (IBM Corporation, New York, NY, United States) at a significance level of $p < 0.001$–0.05.

The structural equation model was conducted using the software Amos 24.0 (IBM Corp., Chicago, IL, USA). According to the hearing thresholds for the better ear, all respondents were divided into five hearing levels: normal hearing ($\leq$25 dB HL), mild hearing loss (26–40 dB HL), moderate hearing loss (41–60 dB HL), severe hearing loss (61–80 dB HL), and profound hearing loss ($\geq$81 dB HL). (I) Pearson correlation analysis was used to explore the relationship among the hearing level, mental health status and psychological impacts as well as the prevention scores of four preventive health measures. Then, we performed the linear regression model to examine the relationship between the hearing level and the scores of four preventive measures to explore whether there was a dose-dependent effect between hearing level and compliance with preventive measures. (II) The Amos 24.0 software was used to establish the structural equation model of the relationship among three variables: hearing level, mental health status and psychological impacts, and compliance with four preventive health measures. (III) The bootstrap method was used to determine the mediating effect of mental health status and psychological impacts between the level of hearing and compliance with four preventive health measures.

Results

Of the 1,697 students with and without hearing loss collected from 25 provinces and 2 municipalities during the study period, 1,589 were available for analysis after excluding unreliable information (i.e., those participants outside the age range between 12 and 26 years old, incomplete or unclear information, etc.) with the questionnaire effective rate reaching 96.2% (97.4% for SNH, 93.4% for SHD). The students who reported any neurological disorders or cognitive impairment were excluded. There were 1,005 (63%) female participants and 584 (37%) male participants with age ranging from 12 to 26 years [12–14 years (421 [27%]), 15–18 years (628 [40%]), 19–22 years (519 [33%]), and 22–26 years (17 [1%])].

There are 1,104 (69.5%) SNH and 485 (30.5%) SHD. There are 373 (76.9%) SHD with profound hearing loss (≥ 81 dB HL in the better ear) and 361 (74.4%) SHD fitted with hearing aids or cochlear implantation. The communication strategies for 380 (78.4%) SHD is the gesture, lip-language, gesture plus lip-language, and word.

Comparison of demographic variables, mental health status and psychological impacts with the compliance with four health measures between SNH and SHD

Figure 1 compares the association of the demographic variables with the high-risk scores (≤2) for four preventive health measures between SNH and SHD. The percent of participants with a high risk of ≤2 prevention score was significantly higher for the SHD than for the SNH in all demographic variables [odds ratio (OR) = 1.78–3.28, 95% CI: 1.05 to 5.04, $p < 0.05$] (Figure 1A, Table 1 first column).

Excluding the general and or special school educational background, parents' education level with senior high school and above, and satisfaction with the current communicative mode, the percent of participants with a high risk of ≤2 prevention score in the preventive measure of washing hands with soap and water was significantly higher for the SHD than for the SNH in all other demographic variables (OR = 1.62–3.41, 95% CI: 1.00 to 6.44, $p < 0.05$) (Figure 1B, Table 1 second column).

Furthermore, the percent of participants with a high risk of ≤2 prevention score in the preventive measure of washing hands immediately after coughing, or sneezing, rubbing the nose was significantly higher for SHD in four demographic variables, including females, aged 18 years old and above, general school educational background, bedtime before 11:00 p.m. (OR = 1.46–2.31, 95% CI: 1.05 to 4.40, $p < 0.05$) (Figure 1C, Table 1 third column). Also, <41.0% of SNH and SHD for both hand hygiene had ≤2 high-risk prevention scores in all demographic variables when compared with <60.0% of SNH and SHD for avoiding sharing of utensils during mealtime (Table 1 first, second, third columns).

Respectively, the percent of SNH and SHD that had ≤2 high-risk prevention scores of wearing masks were <10% and 17% in all demographic variables studied. However, the percent of this preventive measure was significantly higher for the SHD than for the SNH in nine demographic variables, including females, aged 18 years old and above, general school educational background, parents' education level with junior high school and below, parents' profession with individual and non-working, living with father or mother, grandparents or other, communicative means with gesture and (or) lip-language or word, exercising during the COVID-19 pandemic, bedtime before 11:00 p.m. (OR = 1.83–3.20, 95% CI: 1.08 to 7.03, $p < 0.05$) (Figure 1D, Table 1 fourth column).

Figure 2 compares the association of mental health status and psychological impacts with the preventive health measures between SNH and SHD. The percent of the SHD that had ≤2 high-risk prevention scores were significantly higher for avoiding sharing utensils during mealtime and washing hands with soap and water than the SNH regardless of whether their mental health status and psychological impacts on stress, anxiety, depression, and IES-R or not (OR = 1.83–3.21, 95% CI: 1.12 to 5.22, $p < 0.05$) (Figures 2A,B, Table 2 first and second columns).

However, the percent of washing hands immediately after coughing, sneezing, rubbing the nose was only significantly higher for the SHD than for the SNH when they suffered anxiety (OR = 1.63, 95% CI: 1.04 to 2.55, $p < 0.05$) (Figure 2C, Table 2 third column).

When the students suffered anxiety, the percent of the SHD that had ≤2 high-risk prevention scores for wearing masks with or without the pandemic symptoms was significantly higher for the SHD than for the SNH (OR = 1.91, 95% CI: 1.00 to 3.62, $p < 0.05$). On the other hand, when the students did not suffer stress, anxiety, depression, and IES-R, the percent of the compliance with this health measure was significantly lower for the SHD than for the SNH (OR = 1.70–2.14, 95% CI: 1.08 to 3.40, $p < 0.05$) (Figure 2D, Table 2 fourth column).

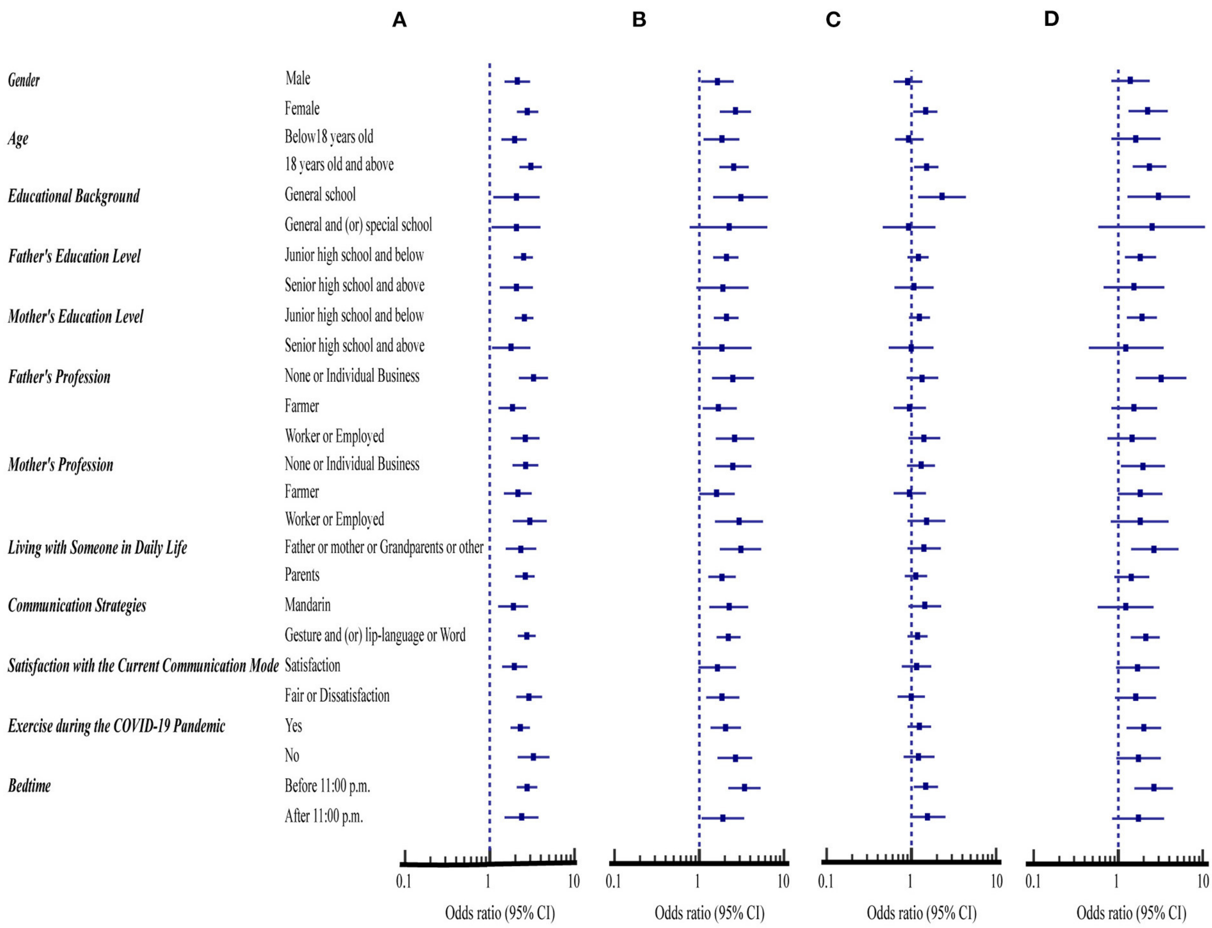

FIGURE 1
Comparison of demographic variables with the compliance with four health measures between students with normal hearing (SNH, $n = 1{,}104$) and with hearing disability (SHD, $n = 485$). **(A)** Avoiding sharing of utensils during mealtime. **(B)** Washing hands with soap and water. **(C)** Washing hands immediately after coughing, or sneezing, rubbing the nose. **(D)** Wearing masks with or without the pandemic symptoms.

Association of demographic variables, mental health, and psychological status with compliance with four health measures in SNH and SHD

Figure 3 summarizes the association of demographic variables, mental health status and psychological impacts with the prevention scores for all students. Multivariate analysis showed that hearing disability and anxiety status (OR = 1.54–1.76, 95%CI: 1.00 to 3.07, $p < 0.05$) were related to an increased risk of sharing of utensils during mealtime while exercise was a protective factor (OR = 0.70, 95%CI: 0.55 to 0.90, $p < 0.01$) for avoiding sharing of utensils during mealtime (Figure 3A).

In addition, hearing loss, male sex, father's education level of junior high school and below, mother's profession of worker or employed, anxiety, and depression were related to increased risks of the compliance with washing hands with soap and water (OR = 1.67–2.95, 95%CI: 1.06 to 6.52, $p < 0.05$) (Figure 3B).

Furthermore, male sex, father's education level of junior high school and below, and bedtime after 11:00 p.m. were risk factors for the compliance with washing hands immediately after coughing, or sneezing, rubbing the nose (OR = 1.45–1.56, 95%CI: 1.11 to 2.20, $p < 0.05$) (Figure 3C). The exercise was the only protective factor for hand hygiene (OR = 0.32–0.39, 95%CI: 0.23 to 0.50, $p < 0.001$).

Similarly, male sex (OR = 2.13, 95%CI: 1.44 to 3.14, $p < 0.001$) was a risk factor while exercise and being age below 18 years old (OR = 0.55–0.62, 95%CI: 0.37 to 0.96, $p < 0.05$) were the protective factors for wearing masks with or without the pandemic symptoms (Figure 3D).

TABLE 1 The percentage of demographic variables with health behavior of ≤2 high-risk prevention scores among students with and without hearing disability.

	Group	Avoiding sharing of utensils during mealtime	Washing hands with soap and water	Washing hands immediately after coughing, or sneezing, rubbing the nose	Wearing masks with or without the pandemic symptoms
Gender					
Male	SNH	30.4% (111)	13.7% (50)	26.8% (98)	9.9% (36)
	SHD	47.9% (105)	20.5% (45)	25.1% (55)	13.2% (29)
Female	SNH	26.4% (195)	7.4% (55)	19.4% (143)	4.6% (34)
	SHD	50.0% (133)	17.7% (47)	25.9% (69)	9.8% (26)
Age					
Below 18 years old	SNH	30.8% (101)	10.4% (34)	23.8% (78)	5.2% (17)
	SHD	46.2% (114)	17.4% (43)	22.7% (56)	8.1% (20)
18 years old and above	SNH	26.4% (205)	9.1% (71)	21.0% (163)	6.8% (53)
	SHD	52.1% (124)	20.6% (49)	28.6% (68)	14.7% (35)
Educational background					
General school	SNH	27.5% (292)	9.5% (101)	21.7% (230)	6.4% (68)
	SHD	43.9% (18)	24.4% (10)	39.0% (16)	17.1% (7)
General and (or) special school	SNH	32.6% (14)	9.3% (4)	25.6% (11)	4.7% (2)
	SHD	49.5% (220)	18.5% (82)	24.3% (108)	10.8% (48)
Father's education level					
Junior high school and below	SNH	30.3% (203)	11.5% (77)	23.7% (159)	7.2% (48)
	SHD	51.8% (197)	21.1% (80)	27.1% (103)	12.4% (47)
Senior high school and above	SNH	23.8% (103)	6.5% (28)	18.9% (82)	5.1% (22)
	SHD	39.0% (41)	12.4% (12)	20.0% (21)	7.6% (8)
Mother's education level					
Junior high school and below	SNH	29.6% (219)	10.9% (81)	22.4% (166)	6.9% (51)
	SHD	51.6% (210)	20.4% (83)	26.5% (108)	12.3% (50)

(Continued)

TABLE 1 (Continued)

	Group	Avoiding sharing of utensils during mealtime	Washing hands with soap and water	Washing hands immediately after coughing, or sneezing, rubbing the nose	Wearing masks with or without the pandemic symptoms
Senior high school and above	SNH	23.9% (87)	6.6% (24)	20.6% (75)	5.2% (19)
	SHD	35.9% (28)	11.5% (9)	20.5% (16)	6.4% (5)
Father's profession					
None or Individual business	SNH	24.1% (82)	7.6% (26)	21.5% (73)	4.4% (15)
	SHD	50.9% (83)	17.2% (28)	27.0% (44)	12.9% (21)
Farmer	SNH	33.2% (105)	12.7% (44)	23.7% (75)	7.6% (24)
	SHD	47.8% (85)	19.7% (35)	23.0% (41)	11.2% (20)
Worker or Employed	SNH	26.6% (119)	8.7% (39)	20.8% (93)	6.9% (31)
	SHD	48.6% (70)	20.1% (29)	27.1% (39)	9.7% (14)
Mother's profession					
None or Individual business	SNH	24.5% (102)	7.9% (33)	22.1% (92)	5.8% (24)
	SHD	46.0% (99)	17.7% (38)	27.0% (58)	10.7% (23)
Farmer	SNH	33.1% (110)	14.2% (47)	23.5% (78)	7.5% (25)
	SHD	51.5% (88)	21.1% (36)	22.8% (39)	12.9% (22)
Worker or Employed	SNH	26.4% (94)	7.0% (25)	19.9% (71)	5.9% (21)
	SHD	51.5% (51)	18.2% (18)	27.3% (27)	10.1% (10)
Living with someone in daily life					
Father or mother or Grandparents or other	SNH	28.5% (70)	9.3% (23)	22.4% (55)	6.9% (17)
	SHD	48.1% (78)	24.1% (39)	29.0% (47)	16.7% (27)
Parents	SNH	27.5% (236)	9.6% (82)	21.7% (186)	6.2% (53)
	SHD	49.5% (160)	16.4% (53)	23.8% (77)	8.7% (28)
Communication strategies					
Mandarin	SNH	27.7% (306)	9.5% (105)	21.8% (241)	6.3% (70)

(Continued)

TABLE 1 (Continued)

	Group	Avoiding sharing of utensils during mealtime	Washing hands with soap and water	Washing hands immediately after coughing, or sneezing, rubbing the nose	Wearing masks with or without the pandemic symptoms
	SHD	41.9%	19.0%	28.6%	7.6%
		(44)	(20)	(30)	(8)
Gesture and (or)	SHD	51.1%	18.9%	24.7%	12.4%
lip-language or word		(194)	(72)	(94)	(47)
Satisfaction with the current communication mode					
Satisfaction	SNH	27.8%	8.4%	20.1%	5.8%
		(235)	(71)	(170)	(49)
	SHD	43.2%	13.0%	22.5%	9.5%
		(73)	(22)	(38)	(16)
Fair or Dissatisfaction	SNH	27.3%	13.1%	27.3%	8.1%
		(71)	(34)	(71)	(21)
	SHD	52.2%	22.2%	27.2%	12.3%
		(165)	(70)	(86)	(39)
Exercise during the COVID-19 pandemic					
Yes	SNH	26.4%	6.8%	16.8%	5.0%
		(215)	(55)	(137)	(41)
	SHD	45.1%	13.0%	20.0%	9.6%
		(160)	(46)	(71)	(34)
No	SNH	31.4%	17.2%	35.9%	10.0%
		(91)	(50)	(104)	(29)
	SHD	60.0%	35.4%	40.8%	16.2%
		(78)	(46)	(53)	(21)
Bedtime					
Before 11:00 p.m.	SNH	25.9%	6.2%	17.2%	4.5%
		(133)	(32)	(88)	(23)
	SHD	49.0%	18.5%	23.5%	11.0%
		(196)	(74)	(94)	(44)
After 11:00 p.m.	SNH	29.3%	12.4%	25.9%	8.0%
		(173)	(73)	(153)	(47)
	SHD	49.4%	21.2%	35.3%	12.9%
		(42)	(18)	(30)	(11)

SNH, students with normal hearing; SHD, students with hearing disability.

Correlation analysis of hearing level with mental health, psychological impacts, and compliance with the preventive health measures

Table 3 showed that the level of the hearing was positively correlated with mental health and psychological impacts ($r = 0.068$ to 0.277, $p < 0.01$). Meanwhile, The level of the hearing was negatively correlated with preventive scores of avoiding sharing of utensils during mealtime, washing hands with soap and water, and wearing masks with or without the pandemic symptoms ($r = -0.202$ to -0.059, $p < 0.05$).

Table 4 indicated that there was a significant effect between the hearing level and three preventive health measures except

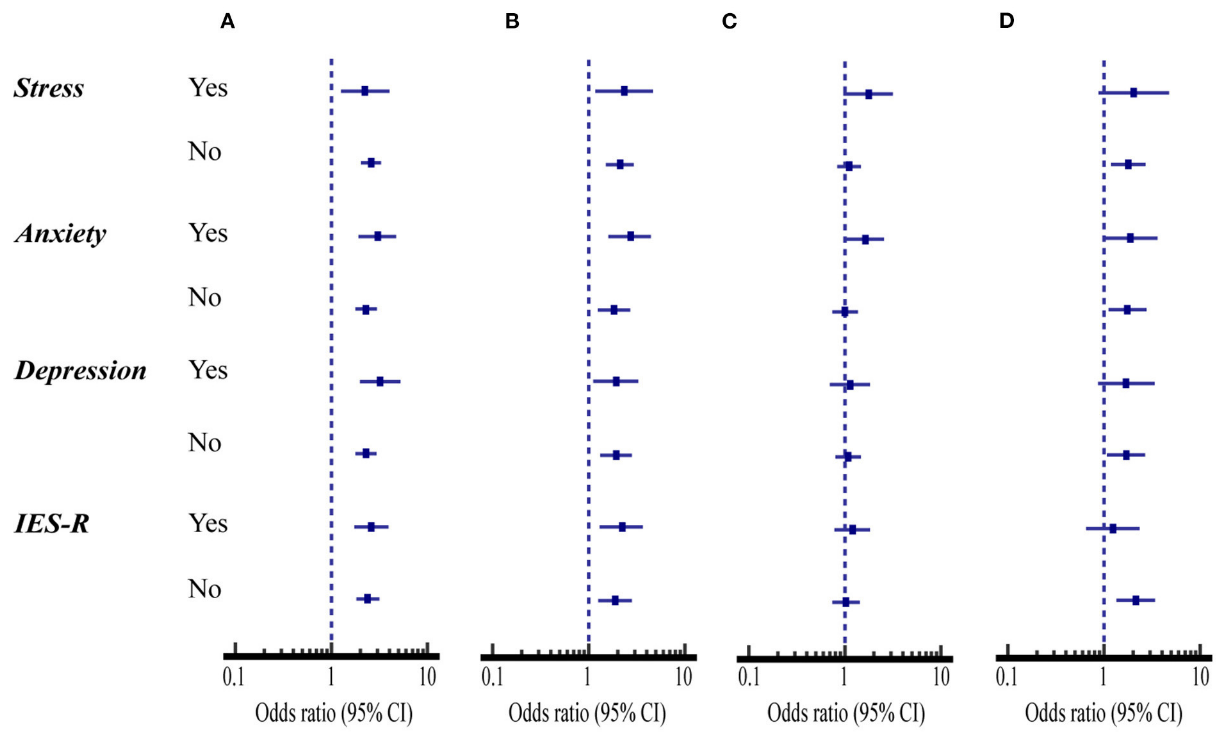

FIGURE 2
Comparison of mental health status and psychological impacts with the compliance with four health measures between students with normal hearing (SNH, $n = 1{,}104$) and with hearing disability (SHD, $n = 485$). **(A)** Avoiding sharing of utensils during mealtime. **(B)** Washing hands with soap and water. **(C)** Washing hands immediately after coughing, or sneezing, rubbing the nose. **(D)** Wearing masks with or without the pandemic symptoms.

washing hands immediately after coughing, or sneezing, rubbing the nose (R^2 =0.004 to 0.041, $p < 0.05$), which indicated that hearing disability was a higher risk factor for lower compliance with those preventative measures.

Mediating effect of mental health and psychological impacts between hearing level and the behavioral compliance with preventive health measures

Figure 4 shows a structural equation model with the hearing level as the independent variable, the preventive scores of four preventive health measures as the dependent variable, and mental health and psychological impacts as the intermediate variables. It was found that the path coefficients of the model were statistically significant ($p < 0.05$) and the fitting indexes were good, indicating that the model had been well-constructed (Table 5). Meanwhile, we used the bootstrap method to detect the mediating effect of mental health status and psychological impacts. Bootstrap repeat sampling was set to 2,000 and with 95% CI. The results showed that the direct effect was −0.073 (95% CI: −0.138 to −0.008), and the indirect effect was −0.044 (95% CI: −0.068 to −0.027) (Table 5). The study revealed that the direct and indirect effects of the hearing level on the prevention scores of four preventive health measures are statistically significant and 95% of the CIs did not include zero. Therefore, mental health and psychological impacts were shown to have a mediating effect on compliance with preventive health measures, and the mediating effect accounted for 37.60% of the total effect.

Discussion

This study compares behavioral compliance with four preventive health measures between SHD and SNH during the COVID-19 pandemic in China. When the prevention scores of these two groups of students were examined in association with different demographic variables, mental health status and psychological impacts, the SHD consistently displayed a significantly lower degree of compliance with all four preventive health measures than SNH (Figures 1–3). Additionally, the direct and indirect effects of the hearing level on compliance with four preventive

TABLE 2 The percentage of mental health status and psychological impacts with health behavior of ≤2 high-risk prevention scores among students.

	Group	Avoiding sharing of utensils during mealtime	Washing hands with soap and water	Washing hands immediately after coughing, or sneezing, rubbing the nose	Wearing masks with or without the pandemic symptoms
Stress[a]					
Yes	SNH	26.6%	14.1%	25.0%	8.6%
		(34)	(18)	(32)	(11)
	SHD	44.8%	27.6%	36.8%	16.1%
		(39)	(24)	(32)	(14)
No	SNH	27.9%	8.9%	21.4%	6.0%
		(272)	(87)	(209)	(59)
	SHD	50.0%	17.1%	23.1%	10.3%
		(199)	(68)	(92)	(41)
Anxiety[b]					
Yes	SNH	31.4%	15.7%	29.6%	9.4%
		(70)	(35)	(66)	(21)
	SHD	57.9%	33.1%	40.6%	16.5%
		(77)	(44)	(54)	(22)
No	SNH	26.8%	7.9%	19.9%	5.6%
		(236)	(70)	(175)	(49)
	SHD	45.7%	13.6%	19.9%	9.4%
		(161)	(48)	(70)	(33)
Depression[c]					
Yes	SNH	27.7%	19.5%	34.6%	10.7%
		(44)	(31)	(53)	(17)
	SHD	55.1%	31.6%	37.5%	16.9%
		(75)	(43)	(51)	(23)
No	SNH	27.7%	7.8%	19.7%	5.6%
		(262)	(74)	(186)	(53)
	SHD	46.7%	14.0%	20.9%	9.2%
		(163)	(49)	(73)	(32)
IES-R[d]					
Yes	SNH	28.6%	13.3%	29.5%	9.5%
		(60)	(28)	(62)	(20)
	SHD	51.0%	25.0%	33.3%	11.5%
		(98)	(48)	(64)	(22)
No	SNH	27.5%	8.6%	20.0%	5.6%
		(246)	(77)	(179)	(50)
	SHD	47.8%	15.0%	20.5%	11.3%
		(140)	(44)	(60)	(33)

IES-R, Impact of Events Scale-Revised.
[a] Yes, 15–42 scores; No, less than or equal to 14 scores.
[b] Yes, 8–42 scores; No, less than or equal to 7 scores.
[c] Yes, 10–42 scores; No, less than or equal to 9 scores.
[d] Yes, 24–88 scores; No, less than or equal to 23 scores.

health measures are significant, and mental health and psychological impacts were shown to have a mediating effect on compliance with preventive health measures (Figure 4).

This finding is likely due to the difference in the demographic variables, mental health status and psychological impacts between these two groups of students. In contrast to SHD, a larger percentage of SNH has a better education

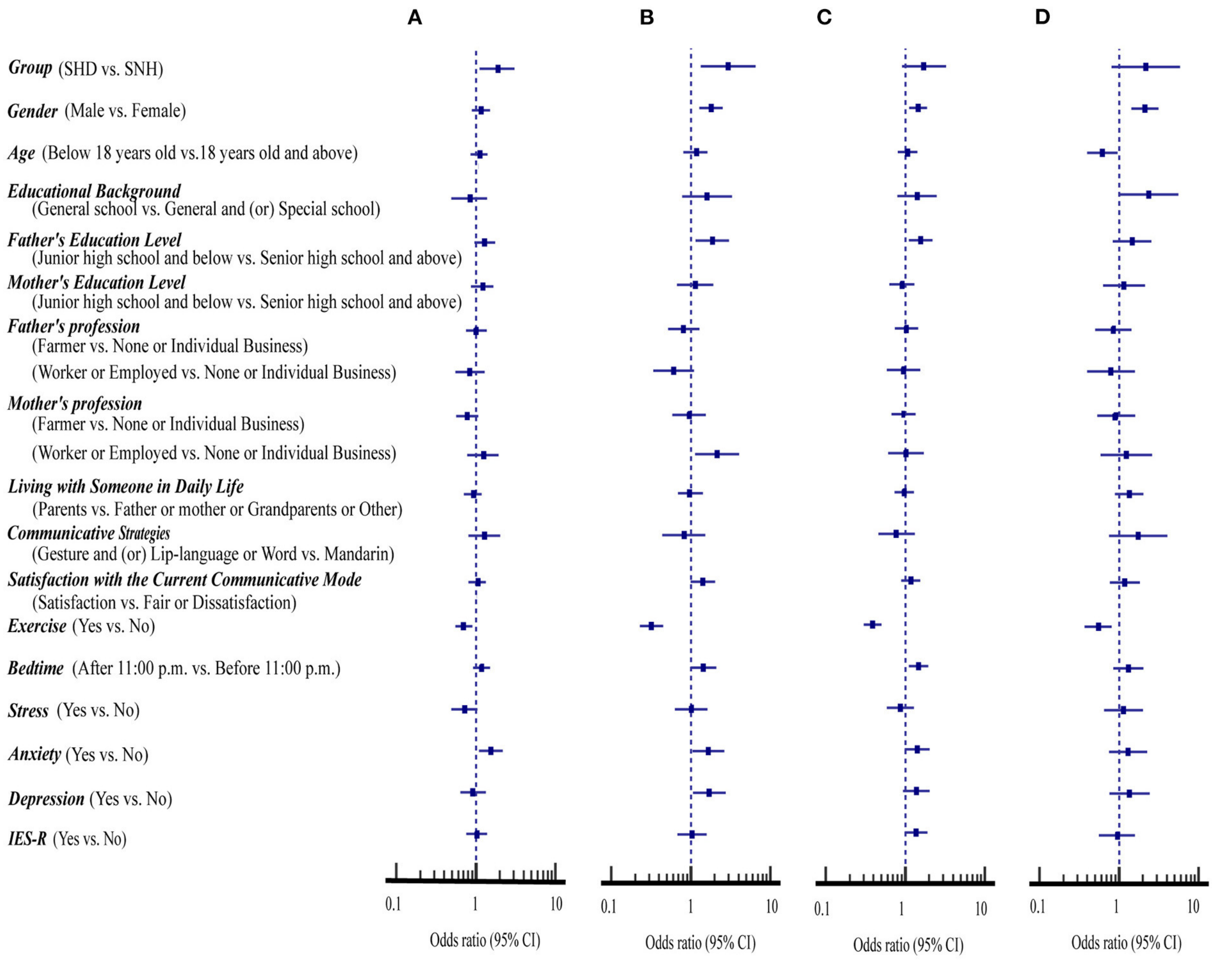

FIGURE 3
Association of demographic variables, mental health status and psychological impacts with the compliance with four health measures in students with and without hearing disability ($n = 1{,}589$). **(A)** Avoiding sharing of utensils during mealtime. **(B)** Washing hands with soap and water. **(C)** Washing hands immediately after coughing, or sneezing, rubbing the nose. **(D)** Wearing masks with or without the pandemic symptoms.

background, satisfying with their current communication mode, doing exercise during the pandemic, and with a bedtime between 9 and 11 p.m. Most SNH is from a family with a steady income and their parents have a better educational background (Table 1). Furthermore, they also suffered less degree of pandemic-induced mental health issues and psychological impacts than SHD (Table 2).

A previous study has shown that optimization of infection management in health care with behavioral change can reduce the risk of infection during COVID-19 (28). The interventions designed to change behaviors are more effective if they target socialization factors. For this reason, individual practice and compliance with basic preventive health measures are essential during the pandemic.

Chinese people are accustomed to communal eating using chopsticks and spoons as the essential eating utensils. The eighth edition of China's diagnosis and treatment protocol for COVID-19 patients has explicitly recommended that COVID-19 patients should eat separate meals after discharge because the pandemic virus can be transmitted through shared cutlery (29, 30).

We found that the percentage of both groups of students with ≤2 high-risk prevention scores is far larger in the preventive health measure of avoiding sharing of utensils during mealtime than the other three preventive health measures in all demographic variables examined (Table 1). This finding suggests the deep influence of the traditional communal eating habit among all participants. The fact that the degree of compliance in this preventive health measure is lower in a large percentage of SHD may be due to a lack of understanding of the benefits of separate eating resulting from their limited communication strategies or stronger communal eating habit on the campus or at home.

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TABLE 3 Correlation analysis of the hearing level, mental health status and psychological impacts, and the prevention scores of four preventive health measures.

Variable	Stress	Anxiety	Depression	IES-R	Avoiding sharing of utensils during mealtime	Washing hands with soap and water	Washing hands immediately after coughing, or sneezing, rubbing the nose	Wearing masks with or without the pandemic symptoms
Hearing level	0.068**	0.106**	0.142**	0.277**	−0.202**	−0.102**	−0.026	−0.059*

IES-R, Impact of Events Scale-Revised; *$p < 0.05$, **$p < 0.01$.

The preventive health measure of hand hygiene is an acquired habit that is greatly associated with self-discipline and habituation (30). The practice of hand hygiene such as hand washing and alcohol-based hand rub can reduce the spread of respiratory infections and nosocomial infection rate (9). Previous studies have shown that young females are more inclined to avoid the risk of infection than males (31). In agreement with these studies, we have found that the degree of compliance with hand hygiene and wearing a mask for preventive health measures is consistently higher in a larger percentage of participants with >2 low-risk prevention scores for the female than the male in both groups of students (Figures 3B–D).

We also found that the degree of compliance with preventive health measures of mask-wearing is significantly lower for the female SHD than for female SNH. Since most female SHD (78.1%) use sign language and lip-reading for communication, the disadvantage of effective social communication created by mask-wearing may significantly reduce their willingness to comply with mask-wearing measures during the pandemic. This finding is corroborated by a recent study that shows hearing-impaired individuals who primarily use facial cues such as facial and lip expressions for social communication are less inclined to wear a mask during the pandemic (32).

The practice of proper mask-wearing is an effective non-pharmaceutical intervention in curtailing COVID-19 virus transmission (33). However, mask-wearing reduces a speaker's voice by 3–4 dB (surgical mask) or 12 dB (N95 mask) in the frequency range of 2,000–7,000 Hz (34). All these studies are supported by our finding that the degree of compliance with mask-wearing is significantly lower for the SHD than for the SNH because 373 (76.9%) SHD have profound hearing loss and 380 (78.4%) SHD rely on gesture and or lip-language or word for social communication. A recent study has shown that such a disadvantage in speech perception and communication induced by mask-wearing can be remedied by wearing a transparent mask (33).

On the other hand, one study has shown that parental education, socioeconomic conditions, and family structure play an important role in influencing adolescent health behavior (35). We have found that the parents' education is below senior high school and the parents' profession are jobless, self-employed, or farmers, their degree of compliance with three preventive health measures is significantly reduced for the SHD than for the SNH (Figures 1A,B,D).

A previous study indicated that male sex, rural residents, respondents with a low level of education, those engaged in agricultural, laboring, and domestic work, and people with disabilities were more likely to have difficulty practicing

TABLE 4 The correlation between hearing level and the scores of four preventive health measures by the linear regression model.

	R^2	Unstandardized coefficients		Standardized coefficients beta	*t*	*P*-value
		β	Std. Error			
Avoiding sharing of utensils during mealtime	0.0409	−0.170	0.021	−0.202	−8.224	<0.001
Washing hands with soap and water	0.0104	−0.0485	0.0119	−0.102	−4.088	<0.001
Washing hands immediately after coughing, or sneezing, rubbing the nose	0.001	−0.016	0.015	−0.026	−1.033	0.302
Wearing masks with or without the pandemic symptoms	0.004	−0.024	0.010	−0.059	−2.370	0.018

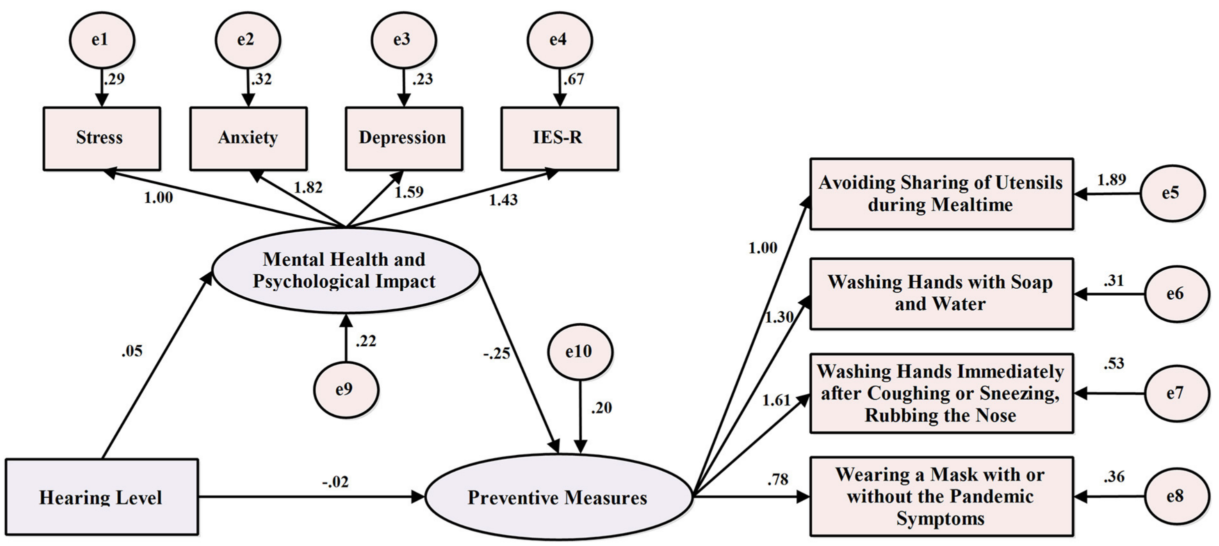

FIGURE 4
Structural equation model of hearing level, mental health status and psychological impacts, and the prevention scores of four preventive health measures.

TABLE 5 Structural equation model fit index.

Fit index	CMIN/DF	RMSEA	GFI	AGFI	TLI	IFI	CFI	PGFI	NFI
Test result	7.902	0.066	0.974	0.953	0.933	0.954	0.953	0.541	0.947
Fit standard	$1 < \chi^2/df < 3$	<0.08	>0.90	>0.90	>0.90	>0.90	>0.90	>0.05	>0.90

CMIN/DF, chi-square minimum degrees of freedom; RMSEA, root mean square error of approximation; GFI, goodness of fit index; AGFI, adjusted goodness of fit index; TLI, Tucker-Lewis index; IFI, incremental fit index; CFI, comparative fit index; PGFI, parsimonious goodness of fit index; NFI, normed fit index.

COVID-19 protective behaviors (36). It has been also reported that the unemployment rate may be high for the worker or employed staff when the parents with low education levels during the COVID-19 pandemic (37). Also, low-income families are prone to tension such that their children may be more susceptible to suffering from anxiety and depression status (37, 38). In agreement with these studies, we found that the SHD and the SNH, whose father's education level was below junior high school, mother's profession was a worker or employed, and with anxiety and depression, have a significantly lower degree of compliance with hand hygiene (Figure 3C).

Previous studies have shown that a lack of social interaction, communication, and access to public information resources produces negative impacts on deafness' mental health and psychological status (20, 39). In this study, we found that SHD consistently shows a significantly lower degree of compliance with the preventive measures of avoiding sharing utensils during mealtime and washing hands with soap and water than SNH regardless of their mental status and psychological impacts (Figures 2A,B). Meanwhile, hearing disability and anxiety status are risk factors for these health behaviors (Figures 3A,B). Conceivably, the SHD who inevitably have limited access to update pandemic information and those who suffer from anxiety are the key educational targets for the above two health behaviors.

It is worth mentioning that students aged below 18 years old performed much better compliance with wearing masks than those 18 years old and above. The majority of students aged 18 and older are already in college and may not be on the daily healthy behavior education as junior and senior students during the pandemic, these students should be the target group to focus on the wearing masks during the COVID-19 pandemic (Figure 3D).

It has been reported that outdoor exercise and limiting screen time can promote better mental and general health during the COVID-19 pandemic (40). In agreement with this finding, we found that students with a bedtime after 11 p.m. have poor hand hygiene behaviors, and physical activity is important in promoting all four preventive health habits (Figures 3A–D).

There was a correlation between hearing level, mental health status and psychological impacts, and the scores of the preventive health measures, which met the basic criteria of intermediary effect (Table 3). The association between hearing level and compliance with the three protective measures further supports our contention that hearing disability is a higher risk factor for lower compliance with preventative measures, and with a dose-dependent effect (Table 4).

Intermediary effect analysis showed that a higher degree of hearing disability and psychological distress can predict worse protective behavior compliance, supporting that hearing level, mental health status and psychological impacts are predictors of the preventive health measures. Meanwhile, mental health status and psychological impacts played an intermediary role between hearing level and compliance with preventive health measures. These results indicated that hearing level not only directly affected compliance with preventive health measures but also indirectly regulated compliance with preventive health measures through mental health status and psychological impacts (Figure 4).

The previous study of the general population at the initial stage of COVID-19 reported lower levels of psychological impacts, depression, anxiety, and stress were associated with higher compliance with precautionary measures (26), which is consistent with our findings on SHD. Our result also found that the higher the degree of hearing disability was, the worse the compliance with protective behavior would be. Furthermore, mental health status and psychological impacts indirectly regulate compliance with preventive health measures, clinical caregivers can indirectly improve the compliance with preventive health measures of people with hearing disability through the enhancement of psychological intervention during COVID-19.

Because of the disproportionate distribution of available COVID-19 vaccines, many parts of the world are still in great short supply of vaccines for effective treatments for the pandemic. It has been indicated that health literacy is an underestimated problem and mass practice of preventive health measures is crucial for the prevention of the spread of the pandemic (41). There is limited evidence on compliance with preventive measures for people with disabilities in the existing literature and our study provides a population perspective on behavioral strategies for hearing disability. As evident by the consistent lower degree of compliance with preventive health measures for SHD than for SNH, our study strongly suggests the importance of the development of health guidance and dissemination of updated pandemic information, essential communication services, extra assistance, and support to persons with a disability such as hearing loss who are more susceptible to a public health emergency and psychological distress.

This study has some limitations that require consideration. Firstly, our study was an online survey utilizing a snowball sampling method voluntarily. Therefore, many SHD did not participate in the questionnaire resulting in a large number of SNH participants and a small number of SHD participants. Secondly, most of the students were profound hearing disability in our study, and future studies will explore preventive health behavior in the general population with mild to moderate hearing loss. Lastly, our respondents are mainly students with or without hearing disability, the observation may not apply to the population in all social strata. Future research is necessary to survey participants from multiple geographic regions across all social strata.

Conclusions

In conclusion, the SHD consistently shows a significantly lower degree of compliance in all four preventive health measures than SNH because of their negative emotional response, and inconvenient access to public information on the COVID-19 pandemic due to their physical disability. Hearing level and mental health status and psychological impacts are predictors of compliance with preventive health measures. Mental health status and psychological impacts have a partial mediating effect between hearing level and compliance with preventive health measures. At the same time, psychological support should also be provided to indirectly improve compliance with health behavior for people with hearing disability. To sum up, to reduce the risk of contraction, update pandemic information, essential communication services, extra assistance, and support should be provided to persons with a physical disability who are more susceptible to a public health emergency.

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 human participants were reviewed and approved by Ethical approval was obtained from the Institutional Review Board of Binzhou Medical University (BMU-IRB-2020-54). Informed consent was obtained from each participant before taking the online survey. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YY, CQ, and PH-SJ designed the study concept, analytical methods, and presentation of the results and were responsible for data visualization. YY, YL, and YX obtained and managed data, implemented methods, and wrote the first draft of the paper. YY was responsible for project administration. YY and YL prepared original data. YY and PH-SJ supervised the study.YY, YL, YX, CQ, and PH-SJ reviewed and edited the manuscript. All authors helped with the interpretation of the results and approved the final 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.

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Daily, self-test rapid antigen test to assess SARS-CoV-2 viability in de-isolation of patients with COVID-19

Seongman Bae[1†], Heedo Park[2,3†], Ji Yeun Kim[1†], Sunghee Park[1], So Yun Lim[1], Joon-Yong Bae[3], Jeonghun Kim[2,3], Jiwon Jung[1], Min Jae Kim[1], Yong Pil Chong[1], Sang-Oh Lee[1], Sang-Ho Choi[1], Yang Soo Kim[1], Man-Seong Park[2,3*‡] and Sung-Han Kim[1*‡]

[1]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [2]BK21 Graduate Program, Department of Biomedical Sciences, Korea University College of Medicine, Seoul, South Korea, [3]Department of Microbiology, Biosafety Center, College of Medicine, Institute for Viral Diseases, Korea University, Seoul, South Korea

EDITED BY
Marc Jean Struelens,
Université Libre de Bruxelles, Belgium

REVIEWED BY
Keun Hwa Lee,
Hanyang University, South Korea
Susanta Kumar Ghosh,
National Institute of Malaria Research (ICMR), India
Aaron T. Irving,
Zhejiang University-University of Edinburgh Institute, China

*CORRESPONDENCE
Sung-Han Kim
kimsunghanmd@hotmail.com
Man-Seong Park
manseong.park@gmail.com

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work and share last authorship

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Background: Isolation of COVID-19 patients is a crucial infection control measure to prevent further SARS-CoV-2 transmission, but determining an appropriate timing to end the COVID-19 isolation is a challenging. We evaluated the performance of the self-test rapid antigen test (RAT) as a potential proxy to terminate the isolation of COVID-19 patients.

Materials and methods: Symptomatic COVID-19 patients were enrolled who were admitted to a regional community treatment center (CTC) in Seoul (South Korea). Self-test RAT and the collection of saliva samples were performed by the patients, on a daily basis, until patient discharge. Cell culture and subgenomic RNA detection were performed on saliva samples.

Results: A total of 138 pairs of saliva samples and corresponding RAT results were collected from 34 COVID-19 patients. Positivity of RAT and cell culture was 27% (37/138) and 12% (16/138), respectively. Of the 16 culture-positive saliva samples, seven (43.8%) corresponding RAT results were positive. Using cell culture as the reference standard, the overall percent agreement, percent positive agreement, and percent negative agreement of RAT were 71% (95% CI, 63–78), 26% (95% CI, 12–42), and 82% (95% CI, 76–87), respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of the RAT for predicting culture results were 44% (95% CI, 20–70), 75% (95% CI, 66–82), 18% (95% CI, 8–34), and 91% (95% CI, 84–96), respectively.

Conclusion: About half of the patients who were SARS-CoV-2 positive based upon cell culture results gave negative RAT results. However, the remaining positive culture cases were detected by RAT, and RAT showed relatively high negative predictive value for viable viral shedding.

KEYWORDS
COVID-19, rapid antigen test, isolation, de-isolation, cell culture

Introduction

Despite the introduction of COVID-19 vaccines, a large number of new patients worldwide are still being infected with SARS-CoV-2 due to the emergence of virus variants or vaccine shortages (1). Along with the rapid distribution of vaccines, proactive testing, contact tracing, and isolation of confirmed COVID-19 patients are still key elements of infection control measures. Many countries, including South Korea, are adopting symptom-based isolation strategies that require isolating COVID-19 patients with mild to moderate symptoms, but without immunocompromising conditions, for at least 10 days after symptom onset until clinical improvement is achieved (2). However, uniform application of the symptom-based isolation strategy entails social costs since some individuals lose their infectivity before 10 days (3). Furthermore, due to the recent emergence of the Omicron variant, the isolation period has been further curtailed from 10 to 5 days in patients with asymptomatic or mild COVID-19 (4). Since there are concerns about the residual infectivity associated with early de-isolation, a rapid antigen test (RAT)-based de-isolation strategy has been endorsed by CDC and European CDC guidelines (4, 5). Despite lower sensitivity of RAT for diagnosing acute SARS-CoV-2 infection compared to nucleic acid amplification testing (NAAT) such as RT-PCR, positive RAT results correlated well with high viral load samples (6). Therefore, positive RAT results were also expected to correlate with positive viral culture, which have been considered a proxy for infectivity (7). However, there are limited studies comparing the results of serially performed RATs during infection with tests for infectivity, such as virus culture (8, 9). In this study, the results of serially performed, self-test RAT were compared with those of virus culture, genomic RNA, and subgenomic RNA tests on saliva samples collected from COVID-19 patients in South Korea.

Materials and methods

Study population and setting

In South Korea, in 2021, asymptomatic or mild symptomatic patients, who were newly diagnosed with COVID-19, were admitted to a community treatment center (CTC) to prevent further spread of SARS-CoV-2, and to monitor the clinical course of COVID-19 (10, 11). Patients who were at high risk of progressing to severe COVID-19, such as the elderly (over 70 years old) and immunocompromised patients, were admitted to a dedicated hospital facility rather than a CTC. According to the government guidelines for COVID-19 patients, all new SARS-CoV-2 patients should be isolated in a CTC or hospital facilities for at least 10 days if symptoms have resolved. During admission to a CTC, patients were asked to self-check their vital signs (body temperature, oxygen saturation, blood pressure, etc.) using portable medical devices and report these data, along with any COVID-19 related symptoms, to the medical staff twice a day. Patients who reported respiratory distress, intractable fever, or desaturation were transported to the hospital as they were considered at risk of progression to severe COVID-19.

This observational study enrolled patients infected with SARS-CoV-2 who were admitted to the University of Seoul CTC (Seoul, South Korea) from June 21, 2021 to August 21, 2021. COVID-19 was confirmed by RT-PCR in all enrolled patients. All patients participated voluntarily and provided written informed consent prior to enrollment. Participants were asked to perform a self-test RAT and collect saliva on a daily basis. The presence of SARS-CoV-2 in saliva samples was detected using RT-PCR (based on both genomic and subgenomic RNA sequences of SARS-CoV-2) and cell culture. The results of tests performed on saliva samples were then compared with the RAT results. The study protocol was approved by the institutional review committee of Asan Medical Center (IRB no. 2020-0336), which oversees the operation of the CTC.

Rapid antigen testing

In this study, the Humasis COVID-Ag Home Test kit (Humasis Co., South Korea) was used for serial self-RAT testing. This RAT is a lateral flow immunochromatographic assay for the qualitative detection of nucleocapsid protein and receptor binding domain (RBD) antigens of SARS-CoV-2. This assay was approved as a screening test for COVID-19 by the Ministry of Food and Drug Safety in South Korea. Tests were performed by patients, according to the manufacturer's protocol; briefly, self-collected nasal swabs from both nares were placed in extraction solution, swirled ten times, and squeezed against the collection tube wall. Extracted sample was applied to a cassette, and an appropriate time was allowed for a monoclonal anti-SARS-CoV-2 antibody reaction. Test results were interpreted after 15 min. There are two lines on the cassette: a colored control line (C) should always appear after adding an appropriate sample volume. A positive result was defined as a colored band at the *T*-test mark on the cassette, regardless of whether it was weak or clear. Negative results were indicated by the absence of a band at the T mark. If the control reaction failed, the test was considered invalid and was repeated. The results were read by two independent observers.

Collection of daily saliva samples

Self-collected saliva samples were obtained from patients from the day of study enrollment until the day of discharge. Each day, patients collected a 2 mL volume of saliva into an airtight container provided at admission; no preservation or transport medium was used. Patients were asked to avoid food, water, and teeth brushing for at least 30 min prior to sample collection. Saliva samples were collected within 1 h by medical staff and transported to a designated laboratory where they were aliquoted and stored at −80°C until use.

Measurement of viral load by real-time RT-PCR assay

The collected saliva samples were inactivated at 65°C for 30 min in a negative pressure laboratory. Viral RNA was extracted from saliva samples using a QIAamp viral RNA Mini kit (Qiagen Inc., Hilden, Germany). To determine the SARS-CoV-2 viral RNA copy number, multiplex real-time RT-PCR assays targeting the S- and N-genes were developed. Multiplex RT-PCR assay mix (20 μL) contained 4 μL of 5 × master mix (LightCycler Multiplex RNA Virus Master, Roche, Basel, Switzerland), 0.1 μL of 200 × enzyme mix, 500 nM of each S and N gene primer, 200 nM of each S and N gene probe, 250 nM of internal control primers, 100 nM of internal control probes, and 5 μL of extracted RNA or *in vitro*-synthesized control RNA. PCR amplification was performed with a LightCycler 96 system (Roche) in the following conditions: reverse transcription at 50°C for 10 min, initial denaturation at 95°C for 5 min, 45 cycles of two-step amplification, denaturation at 95°C for 10 s, and final extension at 60°C for 30 s. To generate calibration curves, serial dilutions from 10^7 to five copies/μL of synthetic control RNA were assayed in six independent sets of reactions (**Supplementary Figure 1**). The detection limit of this assay was five copies/reaction (2.6 log copies/ml of specimen), and viral copy numbers were determined by plotting CT values against log copies/reaction. The primer and probe sequences are provided in (**Supplementary Table 1**).

Detection of N and S gene subgenomic RNAs

SARS-CoV-2 N and S gene subgenomic RNAs were detected using RocketScript RT-PCR Premix (Bioneer Co., Daejeon, South Korea). The shared forward primer was designed in the 5′ leader sequence, and reverse primers were located in the gene sequences encoding the N- and S-proteins (**Supplementary Table 2**). In brief, RT-PCR reactions were performed as follows: reverse transcription at 50°C for 30 min, initial denaturation at 95°C for 5 min, 40 cycles of three-step amplification, denaturation at 95°Cfor 30 s, annealing at 55°Cfor 30 s, extension at 72°C for 1 min, and final extension at 72°C for 5 min. Amplification products were eluted with a QIAquick Gel Extraction kit (Qiagen), and sequencing was carried out by Macrogen Inc. (Seoul, Republic of Korea). Sequences that included the leader sequence and that were ≥97% consistent with the SARS-CoV-2 genome, by BLAST, were confirmed as subgenomic RNAs.

Cell culture

Culture-based isolation of SARS-CoV-2 from saliva was performed by a plaque assay in a Biosafety Level 3 laboratory at Korea University College of Medicine, Seoul, South Korea. Vero cells (9×10^5 cells/well) were seeded into 6-well plates and allowed to incubate for 24 h. Saliva specimens were serially 10-fold diluted using PBS. Aliquots (200 μl) of each diluted sample were inoculated onto the Vero cells and incubated for 1 h (37°C, 5% [v/v] CO_2) with rocking every 15 min and overlaid with 2 mL of Dulbecco's Modified Eagle Medium/Nutrient Mixture F12 (DMEM/F-12) medium containing 0.6% (w/v) oxoid agar. Viral plaque formation was visualized by crystal violet staining after 72 h of incubation at 37°C in a 5% (v/v) CO_2 incubator.

Statistical analyses

Categorical variables were described as number with percentage, and continuous variables were described as mean with standard deviation or median with interquartile range or range, as appropriate. Percent agreement between the results of the self-test RAT and virus culture was calculated as numbers of concordant pairs divided by total number of paired observations. The percent positive agreement was calculated by dividing the number of observations that were positive for both tests by the average of the number of positive observations in each test. The percent negative agreement was calculated by dividing the number of observations that were negative for both tests by the average of the number of negative observations in each test. The sensitivity, specificity, positive predictive value, and negative predictive value of results of COVID-19 self-test RAT were estimated with positive results of virus culture or subgenomic RNA from saliva samples as reference standards. Data were analyzed using R version 4.0.4 (R Project for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the 34 patients with symptomatic COVID-19 who enrolled in this study are summarized in **Table 1**. The mean age was 31.8 years, and 61.8% were male. Most patients (85% [29/34]) were admitted to the CTC within a day or two after diagnosis. The median time from symptom onset and admission to the day of first RAT testing were 5 (interquartile range [IQR], 4–6) and 3 days (IQR, 3–3), respectively. No abnormal infiltration was observed except for one patient on chest imaging performed on the day of admission. All patients were clinically recovered at discharge, but one (2.9%) was transferred to hospital due to intractable fever. The median time between admission and discharge was 10 days (range, 5–14). The median value of viral load at diagnosis was 18.2, and the majority of cases (73.5%) were Delta variants. During the study period, a total of 151 RAT results and 138 saliva samples were collected, resulting in 138 paired RAT results and saliva samples. The median time to negative RAT result was 4 days (interquartile range [IQR], 3–6) from admission and 7.5 days (IQR, 6–8) from symptom onset (**Supplementary Figure 2**).

Results and predictive performance of rapid antigen test compared with viral culture and subgenomic RNA

Of the 138 paired RAT results and saliva samples tested, 27.5% (38/138) of RAT, 11.6% (16/138) of cell culture, and 48.6% (67/138) of subgenomic RNA tests were positive for SARS-CoV-2 (**Table 2**). Of the 16 culture-positive saliva samples, seven (43.8%) corresponding RAT results were also positive. The daily, positive rates using RAT, genomic RNA, subgenomic RNA, and cell culture gradually decreased with time from 5 days after symptom onset (**Figure 1**). The overall percent agreement, percent positive agreement, and percent negative agreement between RAT and viral culture were 71% (95% CI, 63–78), 26% (95% CI, 12–42), and 82% (95% CI, 76–87), respectively. Of the 67 subgenomic RNA-positive samples, 30 (44.8%) were also positive in paired RAT results. The overall percent agreement, percent positive agreement, and percent negative agreement between RAT and subgenomic RNA test were 67% (95% CI, 60–75), 57% (95% CI, 45–68), and 74% (95% CI, 66–80), respectively. The mean Ct values for positive samples were highest in viral culture, followed by subgenomic RNA, RAT, and genomic RNA tests (**Figure 2**). The viral load (median $\log_{10}$ copies/mL, [interquartile range]) was significantly different according to positivity for RAT (4.8 [IQR, 4.1–5.7] vs. 3.6 [1.3–4.5]), culture (5.8 [4.9–6.3] vs. 3.9 [1.3–4.6]), and subgenomic RNA (5.0 [4.5–5.7] vs. 1.3 [1.3–3.6]; all $P < 0.001$) as shown in **Supplementary Figure 3**.

The performance of RAT for predicting positive results in viral culture, subgenomic RNA, and genomic RNA is summarized in **Table 2**. The sensitivity, specificity, positive predictive value, and negative predictive value of the RAT for predicting the results of viral culture were 44% (95% CI, 20–70), 75% (95% CI, 66–82), 18% (95% CI, 8–34), and 91% (95% CI, 84–96), respectively (**Table 2**). The sensitivity, specificity, positive predictive value, and negative predictive value of the RAT for predicting positive subgenomic RNA detection was 45% (95% CI, 33–57), 89% (95% CI, 79–95), 79% (95% CI, 63–90), and 63% (95% CI, 53–72), respectively. The sensitivity of RAT to viral culture increased to 83% (95% CI, 36–100) when applied to samples collected up to 5 days after symptom onset, and decreased to 20% (3–56) when applied to samples collected 5 days after symptom onset. The sensitivity of RAT to subgenomic RNA and genomic RNA was also higher when applied to samples collected up to 5 days after symptom onset than when applied to samples collected 5 days after symptom onset. The performances of genomic RNA PCR and subgenomic RNA PCR for predicting viral culture results are summarized in **Supplementary Table 3**.

TABLE 1 Baseline characteristics of patients.

	Patients (N = 34)
Age, mean ± SD, year	31.8 ± 9.0
Male, no (%)	21 (61.8)
Comorbidity, no (%)	
Diabetes	1 (2.9)
Hypertension	1 (2.9)
Asthma	1 (2.9)
Depression	3 (8.8)
Patient classification by symptom	
Symptomatic	32 (94.1)
Presymptomatic	2 (5.9)
Asymptomatic	0 (0)
Symptoms at admission	
Fever	26 (76.5)
Chill	9 (26.5)
Cough	17 (50.0)
Sputum	5 (14.7)
Sore throat	17 (50.0)
Dyspnea	1 (2.9)
Rhinorrhea	4 (11.8)
Nasal stuffiness	4 (11.8)
Myalgia	17 (50.0)
Headache	9 (26.5)
Loss of taste	1 (2.9)
Loss of smell	4 (11.8)
Diarrhea	1 (2.9)
Days from symptom onset to admission*, median (range)	2 (0–8)
Days from COVID-19 diagnosis to admission*, median (range)	1 (0–2)
Days from symptom onset to first RAT test, median (IQR)	5 (4–6)
Days from admission to first RAT test, median (IQR)	3 (3–3)
Median days from admission to discharge, no. (range)	10 (5–14)
Mean viral load at diagnosis, Ct value (E gene)†	18.2
Infiltrations on chest x-ray at admission, no (%)	1 (2.9)
Delta variant (%)	
Yes	25 (73.5)
No	9 (26.5)

IQR, interquartile range. *Admission indicates admission to a community treatment center for isolation purposes. †Initial viral load at the time of diagnosis (one missing).

TABLE 2 Performance of self-test rapid antigen tests compared with viral culture, subgenomic RNA, and genomic RNA.

	No. of pairs	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
RAT vs. viral culture					
Overall	138	44% (20–70)	75% (66–82)	18% (8–34)	91% (84–96)
≤5 days	40	83% (36–100)	50% (32–68)	23% (8–45)	94% (73–100)
>5 days	98	20% (3–56)	84% (75–91)	12% (2–38)	90% (82–96)
RAT vs. sgRNA					
Overall	138	45% (33–57)	89% (79–95)	79% (63–90)	63% (53–72)
≤5 days	40	81% (58–95)	74% (49–91)	77% (55–92)	78% (52–94)
>5 days	98	28% (16–43)	94% (84–99)	81% (54–96)	60% (48–70)
RAT vs. gRNA					
Overall	138	37% (28–47)	100% (90–100)	100% (91–100)	36% (27–46)
≤5 days	40	73% (54–88)	100% (69–100)	100% (85–100)	56% (31–78)
>5 days	98	22% (13–34)	100% (87–100)	100% (79–100)	32% (22–43)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; sgRNA, subgenomic RNA; gRNA, genomic RNA.

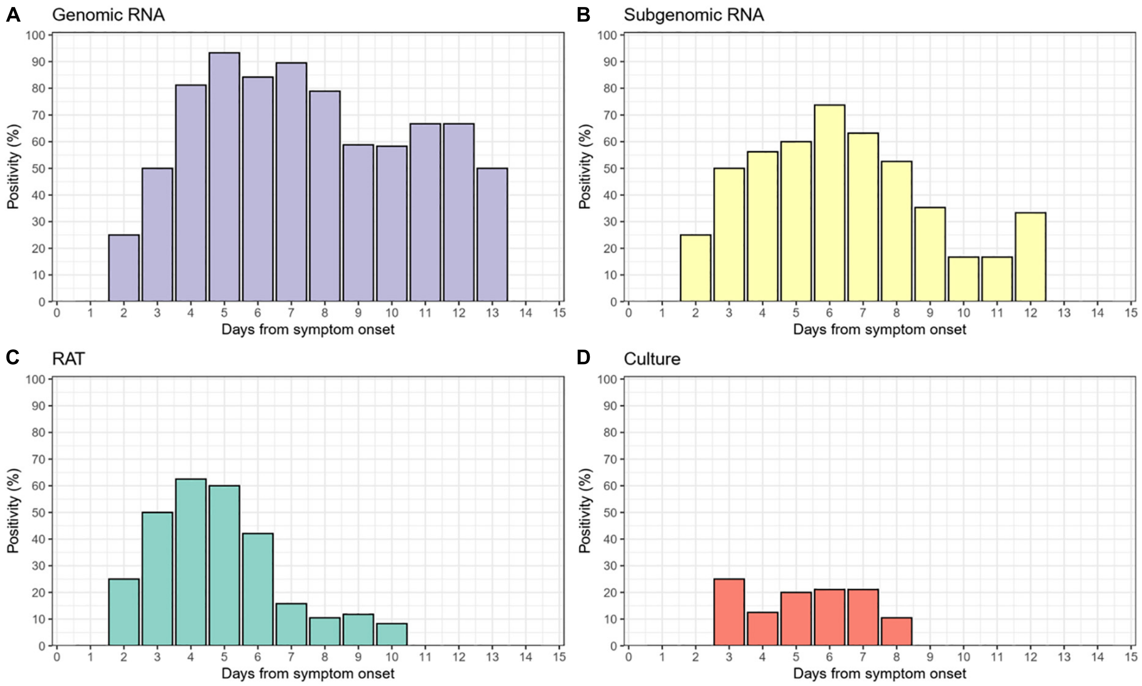

FIGURE 1
Daily positivity of **(A)** genomic RNA, **(B)** subgenomic RNA, **(C)** rapid antigen test (RAT), and **(D)** cell culture.

Results of rapid antigen test, culture, and subgenomic RNA according to the timeline

As shown in **Figure 3A**, most culture-positive cases (83% [5/6]) were also positive with RAT (blue dots) up to 5 days after symptom onset, whereas most culture-positive cases (80% [8/10]) after 5 days were negative with RAT (red dots). Similarly, most subgenomic RNA-positive cases (81% [17/21]), up to 5 days after symptom onset, were also positive for RAT (blue dots), whereas the majority of the subgenomic RNA-positive cases (72% [33/46]) were negative with RAT (red dots) after 5 days (**Figure 3B**). Detailed scatter plots according to positivity of the reference tests are shown in **Supplementary Figure 4**.

Timelines of the test results at the individual patient level are shown in **Figure 4**. Of 7 patients with positive culture results, 4 of whom also had positive RAT results. In detail, four concordant pairs of positive culture with positive RAT (blue rectangle) and four discordant pairs of positive culture with negative RAT (red rectangle) were found (**Figure 4A**).

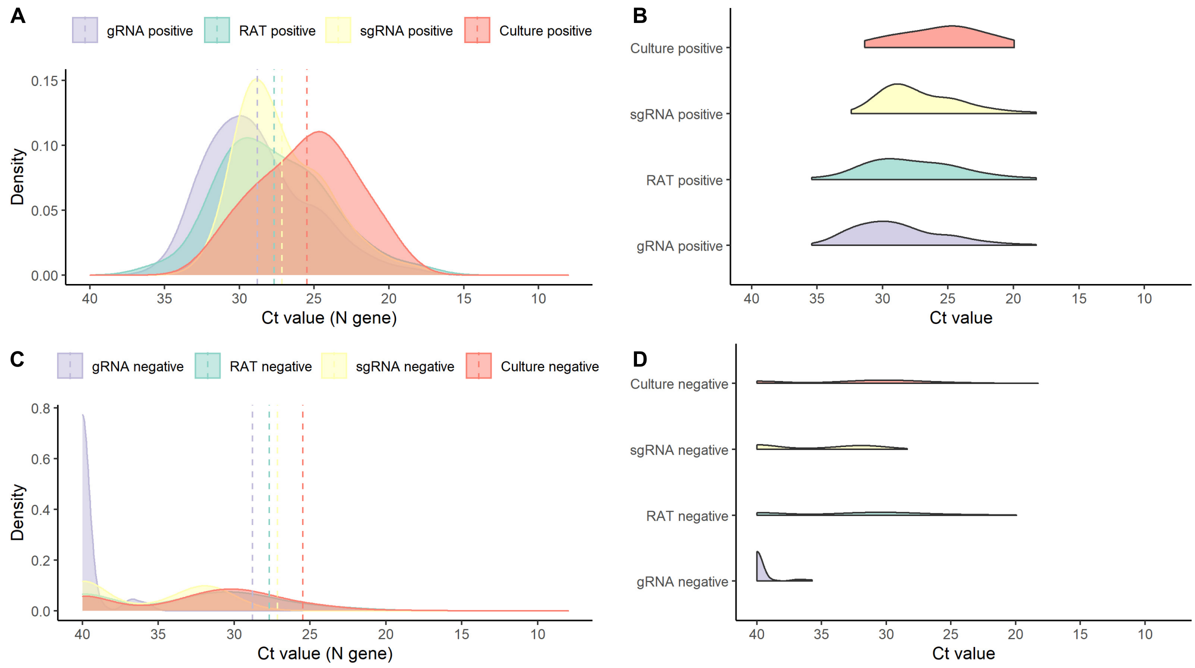

FIGURE 2
Density plots of positive and negative results for each test. **(A)** Density plot for positive results by test. **(B)** Raincloud plot for positive results by each test. **(C)** Density plot for negative results by test. **(D)** Raincloud plot for negative results by each test. sgRNA, subgenomic RNA; gRNA, genomic RNA.

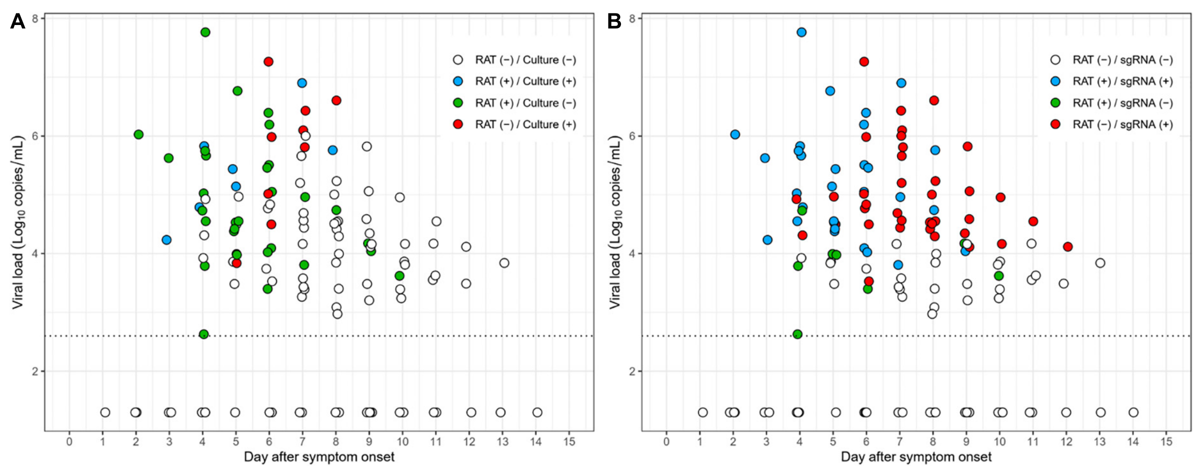

FIGURE 3
Scatter plots depicting RAT results over the study period. **(A)** Results of RAT compared to cell culture. **(B)** Results of RAT compared to subgenomic RNA.

A concordant pair was observed in one patient (Patient 16), but later discordant pairs were observed. On the basis of RAT-determined termination of isolation, the termination of three out of seven patients with culture-positive samples would have been delayed due to RAT results that predicted positive cultures, whereas RAT could have predict positive cultures in the remaining four patients. Using subgenomic RNA detection as the reference, RAT predicted positive subgenomic RNA in 15 of 25 subgenomic RNA-positive patients but failed to predict positive subgenomic RNA in subsequent samples from seven duplicates of these patients (**Figure 4B**). In the remaining ten subgenomic RNA-positive patients, RAT did not predict subgenomic RNA positivity. Results for RAT and cell culture for each patient are shown in **Supplementary Figure 5**.

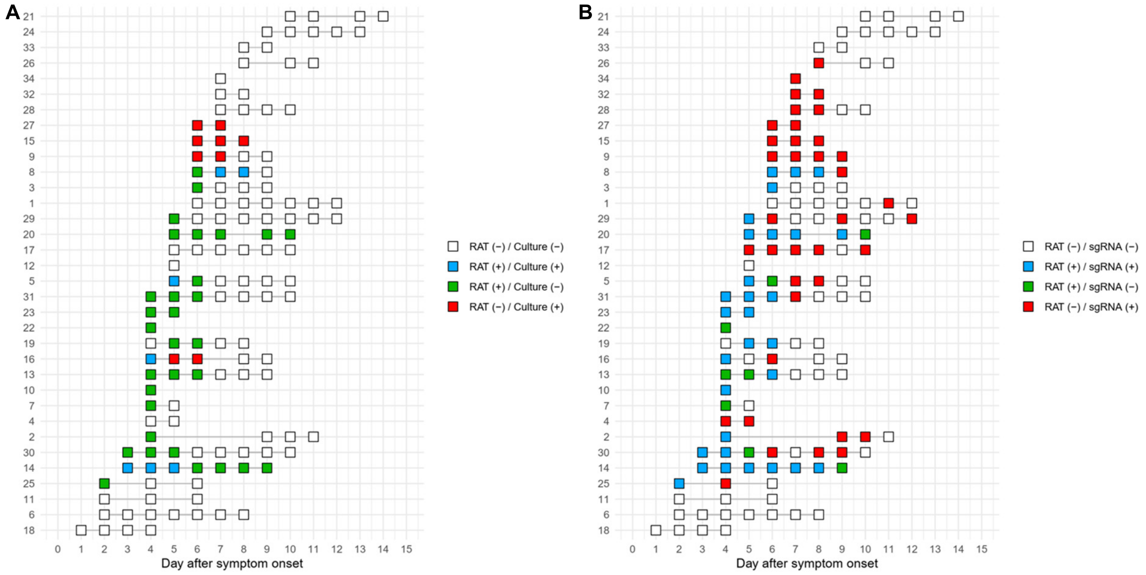

FIGURE 4
Timeline of the test results for RAT compared to cell culture **(A)** or subgenomic RNA **(B)**. The numbers on the *y*-axis represent the individual patient numbers.

Discussion

In this longitudinal study in symptomatic COVID-19 patients, overall agreement between results of RAT and culture was fair at about 70%, but RAT detected culture-positive cases in less than half of the patients. These results, comparing serially self-performed RAT to cell culture from saliva samples, indicates suboptimal sensitivity of RAT for detecting viable viral shedding after diagnosis or symptom onset in COVID-19 patients. Nonetheless, RAT still detected about half of COVID-19 patients with viable viral shedding. Consequently, RAT results could be used for the risk stratification on work restriction of healthcare workers (HCWs), when there is high pressure on healthcare systems, because RAT would detect half of the HCWs with viable viral shedding and who have theoretical risk of post-isolation transmission while no test cannot detect them. This approach may be particularly useful for HCWs who care for immunocompromised patients. Alternatively, the relatively high negative predictive value of RAT may help to allay concerns about the transmission risk of individuals within contingency or crisis settings.

Conventional PCR tests (real-time RT-PCR assays) have the highest sensitivity in diagnosing SARS-CoV-2 infection, but also have several shortcomings including cost, long turnaround time, and prolonged test positivity without viable virus (12–16). PCR-based isolation strategies that maintain isolation until PCR results become negative have been increasingly limited in use due to their unnecessarily long isolation requirements. Symptom-based isolation strategies have been adopted based on previous studies that reported the detection of viable virus did not exceed 10 days, and that no case of secondary attack was shown among close contacts exposed to an index case 5 days after symptom onset (17, 18). However, symptom-based isolation strategies for a pre-specified period are not applicable in populations with prolonged viral shedding, such as severe COVID-19 patients or immunocompromised hosts, and also unnecessarily constrains the social activity of asymptomatic or mild COVID-19 patients whose release of viable virus has ended earlier than the time of their de-isolation. Furthermore, due to the recent emergence of the Omicron variant, the recommended isolation period has been further curtailed from 10 to 5 days in patients with asymptomatic or mild COVID-19 (4). Therefore, there has been a growing public need for tools that can be used as surrogate markers to identify individuals having transmissibility.

Rapid antigen test are intended for use at the point-of-care to detect the presence of viral protein of SARS-CoV-2 and are quick and easy to use, as well as relatively cost-affordable. Although the performance of RAT may vary by company, several studies reported its high sensitivity and specificity (6). It has been reported that the RAT positivity reflects high viral load and correlates well with culture positivity (19, 20). However, RAT showed low sensitivity, detecting only about half of the virus culture-positive samples in this study. The reason for the low sensitivity of RAT test can be demonstrated as follows. First, virus culture was used as a reference test for infectivity, but lack of sensitivity may lead to false-negative results (21). In this context, the detection of subgenomic RNA might more exactly reflect the replication-compatible viral shedding (**Table 2**). It is worth to note that our findings of the sensitivity (94%) and specificity (57%) for the subgenomic RNA detection compared with cell culture, respectively, are consistent with our previous study (sensitivity 100% and specificity 65%, respectively) (22). Second, the timing of the sample collection may affect the results. Given the viral kinetics of SARS-CoV-2 with a gradual decrease in viral load after the time of diagnosis (23), RAT generally performed well in samples containing high viral titers from symptomatic patients at an early stage (24, 25). Therefore, RAT performance may be lower on serial testing that included samples with low viral titer collected at later stages of infection. Third, difference between RAT with nasal swabs and other viral tests using saliva samples may contribute to the results, despite the high correlation between saliva and nasal swabs (26). Finally, sub-optimal sampling and misinterpreting results in in self-testing can affect the sensitivity of the RAT.

Despite this limited performance, RAT-positive samples showed significantly higher viral load than RAT-negative samples. In addition, the RAT-positive rate gradually decreased over time after symptom onset. At the time of this writing, Cosimi et al. reported that RAT has a high negative predictive value (100%), so a negative RAT result could provide reassurance in ending isolation (8). Our findings of high negative predictive value of a negative RAT are consistent with this study (8). In addition, CDC recently recommended continuation of wearing masks around others in public places until two consecutive negative RAT results (27). Taken together, RAT may detect replication-competent SARS-CoV-2 virus, and accuracy of this test can be improved by increasing the frequency or providing adequate guidance for procedure and interpretation (13, 28). Our data on the daily RAT results provide important insights into the contingency or crisis plan during the pandemic. More than half of mild COVID-19 patients revealed positive RAT results 5 days after the onset of symptoms. Consequently, when the strategy for 5 day isolation with a negative RAT result is adopted in a hospital, more than 50% of HCWs would be required to undertake a further isolation period. In addition, the low positive predictive value of RAT might warrant further balancing of work restriction. By contrast, the relatively high negative predictive value of RAT may allay concerns about the transmission risk posed by individuals in contingency or crisis setting because the prevalence of viable viral shedding is low, after symptom onset, in patients with mild COVID-19.

Cell culture has been considered the standard test for SARS-CoV-2 viability, but can only be performed in a biocontainment facility and is time and labor intensive (29, 30). Furthermore, culture is vulnerable to bacterial contamination. Detecting subgenomic RNA showed a higher specificity to predict culture positivity than that of genomic RNA, and was closely correlated with symptom duration, suggesting that it may reflect the presence a replication-competent virus (22). Since viral culture lacks sensitivity and may underestimate the level of viable virus, we compared RAT results with the subgenomic RNA detection data. These analyses revealed that the positive predictive value of RAT increased, but the negative predictive value of RAT decreased, largely due to the positive rate of subgenomic RNA detection being higher than that of viral culture. Given that subgenomic RNA detection is more sensitive for viable viral shedding than viral culture, and a highly sensitive test of viable viral shedding is needed in certain settings (e.g., immunocompromised patient wards), the greater positive predictive value of RAT may point to such tests being more beneficial in high-risk rather than low-risk settings.

It is worth noting that demonstrating the presence of viable virus by cell culture or replication-competent virus by subgenomic RNA detection does not necessarily correlate with transmissibility potential. The current CDC and ECDC recommendations are primarily based on epidemiological data showing that there is no significant risk of SARS-CoV-2 transmission from index patients, 3 or 5 days after symptom onset, to exposed contacts (18, 31). However, such epidemiologic data may be subject to recall and misclassification bias. Therefore, the study of viable viral shedding might provide important complementary data for understanding viral transmission dynamics. In this context, our data showing daily positive rates of viral cultures along with a series of self-test RAT results may be useful for the decision of symptom-based de-isolation or work derestriction with/without supplemental tests.

There are several limitations of this study. Firstly, it is an observational study with a limited sample size. In addition, there were some missing results from serially collected RAT results and saliva samples. Thus, further well-controlled studies with larger sample sizes are needed. Secondly, the fact that patients performed the RAT without guidance from medical professionals may account for the lower-than-expected predictive accuracy of RAT. Given the nature of the at-home test kit, user-dependent variability may be an inherent feature of studies utilizing at-home test kits. Thus, the safe, reliable and accurate termination of COVID-19 isolation based upon RAT results, may necessitate the execution of the RAT by healthcare professionals, although many countries have approved the RAT as “home use” only. Despite the imperfection of self-testing, at-home RAT will be needed continuously considering the importance of early diagnosis of SARS-CoV-2 infection and inequality in accessibility/cost/time according to region and economic status (32, 33). Thirdly, the correlation between RAT results and cell culture/subgenomic RNA results may differ for other commercial SARS-CoV-2 RAT kits. In two independent evaluation studies, the RAT from the same manufacturer (Humasis Co., South Korea), although not the at-home kit used in this study, showed similar sensitivities compared to RATs from other manufacturers, but with lower specificity, from 72.8 to 79.0% (34, 35). Such low specificity may raise concerns about an increased risk for false positives. It is unlikely that the insufficient specificity of the RAT was due to detection of spike antigens in addition to nucleocapsid, because targeting spike antigen could be more specific than nucleocapsid (36). Given the 100% specificity of the Humasis RAT in the current study and the very low false-positive rate (0.05%) of the RAT reported in a recent large study, the low specificity issue does not appear to significantly affect the results of this study (37). In addition, the recent study reported the manufacturing issues as one cause of the cluster of false-positive RAT results (37). Further studies are needed as false positives can be attributed to multiple factors such as batch issues, cross-contamination, pre-existing human antibodies, or highly viscous samples. Fourthly, this study was conducted during the Delta variant epidemic, so it is not known whether the results can be applied to analysis of the Omicron variant. A study carried out during the Omicron variant epidemic reported that the RAT used did detect viral protein of that variant (38). However, there are no data on whether RAT results significantly differ between the variants. Finally, only a few vaccinated patients were included in this study. However, vaccine status is unlikely to affect the results of RAT, even though it does affect viral load kinetics (39, 40).

In conclusion, about half of the patients in this study who shed viable virus after symptom onset returned negative RAT results. Therefore, a negative RAT result cannot be used as a guarantee test for non-infectivity. Nevertheless, the remaining patients with viable virus shedding were identified by positive RAT results, and RAT exhibited relatively high negative predictive value for viable viral shedding. Consequently, RAT may provide an additional layer of data to identify individuals with risk of infectivity in symptom-based de-isolation strategies.

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 human participants were reviewed and approved by the Institutional Review Committee of Asan Medical Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SB, M-SP, and S-HK contributed to the conception and design of the study. SB, SP, and SL involved in participant recruitment and data curation. JYK, HP, J-YB, JK, and M-SP performed laboratory works. SB, SP, SL, and JYK performed formal analysis. SB, HP, M-SP, and S-HK wrote the first draft of the manuscript. MK, YC, SL, SC, and YK wrote sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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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/fmed.2022.922431/full#supplementary-material

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Saeed Hamood Alsamhi,
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Bilal Ahmed Usmani,
Aga Khan University, Pakistan
Radhya Sahal,
University College Cork, Ireland

*CORRESPONDENCE
Alexander Avian
alexander.avian@medunigraz.at

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Predictors for adherent behavior in the COVID-19 pandemic: A cross-sectional telephone survey

Andrea Siebenhofer[1,2], Clemens Könczöl[3], Klaus Jeitler[1,4], Daniela Schmid[5], Phillip Elliott[2] and Alexander Avian[4]*

[1]Institute of General Practice and Evidence Based Health Services Research, Medical University Graz, Graz, Austria, [2]Institute of General Practice, Johann Wolfgang Goethe University Frankfurt, Frankfurt, Germany, [3]Institute of Psychology, University of Graz, Graz, Austria, [4]Institute for Medical Informatics, Statistics and Documentation, Medical University Graz, Graz, Austria, [5]Austrian Agency for Health and Food Safety Ltd. AGES, Vienna, Austria

Background: During the COVID-19 pandemic, protective measures have been prescribed to prevent or slow down the spread of the SARS-CoV-2 virus and protect the population. Individuals follow these measures to varying degrees. We aimed to identify factors influencing the extent to which protective measures are adhered to.

Methods: A cross-sectional survey (telephone interviews) was undertaken between April and June 2021 to identify factors influencing the degree to which individuals adhere to protective measures. A representative sample of 1,003 people (age >16 years) in two Austrian states (Carinthia, Vorarlberg) was interviewed. The questionnaire was based on the Health Belief Model, but also included potential response-modifying factors. Predictors for adherent behavior were identified using multiple regression analysis. All predictors were standardized so that regression coefficients (β) could be compared.

Results: Overall median adherence was 0.75 (IQR: 0.5–1.0). Based on a regression model, the following variables were identified as significant in raising adherence: higher age (β = 0.43, 95%CI: 0.33–0.54), social standards of acceptable behavior (β = 0.33, 95%CI: 0.27–0.40), subjective/individual assessment of an increased personal health risk (β = 0.12, 95%CI: 0.05–0.18), self-efficacy (β = 0.06, 95%CI: 0.02–0.10), female gender (β = 0.05, 95%CI: 0.01–0.08), and low corona fatigue (behavioral fatigue: β = −0.11, 95%CI: −0.18 to −0.03). The model showed that such aspects as personal trust in institutions, perceived difficulties in adopting health-promoting measures, and individual assessments of the risk of infection, had no significant influence.

Conclusions: This study reveals that several factors significantly influence adherence to measures aimed at controlling the COVID-19 pandemic. To enhance adherence, the government, media, and other relevant stakeholders should take the findings into consideration when formulating policy. By developing social standards and promoting self-efficacy, individuals can influence the behavior of others and contribute toward coping with the pandemic.

KEYWORDS
COVID-19, adherence, health belief model, social norms, self-efficacy, risk perception, perceived health risk, pandemic fatigue

Introduction

Since the beginning of the pandemic in December 2019, Coronavirus disease 2019 (COVID-19) has presented a significant challenge to health care systems around the world, with the numbers of hospitalizations due to COVID-19 diseases frequently surpassing system capabilities. In order to slow down transmission rates, almost every government in the world has developed a prevention strategy involving, for example, the use of face masks, hygiene guidelines, and social distancing (including stay-at-home orders), adherence to which was also recommended by the World Health Organization (1).

To develop and implement effective measures, it is important to obtain information on knowledge about COVID-19 in the broader population, and on peoples' attitudes and willingness to adhere to restrictions and recommendations (2). In addition to a recently published systematic review, meta-analyses involving a large number of quantitative studies published worldwide between January 1 and June 30, 2021, showed that at least 70% of questions about knowledge and what constitutes good attitudes and practice with regard to prevention-orientated behavior were answered correctly (3). However, people from low-income countries, men, younger people, and less educated persons generally had lower standards of practice. Another review published by Wake in 2020 also showed that the majority of the study population had a high level of knowledge, a good attitude, and high standards of practice. Moreover, besides variables such as marital status and media consumption, the study revealed the significant influence of age, gender, educational status, and income (4).

For management of the pandemic to be effective, it is important that epidemiological measures are adhered to. However, during the course of pandemics, willingness to comply with measures may change. A large cohort study in the UK involving the analysis of the patient data of more than 50,000 persons during two waves of the pandemic showed that most individuals complied with prevention behaviors (5). Data published by the Austrian Corona Panel during the first 10 weeks of the first wave in spring 2020 revealed that at least two-thirds of participants believed that measures introduced by the government were appropriate. But levels of agreement to all individual measures decreased steadily over the period (6). The COSMO-Spain Survey also showed that the level of adherence was considerable during three rounds of measurements from July to November 2020, and compliance with the mandatory use of facemasks reached ≥80% in all three periods (7). This is consistent with the results of the UK population study which showed that mask wearing was the most accepted measure (5).

The health belief model is widely used to develop a conceptual understanding of individual adherence to preventive activities (8–12). The basic assumptions of this model are that people are more likely to show certain health behaviors if they perceive a high risk of falling ill (perceived susceptibility), if the disease is perceived as serious (perceived severity), if those adopting the behavior see an advantage for themselves (perceived benefits), and if the obstacles to assuming this behavior are not too high (perceived barriers). Other important aspects of this model are a person's self-efficacy expectations and whether the person has been exposed to convincing arguments (cues to action) (13, 14). Lessons learned from previous pandemics such as swine-origin influenza (15), SARS (16), and EBOLA (17) also indicate that factors such as an individual's perceived risk, self-efficacy, and knowledge play an important role in adherence to preventive strategies.

These days, the health belief model is also used in SARS-CoV-2 research. Previous research on factors modifying adherence to protective measures to contain the COVID-19 pandemic show that an individual's perception of certain aspects of the health belief model and his or her preventive behaviors are influenced by social aspects, sociodemographic characteristics, and attitudes. Research shows that trust in science, government and administration, the media, and in the capabilities of the health system, has a significant impact on health behavior in connection with COVID-19 (18–21). Inconsistent results have been found for socio-demographic variables such as age, gender, education (22–27), and social norms (20, 28, 29). In one study published by Eichenberg et al. based on an online survey conducted in Austria, participants were categorized into four groups depending on their perceived susceptibility and their engagement in health-promoting behaviors (30). All four groups differed significantly with regard to almost all personality dimensions. Those who underestimated the COVID-19 pandemic and those for whom protective measures led to high emotional discomfort and stress showed significantly lower adherence to protective measures. In contrast, those with high levels of positive personality traits and that also considered governmental measures as appropriate, and those for whom the virus presented a danger and whose health depended on the effectiveness of the measures, were significantly more compliant. Data from Macao, China from a telephone interview study with 617 people in April 2020 (24) showed that the variables perceived benefit, exposure to a cue to action, perceived severity, and reward for use, were positively associated with a number of precautionary measures (wearing a face mask, proper handwashing, social distancing, avoiding touching one's face, flushing a toilet properly, and carrying a hand sanitizer). On the other hand, perceived barriers and social distancing were negatively associated with several protective measures. Most recently in December 2021, the Austrian Corona Panel published data collected consecutively over the first 12 months of the pandemic showing that people with lower health risk perceptions, less respect for social norms, and lower levels of trust in institutions were less likely to adopt preventive behaviors (31).

Another aspect that has frequently been examined in connection with the pandemic is corona fatigue (5, 32–34). The WHO defined pandemic psychological fatigue as a feeling of distress or frustration due to "sustained and unresolved adversity" (34) which is a feeling of tiredness of the pandemic and emotional exhaustion. According to a longitudinal telephone survey from January to December 2020 of over 30,000 persons (33), low public confidence in the government had a negative impact on precautionary behaviors and was associated with greater psychological fatigue. In contrast to other influencing aspects, corona fatigue changes over time.

All these papers aimed to examine potential mitigating factors to the introduction by governmental and stakeholder institutions of further recommendations to improve pandemic control. Based on the health belief model in a representative population in two states (Carinthia and Vorarlberg) in Austria, the aim of this study is to confirm known and identify new factors influencing adherence.

Methods

Cross-sectional data from telephone interviews with 1,003 people living in Austria during the COVID-19 pandemic in spring 2021 were used for the analyses.

Health belief model

We used the health belief model (HBM) adapted for use in COVID-19 research by Hsing et al. (35) and further expanded it by taking into consideration potential modifying aspects such as demographics, and time-dependent aspects such as corona fatigue. Figure 1 shows the key components of the HBM model used in this project.

Questionnaire

The presented model (Figure 1) considers behavioral aspects and attitudes. These aspects also take the respondent's knowledge into consideration. The KAP-survey concept (knowledge, attitude, practice) was therefore used in the development of the questionnaire (2). To create an item pool for the COVI-Ad questionnaire, a literature review was carried out. Questionnaires that were based either on the health belief model or single aspects of it, and that had already been used during the COVID-19 pandemic and other pandemics or epidemics, were screened. New items were formulated for aspects that were not covered in these questionnaires. To make it easier to respond to the items during telephone interviews, the number of response categories was kept to a minimum. The resulting questionnaire was discussed within an expert group meeting (psychologist, medical doctors). After minor changes, eight telephone interviews were carried out in advance to assess the comprehensibility and feasibility of the questionnaire. The final questionnaire consisted of 68 items with a closed- and two items with an open-response format. A translated version of the German questionnaire can be found in the Supplementary material. Since the aim of the questionnaire is to map the relevant aspects of the adapted health belief model, the items were analyzed separately for each aspect. Explorative factor analysis (VARIMAX rotation) was carried out separately for all aspects apart from sociodemographic variables and single-item aspects. Internal consistency (Cronbach's alpha) was calculated for each resulting factor.

Behavior

Adherence to COVID-19 measures was assessed on the basis of six items (response format yes/no)—social distancing (refraining from meeting a large number of people), physical distancing (keeping distance to other people), respecting a curfew from dusk to dawn, wearing FFP2 masks, testing, and testing when symptoms are present. Participants were additionally asked if they had ever ignored any of the measures being assessed. As a result of factor analysis of these six items, four could be assigned to factor adherence. These measures were social distancing, physical distancing, respecting a curfew from dusk to dawn, and wearing FFP2-masks (Cronbach's $\alpha = 0.681$).

Health beliefs

Five aspects of the adapted health belief model were measured using 18 items. To assess *perceived severity,* respondents were asked to compare COVID-19 to influenza (response format: harmless/comparable/more dangerous). Furthermore, the personal health risk and economic risk resulting from measures to combat the coronavirus were assessed on a Five-point Likert type response scale. No satisfactory result could be achieved in the factor analysis of perceived severity. All three perceived severity items were therefore analyzed separately. *Perceived Susceptibility* was assessed using a single item (response format: not at all/slightly/high). The aspect *Perceived barriers due to health-promoting measures* consisted of seven items (response format: yes/partly/no) and asked respondents whether they thought the measures were annoying, excessive, would be able to prevent the virus from spreading, had been scientifically proven to be effective, were constitutional or violated legal regulations, were feasible in reality, and whether they limited everyday activities. The first five items could be assigned to one factor (Cronbach's $\alpha = 0.792$). The other two items were assigned to another factor (practicability of health-promoting measures), which, however, had too little internal consistency ($\alpha = 0.281$) to be considered in the further analysis. *Incentives to engage in health-promoting*

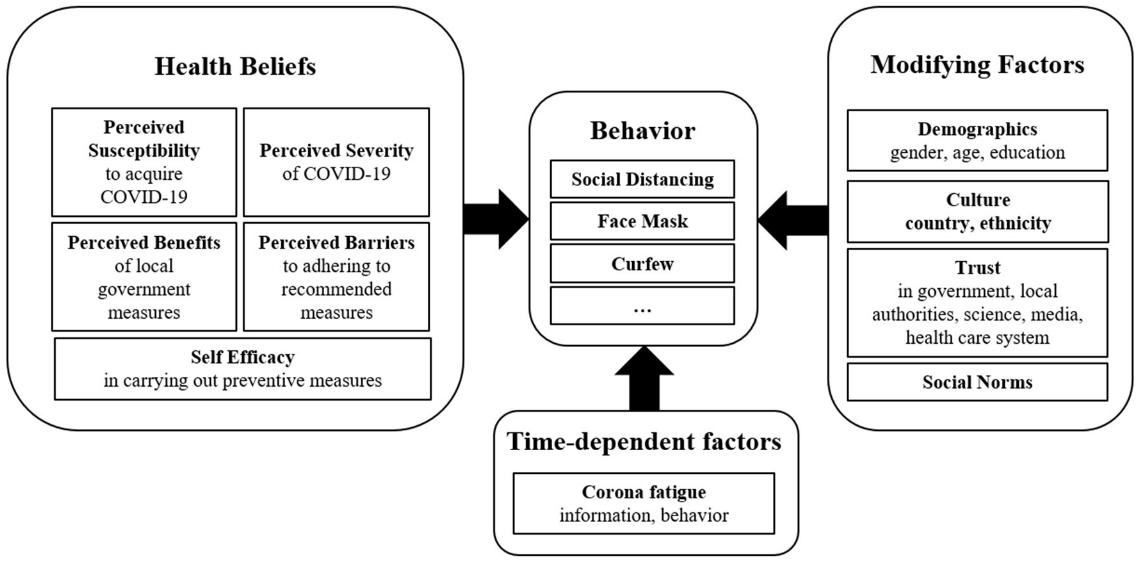

FIGURE 1
Model for explaining adherent behavior, based on the health belief model, modifying aspects, and time varying aspects.

measures were assessed to ascertain the perceived benefits of health-promoting measures, whereby the respondents were first asked whether they considered the measures to make sense. For measures that were not considered to make sense, respondents were asked how likely it is that they would adhere to them (response format: quite likely, sometimes, quite unlikely) when adherence to the measures was officially checked, when high penalties existed for non-adherence, when someone they trusted could justify use of the measures, and when significant scientific evidence confirmed effectiveness. All these aspects were included in the resulting factor (Cronbach's $\alpha = 0.744$). To measure *self-efficacy,* the respondents were first asked whether they considered the measures to make sense. For measures they considered to make sense, respondents were asked how likely it was that they would adhere to them when they were in the company of friends that were not (response format: quite likely, sometimes, quite unlikely).

Modifying factors

The following demographic variables were assessed: age (years), gender (female, male, other), living situation (living with children: yes/no, living alone: yes/no), employment status [retired, unemployed, self-employed, employed, short-time work, homemaker, parental leave/sabbatical/care leave, student (school, university, etc.)]. Educational levels were divided into five groups. EL1: Compulsory education including school leavers with no certificate of education, EL2: Apprenticeship, EL3: College for higher vocational education, EL4: Academic secondary school, EL5: University. The influence of culture was measured according to migration background (both parents born outside Austria).

TABLE 1 Internal consistency of the factors used to evaluate the pandemic.

	Cronbach's α
Adherence	0.681
Perceived barriers due to health-promoting measure	0.792
Perceived incentives to engage in health-promoting measures	0.744
Trust in institutions	0.828
Social norms	0.755
Information fatigue	0.766
Behavioral fatigue	0.669

For the **trust** aspect, respondents were asked whether they trusted information on corona that stemmed from politicians (prime-minister, minister of health, mayor), political institutions (European Union), scientific organizations, newspapers, public TV, private TV, social media, medical doctors, and friends (response format: yes/partly/no). All three items concerning trust in politicians (prime-minister, minister of health, mayor) and the items concerning trust in political institutions, scientific organizations, newspapers, and public TV were assigned to the factor trust in institutions ($\alpha = 0.828$). Two further factors concerning trust, were not considered in the further analysis because of insufficient internal consistency (trust in alternative media, $\alpha = 0.279$; trust in friends and medical doctors, $\alpha = 0.418$). A single item was used to assess social norms.

Aspect	Scales and single items	Scale/Item content
Behavior	Adherence	Social distancing, physical distancing, curfew from dusk to dawn, wearing FFP2 masks
Health beliefs	Perceived susceptibility	Perceived susceptibility
	Perceived severity	Comparison to Influenza, personal health risk and economic risk resulting from measures
	Perceived benefits	Incentives to engage in health-promoting measures
	Perceived barriers	Annoying, excessive, prevent the virus from spreading, scientifically proven to be effective, constitutional or violated legal regulations, feasible in reality, limited everyday activities
	Self efficacy	How likely is it to adhere to measures when someone is in the company of friends that are not adherent
Modifying factors	Demographics	Age, gender, living situation, employment status, educational levels
	Trust	Trust in politicians, political institutions, scientific organizations, newspapers and public TV
	Social norms	Majority of the people they cared about (e.g. family, friends) adhered to specific measures
	Culture	Migration status
Time-dependent factors	Information fatigue	Interest in receiving daily information on how many people had tested positively for Corona, the number of ICU admissions and confirmed deaths, the importance of this information, tired of hearing about COVID-19, sick of COVID-19 discussions on TV, the radio and in newspapers etc.
	Behavior fatigue	Feeling overwhelmed by the COVID-19 measures, unwillingness to adhere to regulations because they changed so frequently, feeling tired of limiting oneself to protect high-risk groups and losing the motivation to fight the pandemic

FIGURE 2
Scales and items used in the survey.

Respondents were asked whether the majority of the people they cared about (e.g., family, friends) adhered to specific measures (response format: yes/no).

Time-dependent factors

The *corona fatigue* aspect contained all six items from Lilleholt et al.'s (32) corona fatigue questionnaire and has a two-dimensional structure (information fatigue, behavioral fatigue). As the questionnaire was used in a telephone interview, response formats were adapted to take this into account. In this study, the response format was simplified to: agree/partly agree/do not agree. In addition, one item (unwilling to speak to people who downplay the risk of COVID-19) was added and used the same response format. Six further items (response format: yes/partly/no) dealt with fatigue resulting from changing regulations (two items), daily news on the number of people that had tested positively, that had been admitted to an intensive care unit (ICU), or had died (three items), and resignation due to the length of the pandemic (one item). As the factors proposed by Lilleholt et al. (32) only had an internal consistency of $\alpha = 0.612$ (information fatigue) and $\alpha = 0.617$ (behavioral fatigue), the 13 items were analyzed together. This resulted in a three-factor model, with two factors showing adequate internal consistency. These two factors were entitled information fatigue and behavioral fatigue (information fatigue: $\alpha = 0.766$; behavioral fatigue: $\alpha = 0.669$) (Table 1). The information fatigue factor included items concerning interest in receiving daily information on how many people had tested positively for Corona, the number of ICU admissions and confirmed deaths, as well as the importance of this information. Respondents also rated how tired they were of hearing about COVID-19 and how sick they were of COVID-19 discussions on TV, the radio and in newspapers, etc. Items making up

TABLE 2 Demographics of participants ($N = 1,003$).

		Median (IQR) *n* (%)
Age in years		50 (38–64)
Gender	Female	522 (52.0%)
	Male	479 (47.8%)
	Other	2 (0.2%)
Educational level	EL1: Compulsory education—including school leavers with no certificate of education	106 (10.6%)
	EL2: Apprenticeship	352 (35.3%)
	EL3: College for higher vocational education	214 (21.5%)
	EL4: Academic secondary school	183 (18.4%)
	EL5: University	141 (14.2%)
Employment status	Retired	300 (29.9%)
	Unemployed	28 (2.8%)
	Self-employed	123 (12.3%)
	Employed	398 (39.7%)
	Short-time work	70 (7.0%)
	Homemaker	21 (2.1%)
	Parental leave/sabbatical/care leave	16 (1.6%)
	Student (school, university, etc.)	40 (4.0%)
Living alone	Yes	166 (16.6%)
Living with children	Yes	332 (33.1%)
Migration background	Yes	140 (14.0%)

EL, educational level.

the behavioral fatigue factor were feeling overwhelmed by the COVID-19 measures, unwillingness to adhere to regulations because they changed so frequently, feeling tired of limiting oneself to protect high-risk groups and losing the motivation to fight the pandemic. The third factor was COVID-19 anxiety, which was excluded from further analysis due to insufficient internal consistency ($\alpha = 0.374$). An overview of the used scales is given in Figure 2.

Survey

The survey was conducted by two professional call centers in two Austrian states from April 20 to June 9. Overall, 500 volunteers that were representative of the population of Carinthia in terms of age, gender, and educational status and were $\geq$16 years, and 503 from the population of Vorarlberg, participated in the interview study. To achieve this sample size 3,690 persons in Carinthia (response rate 13.6%) and 3,526 in Vorarlberg (response rate 14.3%) were contacted. Participation was voluntary and participants received no incentives.

Statistics

Baseline characteristics are presented as mean $\pm$ SD or median (IQR), as appropriate. Categorical variables are provided as absolute and relative numbers. In a first step univariate linear regression analysis was performed, whereby adherence served as the outcome. Predictors were the factors and the single-item aspects described above, along with sociodemographic variables (age, gender, employment status, living with children, living status, education). Dummy coding was used for categorical variables with more than two categories. To enhance comparability, all factors and single-item aspects apart from age were transformed to range from 0 to 1. To ensure the resulting betas were comparable, the age variable was therefore divided by 100. Univariate significant predictors were checked for multicollinearity (variance inflation factor <2.5). Remaining variables were included in a multivariate regression analysis (backwards selection). Exploratory data analysis was used to assess the influence of the predictors on the single measures by using logistic regression analysis. For this analysis, univariate significant predictors were also checked for multicollinearity (variance inflation factor <2.5). The remaining variables were subjected to multivariate logistic regression analysis (backwards selection). SPSS 26 was used for data analysis (36), a value of $p < 0.05$ was considered significant.

Results

Demographics

The median age of participants was 50 (38–64) years and 52% of respondents were female. Female respondents were older (female: median 54 years IQR: 41–66; male: 44, 35–62). About 1/3 had a university or high school diploma (EL4 and EL5), while 40% were employed and 30% had retired (Table 2).

Health belief model: Descriptive analysis

Overall, respondents' median adherence was 0.75 (IQR: 0.5–1.0). Social norms (median: 1, IQR: 0.67–1.00) and trust in institutions (median: 0.64, IQR: 0.5–0.83) were also rated highly. Respondents rated a COVID-19 infection as more dangerous than an influenza infection (median: 1.0, 0.5–1.0). We also measured self-efficacy (median: 0.5, IQR: 0.5–1.0), personal health risk (median: 0.50, IQR: 0.25–0.75), perceived barriers due to health-promoting measure (median: 0.50, IQR: 0.25–0.75), perceived incentives to engaging in health-promoting measures (median: 0.50, IQR: 0.25–0.75), economic risk stemming from the measures to combat the coronavirus (median: 0.50 IQR: 0.2–0.7), and perceived susceptibility (median: 0.5, IQR: 0.0–1.0). Low ratings were observed for

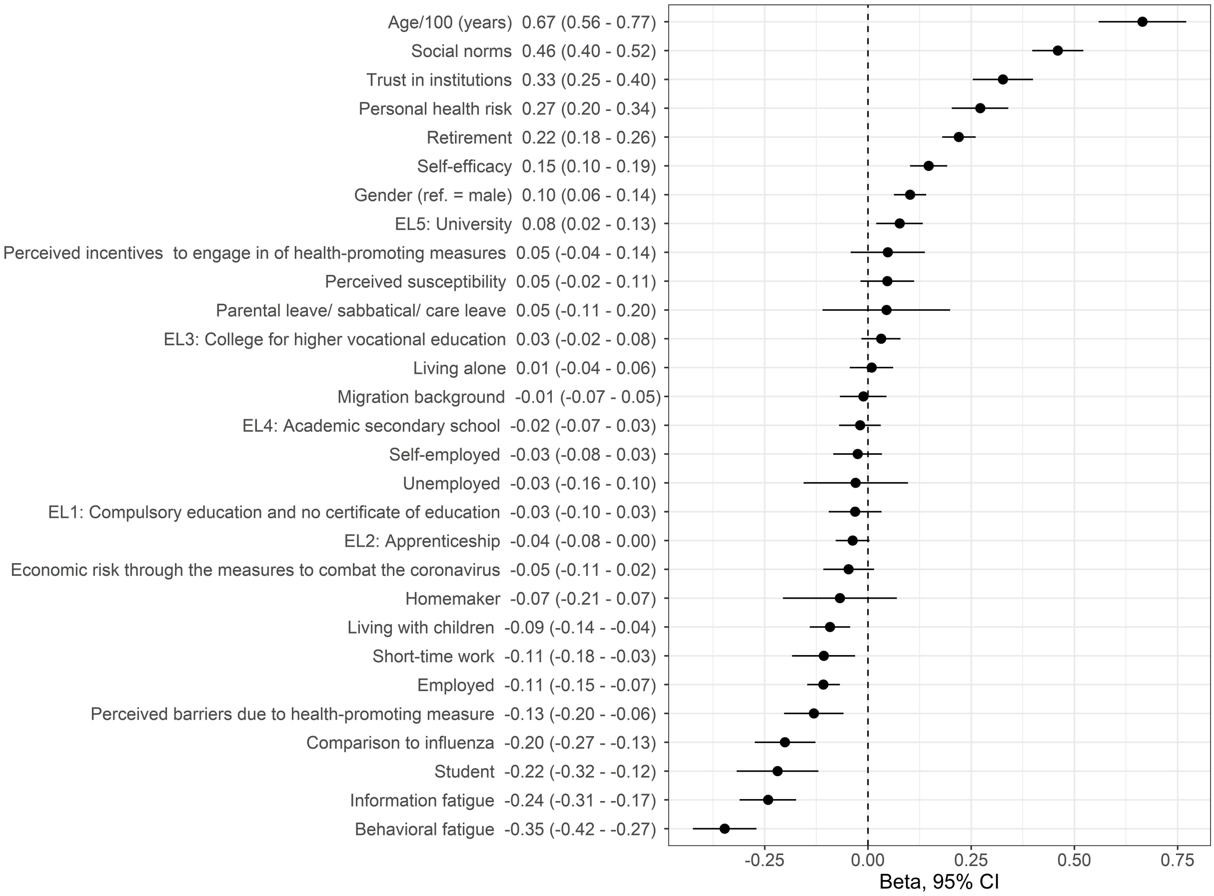

FIGURE 3
Association between adherence and aspects of the health belief model, modifying aspects, and health beliefs, as derived from univariate regression analysis. Beta-coefficients with 95% confidence intervals are shown. Variables are ordered according to beta-coefficient (EL, educational level).

information fatigue (median: 0.4, IQR: 0.2–0.7) and behavioral fatigue (median: 0.25, IQR: 0.00–0.38).

Influence on adherence

In a first step, the following variables were significant univariate predictors of adherence to health-promoting behaviors: age, gender, employment status (retirement, employed, short-time work, student), university degree (EL 5), living with children, two perceived severity items (comparison to influenza, personal health risk), self-efficacy, perceived barriers due to health-promoting measure, trust in institutions, social norms, information fatigue, and behavior (Figure 3, Supplementary Table 1).

In a second step, multivariate regression analysis indicated that six independent predictors explained 29% of the variance in adherence [$R^2_{adjusted} = 0.285$, $F_{(1)} = 59.85$, $p < 0.001$]. Higher age (β: 0.43 95%CI: 0.33–0.54; $p < 0.001$), social norms (β: 0.33 95%CI: 0.27–0.40; $p < 0.001$), perceived personal health risk (β: 0.12 95%CI: 0.05–0.18; $p < 0.001$), self-efficacy (β: 0.06 95%CI: 0.02–0.10; $p = 0.002$), female gender (β: 0.05 95%CI: 0.01–0.08; $p = 0.002$), and decreased behavioral fatigue (β: −0.11 95%CI: −0.18 to −0.03; $p = 0.045$) were associated with increased health-promoting behavior (Figure 4).

Influence on single measures of adherence

Multivariate regression analysis of individual measures indicated that two to seven independent predictors explained 9–27% of variance. Twelve different predictors were included in the final six models. No predictor was included in all final models. The predictors that were most often included were behavioral fatigue (four times) and age (three times) (Table 3, Supplementary Figure 2; univariate results: Supplementary Figure 1).

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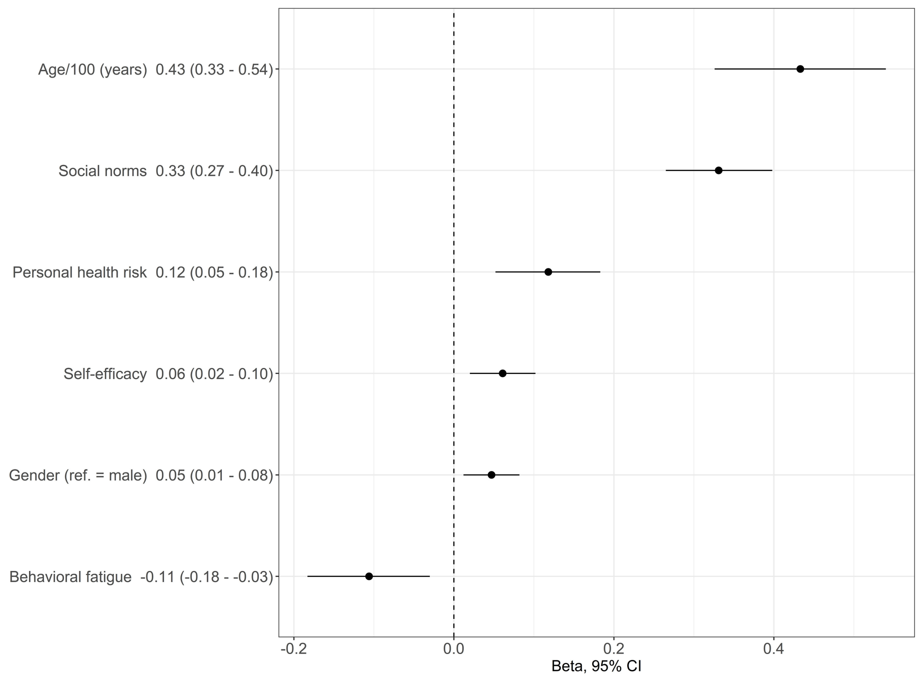

FIGURE 4
Association between adherence and aspects of the health belief model, modifying aspects and health beliefs, as derived from multivariate regression analysis. Beta-coefficients with 95% confidence intervals are shown.

Discussion

In this representative cross-sectional telephone survey conducted in Austria, increasing age, social norms, perceived personal health risk, self-efficacy, female gender, and lower behavioral fatigue were independent predictors of greater adherence to a bundle of measures such as social distancing, physical distancing, respecting dusk-to-dawn curfews and wearing FFP2-masks (Figure 5). The predictors differed depending on the measure.

Age and gender

The survey revealed that higher age and female gender were independent predictors of adherent behavior. Even though previously published studies were inconclusive, a large percentage of studies support our results (23, 24, 37–39). For example, one Canadian study of over 2,000 persons between 18 and 100 years old showed that age and male gender were associated with lower adherence to different COVID-19 protective measures such as working remotely from home, social distancing, and maintaining a physical distance of 2 m from others (23). Another study that used cluster analysis to compare adopters and non-adopters of COVID-19 measures in 5,893 persons between 18 and 94 years old confirmed that older and female persons had lower odds of being in the non-adapter cluster (37). No influence of age or gender was found in a survey of elderly persons (aged over 60 years), which may reflect homogeneity across these variables within the study group (22). Wolfe's paper, which focused on age differences in COVID-19 risk-taking, also revealed that risk perception for the self and others partially mediated the effect of age differences on taking risks (38). One reason why the younger population seems to be less adherent to protection measures may be that they are less vulnerable to the consequences of an infection with SARS-Covid-2. It is well-known that the likelihood of complications, hospitalization, and death is dependent on age, and this has been extensively communicated in the media and by public institutions. Another reason may be that people of younger age are still actively involved in the workforce and may frequently feel that the risk of financial loss offsets concerns about becoming infected.

Results on the effect of gender differences are contradictory. One study of 21,649 persons from eight OECD countries (Australia, Austria, France, Germany, Italy, New Zealand, the UK, and the US) underpins our findings that women have been more adherent to pandemic rules in all countries and take the pandemic more seriously (40). In addition, the paper by Abd Elhameed Ali et al., which also presented results from over 700 people, shows female gender to be positively related to better knowledge about COVID-19 measures and greater adherence

TABLE 3 Association between individual measures and aspects of the health belief model, modifying aspects and health beliefs, as derived from multivariate regression analysis.

	Physical distancing	Wearing FFP2 masks	Respecting dusk-to-dawn curfew	Social distancing	Testing when symptoms are present	Testing
Age	20.5 (6.0–71.3)		17.9 (1.7–192.5)	5.3 (1.2–22.9)		
Female					2.3 (1.0–5.5)	
Employed				0.6 (0.4–0.9)		2.1 (1.4–3.3)
Living with children		0.4 (0.2–0.9)				
Perceived health risk	2.6 (1.3–5.2)			2.7 (1.2–6.0)		
Comparison to influenza				4.6 (1.8–11.9)		0.3 (0.1–0.5)
Perceived incentives to engage in health-promoting measures			3.5 (1.4–9.3)			
Information fatigue			4.6 (1.4–14.8)			0.2 (0.1–0.4)
Behavioral fatigue		0.2 (0.1–0.8)		0.3 (0.1–0.6)	0.1 (0.0–0.3)	0.4 (0.2–1.0)
Social norms	5.2 (2.7–10.1)			8.6 (4.2–17.9)		
Self-efficacy			2.3 (1.1–4.8)	2.2 (1.4–3.6)		
Trust in institutions		10.0 (2.8–35.6)				

OR with 95% confidence intervals are shown.

to containment measures (26). In contrast, an online survey of 893 Brazilians by Carvalho and Machado that was primarily concerned with the correlation of adherence to pandemic rules and psychopathy traits showed no gender differences (25). In summary, it can be seen that the influence of gender and age found in our study is found in many but not all studies.

Social norms

In our study we could also show that social norms are strongly associated with increased health-promoting behavior. Even though the results found in the literature appear to be inconsistent (20, 28), this paper supports recent findings indicating that social norms have a significant impact on adherence to COVID-19 measures in the general population (31, 41). In the Corona pandemic, social norms have played an important role in reducing individual transmission risk, as well as the transmission rate in the population as a whole. As studies suggest that social norms and social identities influence behavioral changes, it is important to mention the potential impact of influencing social norms and attitudes to specific COVID-19 measures, especially in vulnerable groups. According to Neville et al. (42), public health messages aimed at changing behaviors should focus on specific groups and present the desired behavior, without including any reference to unwanted behaviors. These messages should be presented by people that are perceived as "one of us." The intended behavioral change should be framed in an identity-affirming manner, and group members should be seen to change their behavior without losing their influence and without polarization within the group. As social norms are formed by all members of a group, each individual has an influence. According to a review by Tankard and Paluck (43), understanding norms requires information on individual behavior, the group as a whole, and institutional signals. Each of these may be influenced by COVID-19 measures and information strategies that focus on providing consistent information that takes into account group identities and aim to enhance people's self-efficacy. Even if an influence of social norms on behavior cannot be found in all

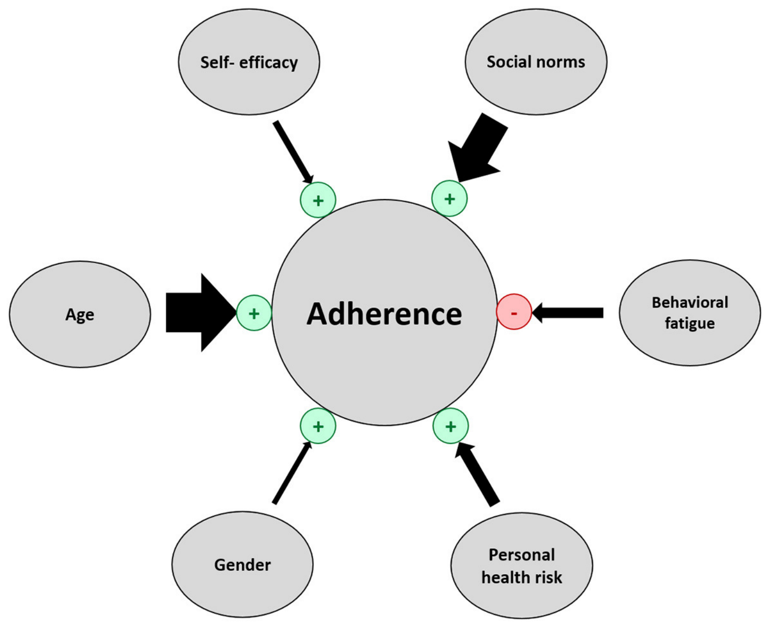

FIGURE 5
Predictors of adherent behavior. Arrow width corresponds to the absolute value of beta (regression coefficient). Predictors that increase adherence are marked in green "+" and predictors that decrease adherence are marked in red "−".

studies, as in our study, social norms may play an important role in adherence.

Perceived health risk

Another factor we found to have an impact on adherence is perceived personal health risk. This means the more dangerous the virus is considered to be, the more willing a person is to take protective action. These findings confirm further cross-sectional studies such as Lang et al. (37) showing that people who were unconcerned that an infection with the virus might lead to severe symptoms had higher odds of being non-adopters of non-pharmaceutical preventive interventions. Furthermore, in a sample of over 6,600 persons in the US, Bruine de Bruin and Bennett also found people that considered high risk to be associated with an infection with the coronavirus to be more likely to adopt protective behaviors (44). It is interesting, however, that the perceived threat of a SARS-COVID-19 infection having serious repercussions seems to have declined over the course of the pandemic. Results from a longitudinal survey from three rounds of interviews in Spain conducted between July and November 2020 revealed that the perceived threat of becoming seriously ill if infected with COVID-19 infected decreased over time, although the probability of becoming infected remained stable (7). In addition, another study involving 30,000 interviews conducted in 39 rounds in Hong Kong also analyzed temporal changes in the perceived severity of the disease and found it to be positively associated with the incidence of infected people (33).

Besides the perceived health risk, there are also known differences in the health risk due to COVID-19 between groups. In the case of diabetics, for example, it is possible to determine the individual risk with the help of models (45). Furthermore, modern technologies can be useful in early diagnosis and accurate classification of COVID-19 patients (46) and combat COVID-19 (47, 48).

Behavioral fatigue

In our study, lower behavioral fatigue was associated with greater health-promoting behavior. These results have been confirmed in further studies showing that behavioral fatigue associated with the Corona pandemic impacted people's adherence to measures to reduce transmission risk in the population (5, 32, 33).

Martinez-Garcia et al. analyzed data from a survey of 20,054 persons that was conducted in Spain from April to September 2020 and showed that adherence to containment measures declined over time (49). While they found that the psychological impact was the most important predictor of adherence to containment measures in the beginning, the economic impact played a greater role at the end of the period under review. The authors recommended the use of psychological and economic support programs to enhance adherence in the population.

Reicher and Drury also concluded that lower adherence may be related to the availability of financial resources in the population and not only to psychology. Measures to counteract behavioral fatigue should therefore consider the specific needs of communities (50).

Liao et al. showed that psychological fatigue is also associated with public confidence in government, and psychological distress. Thus, fatigue is not only a predictor of adherence but also has an effect on other health-related aspects and may be influenced by official measures and strategies (33).

Based on qualitative data from our survey (not shown), we would also suggest that behavioral fatigue is influenced by changes in behavior. People may, for example, develop strategies to reduce their individual transmission risk (e.g., daily testing rather than wearing FFP2 masks), which may explain why some people do not follow all governmental measures. Behavioral fatigue may therefore be lower and adherence higher than shown in the results, as it is generally based on a measurement of adherence to concrete measures.

Self-efficacy

Comparable to other studies [e.g., (51)] self-efficacy was also found to be a predictor of adherence to COVID-19 measures. Even though the other predictors in the model have a larger influence on adherence, self-efficacy nonetheless plays an important role in dampening the Corona pandemic, as self-efficacy enhances adherence and reduces an individual's risk of infection. Moreover, COVID-19-related self-efficacy is also reported to be positively correlated with mental health, preventive behavior, and knowledge about COVID-19 (52). Additionally, enhancing self-efficacy not only influences an individual's transmission risk, but may also reduce the rate of new infections in the population as a whole. This is because self-efficacy appears to strengthen social norms and lead to more preventive behavior. On the other hand, Alemany-Arrebola et al. found that self-efficacy was sometimes negatively affected by aspects related to COVID-19, such as perceived stress associated with the pandemic, confinement, and critical events (illness and death of a relative/friend due to COVID-19) (53). These aspects increase individuals' anxiety levels and reduce their self-reported perceptions of (academic) self-efficacy. In summary, self-efficacy is an important aspect of adherence that was also found in other studies.

Strengths and limitations of the study

The study has several strengths and limitations. The cross-sectional telephone study was performed by trained and experienced interviewers. Participants were representative of the broader population above 16 years of age in terms of age, gender, and educational status. As only about 14% of contacted persons were willing to participate in a telephone interview, a self-selection bias cannot be ruled out. This bias—also called the volunteer effect—is characterized by differences in the likelihood that certain people will answer a survey, depending on e.g., the content or design of the survey, offered incentives, their personality, socio-economic status, and gender (54–56). In our sample, 38.9% of respondents said they are tired of hearing about COVID-19. It cannot be ruled out that the overall number of people that are tired of hearing about COVID-19 is higher and that these people are less likely than others to answer a survey on COVID-19. Nevertheless, since the aim of this study was not to analyze the percentage of people that are adherent but to analyze the underlying factors that influence adherence, this self-selection bias should not have affected results. It is also possible that some of the questions were answered differently than they would have been in paper-pencil or online surveys. It has been shown [e.g., (57, 58)] that the method of survey influences responses in different ways, but with no specific bias in favor of a specific method. Since we wanted to reach older people and face-to-face interviews were not possible due to the pandemic, we decided not to use online surveys, so that people with no internet account, who tend to be older, could also be reached.

One shortcoming of our study is that the survey was performed in spring 2021 and at a time when the infection rate was low and the population expected protective measures to be relaxed during the upcoming summer season. Nevertheless, we have assumed that while the amount of corona fatigue may change over time, its impact in terms of β or OR will be comparable over time. This is supported by Lang et al. (37) who clustered data from almost 4,500 persons from a Canadian cross-sectional survey and found similar rates among adopters and non-adopters of COVID-19 measures. He effectively confirmed our results as non-adopters tend to be younger males that are less worried about COVID-19.

TABLE 4 Summary table.

What previous studies found:	• The health belief model is widely used to develop a conceptual understanding of individual adherence to preventive activities. • Inconsistent results have been found for socio-demographic variables such as age, gender, education, and social norms. • Another aspect that has frequently been examined in connection with the pandemic is corona fatigue.
What this study adds:	• In this study, the findings from the health belief model are examined together with findings from other areas. • It follows that both aspects of health belief model (e.g., social norms) and other aspects (e.g., corona fatigue) are important for adherence.

Conclusion

The results of this representative Austrian cross-sectional telephone study show that when the health belief model is combined with aspects that vary over time and other modifying aspects, it can make a valuable contribution toward explaining adherence (Table 4). Age, social norms, perceived personal health risk, self-efficacy, female gender, and lower behavioral fatigue increase overall adherence to government measures to control the COVID-19 pandemic. Furthermore, adherence to individual measures was also influenced by other aspects of the model (e.g., wearing FFP2-masks by trust in institutions, and dusk-to-dawn curfews by information fatigue), showing that strategies need to be tailored depending on what particular behavior is being targeted.

Strategies to improve adherence should therefore be adapted depending on the goal (overall adherence or adherence to individual measures) and on the group of persons that is being targeted (e.g., informal and formal group leaders or vulnerable groups) rather than being addressed to everyone. Furthermore, institutional signals play an important role and, if used imprudently, can thwart efforts to change behavior.

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 human participants were reviewed and approved by Ethics Committee of the state of Carinthia/Austria (M2021-15). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AS, AA, KJ, and DS developed a concept for the paper. AA conducted the analysis. AS, AA, CK, DS, and PE were responsible for the writing process. KJ and CK contributed to the analysis. AS, AA, CK, KJ, and PE contributed to interpreting results and drafting the manuscript. All authors critically reviewed all drafts of the manuscripts and approved the final manuscript before submission.

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Conflict of interest

Author DS was employed by Austrian Agency for Health and Food Safety Ltd. AGES.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.894128/full#supplementary-material

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Lorenzo Zino,
University of Groningen, Netherlands
Nick Ruktanonchai,
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Jing Lee,
Safety Engineering, China

*CORRESPONDENCE
Qunhong Wu
wuqunhong@163.com
Huan Liu
liuhuan00813@126.com

†These authors have contributed equally to this work and share first authorship

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Epidemiological trend in scarlet fever incidence in China during the COVID-19 pandemic: A time series analysis

Yunxia Ma[1†], Shanshan Gao[1†], Zheng Kang[1], Linghan Shan[1], Mingli Jiao[1], Ye Li[1], Libo Liang[1], Yanhua Hao[1], Binyu Zhao[2], Ning Ning[1], Lijun Gao[1], Yu Cui[1], Hong Sun[1], Qunhong Wu[1]* and Huan Liu[1]*

[1]Department of Social Medicine, Health Management College, Harbin Medical University, Harbin, China, [2]Department of Biostatistics, School of Public Health, Harbin Medical University, Harbin, China

Objective: Over the past decade, scarlet fever has caused a relatively high economic burden in various regions of China. Non-pharmaceutical interventions (NPIs) are necessary because of the absence of vaccines and specific drugs. This study aimed to characterize the demographics of patients with scarlet fever, describe its spatiotemporal distribution, and explore the impact of NPIs on the disease in the era of coronavirus disease 2019 (COVID-19) in China.

Methods: Using monthly scarlet fever data from January 2011 to December 2019, seasonal autoregressive integrated moving average (SARIMA), advanced innovation state-space modeling framework that combines Box-Cox transformations, Fourier series with time-varying coefficients, and autoregressive moving average error correction method (TBATS) models were developed to select the best model for comparing between the expected and actual incidence of scarlet fever in 2020. Interrupted time series analysis (ITSA) was used to explore whether NPIs have an effect on scarlet fever incidence, while the intervention effects of specific NPIs were explored using correlation analysis and ridge regression methods.

Results: From 2011 to 2017, the total number of scarlet fever cases was 400,691, with children aged 0–9 years being the main group affected. There were two annual incidence peaks (May to June and November to December). According to the best prediction model TBATS (0.002, {0, 0}, 0.801, {<12, 5>}), the number of scarlet fever cases was 72,148 and dual seasonality was no longer prominent. ITSA showed a significant effect of NPIs of a reduction in the number of scarlet fever episodes ($\beta 2 = -61526$, $P < 0.005$), and the effect of canceling public events (c3) was the most significant ($P = 0.0447$).

Conclusions: The incidence of scarlet fever during COVID-19 was lower than expected, and the total incidence decreased by 80.74% in 2020. The results of this study indicate that strict NPIs may be of potential benefit in preventing scarlet fever occurrence, especially that related to public event cancellation. However, it is still important that vaccines and drugs are available in the future.

KEYWORDS

COVID-19, scarlet fever, SARIMA, TBATS, non-pharmaceutical interventions, ITSA

1. Introduction

Streptococcus pyogenes (group A *Streptococcus*, GAS) is the most virulent of all clinically important streptococci and is considered the fifth most deadly pathogen globally, posing not only a major threat to humans but also a heavy global disease burden (1–3). One study estimated that at least half a million people worldwide die each year from severe GAS infection (4). Scarlet fever is an acute respiratory infection caused by GAS and is usually spread by respiratory droplets or direct contact with mucus, saliva, or the skin of an infected person (5, 6). Although scarlet fever is a benign infectious disease, it is prone to clusters of outbreaks accompanied by complications including otitis media, pneumonia, and sepsis, which causes a constant drain on healthcare resources (7, 8). In the mid-19th century, scarlet fever was a major cause of death among children worldwide (9, 10). By the 20th century, the mortality rate had decreased considerably due to improved sanitation and widespread use of effective antibiotics (9, 11). Since the 21st century, the re-emergence of scarlet fever has become a major public health concern in several countries and regions. In 2011, the incidence of scarlet fever increased rapidly in South Korea (12). In addition, in 2014, the incidence of scarlet fever in the United Kingdom reached a new highest level in 50 years (13).

Scarlet fever was classified as a category B notifiable disease in China in 1950 and caused a significant economic burden in the early 1980s, after which the incidence gradually declined (14). The disease returned in 2011, associated with the rapid economic development, living standards, population mobility, and host population genetics in China (5). One study confirmed that the average annual incidence of scarlet fever in China was twice as high between 2011 and 2016 as that before between 2004 and 2011 (15). This may be closely related to the national policy of liberalizing the second child, which puts the population of children susceptible to scarlet fever at great risk (16). The preventive management of scarlet fever in China should increase to a new level. However, there are relatively few studies on scarlet fever in China, which mainly focus on specific regions or cities, and the results of these studies may be diverse, fragmented, and inconclusive. Therefore, a comprehensive and systematic study of scarlet fever in mainland China is needed (6, 17). In addition, there is still no effective vaccine available for preventing scarlet fever; therefore, the importance of effective non-pharmaceutical interventions (NPIs) should be emphasized.

The coronavirus disease 2019 (COVID-19) pandemic has been spreading since the end of 2019. To contain the spread of the epidemic in a timely and effective manner, governments have actively adopted NPIs such as masking, lockdown policies, and distancing (18–21). Results from a global study noted that a number of NPIs reduced the time-varying reproduction number of COVID-19 by 3–24% by day 28 after introduction (22). As the first epicenter of COVID-19, the epidemic was effectively controlled in China after the adoption of strict NPIs. A study found that the proportion of serious and critical COVID-19 cases fell from 53.1 to 10.3% in the 3 months following the implementation of NPIs (23). It has also been found that NPIs have a positive effect on the prevention and control of respiratory infections (24–26). To our knowledge, few studies have been conducted, using quantitative analysis, on the effect of NPIs for a specific disease, such as scarlet fever, during the COVID-19 era. In addition, the rigorous NPIs adopted in China may help in studying changes in the incidence of scarlet fever during COVID-19. Thus, a robust and accurate predictive model, which is important for predicting the incidence of scarlet fever in the COVID-19 era, is needed to detect and analyze trends during this period.

Many forecasting methods have been widely adopted as effective policy support tools to assess and analyze the temporal patterns of infectious disease incidence, among which the autoregressive integrated moving average (ARIMA) model has proven to be more effective (27–29). Research has shown that scarlet fever has multiple seasonal patterns (15), and the advanced innovation state-space modeling framework that combines Box-Cox transformations, Fourier series with time-varying coefficients, and autoregressive moving average (ARMA) error correction method (TBATS) model works better in dealing with complex time series analyses with seasonal cycles, non-integer seasonality, and dual calendar effects (30). To the

Abbreviations: COVID-19, Coronavirus disease 2019; NPIs, non-pharmaceutical interventions; RMSE, residual mean squared error; MAPE, mean absolute percentage error; TBATS, the advanced innovation state-space modeling framework by combining Box-Cox transformations, Fourier series with time-varying coefficients and autoregressive moving average error correction method; SARIMA, the seasonal autoregressive integrated moving average; ITSA, Interrupted time series analysis; OxCGRT, Oxford COVID-19 Government Response Tracker; ADF, Augmented Dickey-Fuller.

best of our knowledge, few studies have used these advanced methods to analyze and assess the long-term epidemiological trends and seasonality of scarlet fever. To demonstrate their applicability, the level of precision was compared using an ARIMA model with seasonality (SARIMA).

In summary, this study aimed to examine the demographic and spatiotemporal distribution and characteristics of scarlet fever re-emergence in mainland China from 2011 to 2017. We also verified whether the adoption of strict NPIs in China, had an impact on the incidence of scarlet fever in the COVID-19 era, and which specific measures had the greatest impact. The findings might provide evidence and support for future scarlet fever prevention and control.

2. Materials and methods

2.1. Ethical statement

Pooled data were obtained from publicly available monitoring platforms and ethical approval or informed consent was considered unnecessary.

2.2. Data collection

Scarlet fever is a nationally notifiable infectious disease in China. The scarlet fever data used in this study were obtained from two main sources. (1) Data on the regional distribution and demographic characteristics of scarlet fever in mainland China were extracted from the China Public Health Science Data Center (https://www.phsciencedata.cn/Share/index.jsp)[1]. As the latest demographic data were only updated until 2017, only the data in the years 2011–2017 were included in the preliminary descriptive analysis of the demographics. (2) Monthly data of new cases of scarlet fever in China from January 1, 2011 to December 31, 2020, were collected from the National Heath Commission of the People's Republic of China (http://www.nhc.gov.cn/wjw/index.shtml)[2]. This study constructed SARIMA and TBATS models using the 2011–2018 data, and evaluated the predictive effect of the models using the 2019 data.

The source of data for comprehensive NPIs in the interrupted time series analysis (ITSA) is the Oxford COVID-19 Government Response Tracker (OxCGRT), which was developed by Oxford scholars in 2020 to track the government's response to the coronavirus pandemic. In addition, this study conducted analysis on the following eight specific NPIs included in containment and closure policies in the OxCGRT: school closures (c1), workplace closures (c2), cancellation of public events (c3), restrictions on public gatherings (c4), closures of public transport (c5), stay-at-home requirements (c6), restrictions on internal movements (c7), and international travel controls (c8). The data for each NPIs are from Our World in Data (https://ourworldindata.org/covid-stringency-index)[3].

1 *The China Public Health Science Data Center*. Available from: https://www.phsciencedata.cn/Share/index.jsp.

2 *The National Heath Commission of the People's Republic of China*. Available from: http://www.nhc.gov.cn/wjw/index.shtml.

3 *Our Word in Data*. Available from: https://ourworldindata.org/covid-stringency-index.

2.3. TBATS model

Traditional seasonal exponential smoothing methods cannot be used to describe complex seasonal time series including multiple and non-integer seasonal patterns. The BATS (p, q, m_1, m_2, ..., m_T) method is thus proposed, where B represents the Box-Cox conversion, A represents the ARMA model, and T and S represent the trend and seasonal patterns in the target series, respectively (31, 32). The key parameters of the BATS model are the ARMA method (p and q) and the seasonal period (m_1, ..., m_T). The advanced TBATS (ω, p, q, ϕ, $\{m_1, k_1\}$, $\{m_2, k_2\}$ ..., $\{m_T, k_T\}$) model was developed by adding a Fourier series-based trigonometric representation of the seasonal components to the traditional BATS method, which can handle complex time series as well as linear and non-linear time series (33) while adapting to dynamic seasonal patterns over time (30). The parameters (p, q, and m) of the TBATS model are consistent with those of the BATS model, where k is the number of corresponding Fourier terms used for each seasonality, ω is the Box-Cox transformation, and ϕ is the damping parameter that facilitates trend extrapolation to the model when the trend pattern is weakened (31, 34). The TBATS model has many parameters, and this study automated the determination of the values of each parameter in R software using the principle of Akaike information criterion (AIC) minimization to fit the model. It is worth mentioning that the TBATS model has the potential to decompose the time series into different components, enabling the identification and extraction of one or more seasonal features that may not be present in the object series graphs.

2.4. SARIMA model

The ARIMA model is a classical time-series predictive analysis method proposed by Box and Jenkins, which is mainly used to fit time series that are stationary (or can be converted to stationary). Scarlet fever frequently has notable seasonal effects (29), hence the use of the SARIMA method. The SARIMA (p, d, q) (P, D, Q) model is based on the ARIMA model (27). In this method, the seasonality of scarlet fever was considered as the explanatory variable while the monthly scarlet fever incidence was the response variable, and the model's equation is

$$\begin{cases} \varphi(B)\,\Phi\left(B^{s}\right)\Delta^{d}\Delta_{s}^{D}X_{t}=\theta(B)\,\Theta\left(B^{s}\right)\varepsilon_{t} \\ E(\varepsilon_{t})=0, Var(\varepsilon_{t})=\sigma_{\varepsilon}^{2}, E(\varepsilon_{t}\varepsilon_{s})=0, s\neq t \\ E(X_{s}\varepsilon_{t})=0, \forall_{s}<t \end{cases} \quad (1)$$

where B indicates the backward shift operator, ε_t signifies the errors of prediction, S denotes the periodicity of the scarlet fever incidence series ($S = 12$ in this study), while d and D, are the non-seasonal and seasonal differences in times, respectively. p and q are the orders of the autoregressive and moving average models, respectively. P and Q are the orders of the seasonal autoregressive and moving average models, respectively. This study used an automated time-series modeling for the specified sample data.

Building the SARIMA model followed these key steps: First, the stationarity of the scarlet fever incidence series was examined using the Augmented Dickey-Fuller (ADF) method (35). When the result of the ADF test was significant, the sequence was proved to be stationary. For the non-stationary scarlet fever series, log transformation or differencing was adopted to fulfill the stationarity assumption. Second, an autocorrelation function (ACF) graph and partial autocorrelation (PACF) plots were used to select reasonable parameters for the SARIMA model (36). Meanwhile, the auto.arima function of R 4.1.1 software had been used to select a best SARIMA model according to either the minimum of the AIC, AICc, or BIC. Third, we evaluated the fit of the model to make predictions. Generally, if a model was appropriate, the residuals of the model should meet the independent distribution assumption; that is, there was no correlation between the residuals. Finally, the residual was determined as a white noise series using the Ljung-Box Q test (37).

2.5. Performance statistics index

To assess the accuracy of the model predictions, two metrics, the root mean square error (RMSE) and mean absolute percentage error (MAPE), were used to compare the forecasting capabilities of the TBATS and SARIMA models. The smaller the measure, the better the corresponding model. The calculation formula is as follows:

$$RMSE = \sqrt{\frac{1}{n}\sum\nolimits_{t=1}^{n}\left(y_t - \hat{y}_t\right)^2} \quad (2)$$

$$MAPE = \frac{1}{n}\sum\nolimits_{t=1}^{n}\frac{\left|y_t - \hat{y}_t\right|}{y_t} \quad (3)$$

2.6. Statistical analysis

First, we conducted a descriptive analysis of the demographic and spatiotemporal distribution of scarlet fever incidence in mainland China from 2011 to 2017. Second, the TBATS and SARIMA models were evaluated using two indicators, RMSE and MAPE, to select the best model to predict scarlet fever incidences in 2020 and to observe the changes in the actual and expected number of cases. Finally, this study used ITSA to explore whether comprehensive NPIs had an effect on the number of cases and further analyzed which specific NPIs had a significant effect on scarlet, using correlation analysis and ridge regression. It is worth noting that each NPI must be standardized prior to the statistical analysis.

Multiple statistical packages including "forecast," "tseries," and "tbats" in R (version 4.1.1, R Development Core Team, Vienna, Austria) were employed to establish the SARIMA and TBATS models. All the estimated parameter values were statistically significant ($P < 0.05$). In addition, statistical R packages such as "prais" and "sandwich" were used for the ITSA. Correlation and ridge regression analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic and distributive features of scarlet fever from 2011 to 2017

The characteristics of the patients with scarlet fever in mainland China are shown in Table 1. From 2011 to 2017, 400,691 cases of scarlet fever were reported in mainland China, with an average of 57,000 cases per year and the highest incidence occurred in 2017. More than half of all patients were males, with a male-to-female ratio of 1.59:1. Second, the majority of the patients were children aged 0–9 years (92.83%). In addition, kindergarten children, students, and scattered children were the main groups diagnosed with scarlet fever between 2011 and 2017.

3.2. Spatiotemporal analyses

The distribution by the total number of scarlet fever and by province in China from 2011 to 2017 revealed a high degree of dispersion (Figure 1). Northern regions such as Shandong, Liaoning, and Heilongjiang had a high incidence of scarlet fever. In contrast, the incidence was very low in areas such as Hainan and Tibet. Based on the monthly number of reported cases by province in China from 2011 to 2017 and ranked by the total number of scarlet fever cases over the seven years, Shandong and Liaoning showed the most prominent incidence rates. Among the months observed, the incidence was highest in May, June, November, and December, and the highest incidence in December was observed in Shandong Province (Figure 2).

A clear cyclical and seasonal pattern of monthly scarlet fever incidence and trend was observed from January 2011 to

TABLE 1 Demographic and distributive features of scarlet fever in mainland China from 2011 to 2017.

Variable	Total $N = 400,691$ (%)	2011 $n = 63,878$ (%)	2012 $n = 46,459$ (%)	2013 $n = 34,207$ (%)	2014 $n = 54,247$ (%)	2015 $n = 68,249$ (%)	2016 $n = 59,282$ (%)	2017 $n = 74,369$ (%)
Sex								
Male	245,777 (61.34)	39,826 (62.35)	29,039 (62.50)	20,736 (60.62)	32,932 (60.71)	41,502 (60.81)	36,390 (61.38)	45,352 (60.98)
Female	154,914 (38.66)	24,052 (37.65)	17,420 (37.50)	13,471 (39.38)	21,315 (39.29)	26,747 (39.19)	22,892 (38.62)	29,017 (39.02)
Age, years								
0–9	371,968 (92.83)	58,825 (92.09)	41,723 (89.80)	31,268 (91.41)	50,348 (92.81)	63,963 (93.72)	55,589 (93.77)	70,252 (94.46)
10–19	24,727 (6.17)	4,401 (6.89)	4,082 (8.79)	2,468 (7.21)	3,321 (6.12)	3,710 (5.44)	3,147 (5.31)	3,598 (4.84)
20–29	2,440 (0.61)	437 (0.68)	436 (0.94)	287 (0.84)	357 (0.66)	335 (0.49)	319 (0.54)	269 (0.36)
30–39	914 (0.23)	112 (0.18)	125 (0.27)	114 (0.33)	135 (0.25)	137 (0.20)	139 (0.23)	152 (0.20)
40–49	346 (0.09)	57 (0.09)	52 (0.11)	34 (0.10)	51 (0.09)	55 (0.08)	43 (0.07)	54 (0.07)
50–59	170 (0.04)	27 (0.04)	22 (0.05)	25 (0.07)	20 (0.04)	31 (0.05)	28 (0.05)	17 (0.02)
≥60	126 (0.03)	19 (0.03)	19 (0.04)	11 (0.03)	15 (0.03)	18 (0.03)	17 (0.03)	27 (0.04)
Occupation								
Children in kindergarten	168,601 (42.08)	25,357 (39.70)	18,956 (40.80)	13,303 (38.89)	21,476 (39.59)	29,014 (42.51)	26,283 (44.34)	34,212 (46.00)
Students	151,778 (37.88)	25,809 (40.40)	17,958 (38.65)	13,352 (39.03)	21,912 (40.39)	25,299 (37.07)	21,195 (35.75)	26,253 (35.30)
Scattered children	75,810 (18.92)	11,822 (18.51)	8,698 (18.72)	7,040 (20.58)	10,252 (18.90)	13,337 (19.54)	11,251 (18.98)	13,410 (18.03)
Farmers	1,503 (0.38)	246 (0.39)	257 (0.55)	196 (0.57)	214 (0.39)	234 (0.34)	188 (0.32)	168 (0.23)
Housework and unemployment	903 (0.23)	142 (0.22)	150 (0.32)	101 (0.30)	143 (0.26)	127 (0.19)	99 (0.17)	141 (0.19)
Workers	455 (0.11)	80 (0.13)	78 (0.17)	60 (0.18)	71 (0.13)	60 (0.09)	65 (0.11)	41 (0.06)
Others	1,641 (0.41)	422 (0.66)	362 (0.78)	155 (0.45)	179 (0.33)	178 (0.26)	201 (0.34)	144 (0.19)

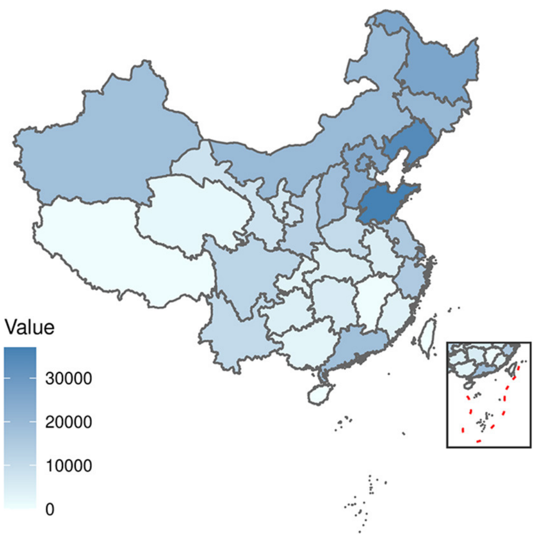

FIGURE 1
Distribution of the total number of scarlet fever cases in each province in China from 2011 to 2017.

December 2018 (Figure 3). Since 2013, the incidence of scarlet fever in mainland China has been fluctuating and increasing, and has continued to show an increasing trend in recent years.

3.3. Sample simulation and prediction

The ndiffs show that the scarlet fever time series was not smooth; first-order difference ($d = 1$) and seasonal difference ($D = 1$) were determined, and the final ADF test was statistically significant ($P < 0.01$), making the series smooth. The ACF and PACF graphs (Figure 4) were generated to help estimate the other parameters. The model automatically selected SARIMA (2, 1, 2) $(0, 1, 1)_{[12]}$ as the best fit [AIC = 1,356.48, Bayesian information criterion (BIC) = 1370.99] using time-series modeling software on the specified sample data. Therefore, in this study p, d, q = 2, 1, 2 and P, D, Q = 0, 1, 1, respectively. The Ljung-Box Q test further indicated that the model residuals were consistent with the white noise series ($\chi^2 = 0.0018521$, $P > 0.05$), indicating that the residual series was purely random and that the SARIMA model extracted sufficient information. In addition, sensitivity analyses were constructed by varying p, q in SARIMA. Based on similar studies where the range of p, q should not be too large, the range of values for p, q in this study was 0–3. The results of the sensitivity analysis (Supplementary Table 1) imply that the SARIMA (2, 1, 2) $(0, 1, 1)_{[12]}$ model identified can effectively and adequately track the epidemiological trends of scarlet fever in mainland China. The TBATS model included numerous parameters and was automatically modeled in R using the "tbats" function to obtain the model parameters $\omega = 0.003$, $\phi = 0.822$, $p = 0$, $q = 0$,

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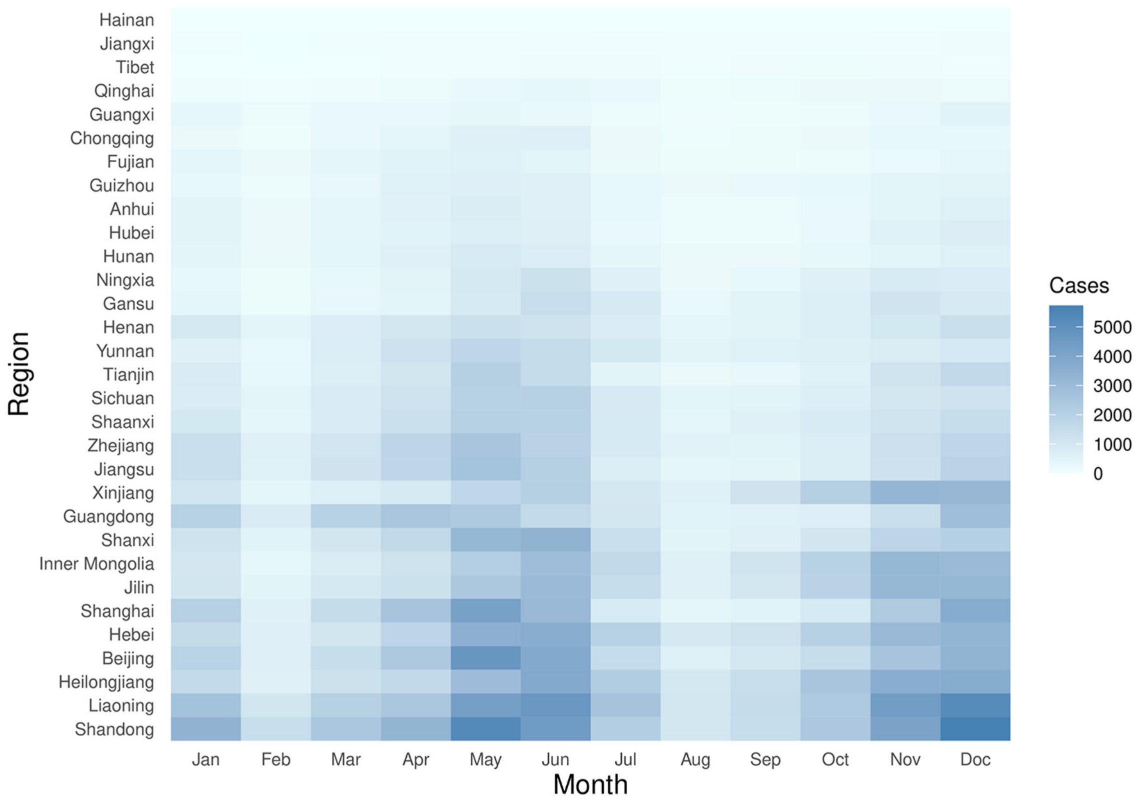

FIGURE 2
The time series of monthly number of cases from 2011 to 2017, standardized by the monthly number of cases reported by each province according to the total number of scarlet fever cases recorded in the 7 years.

seasonal cycle length $m_T = 12$, $k_T = 5$, and model AIC = 1716.454. A final TBATS model (0.003, {0, 0}, 0.822, {<12, 5>}) was obtained.

3.4. Model performance evaluation

The results of the model performance metrics for SARIMA (2, 1, 2) (0, 1, 1)$_{[12]}$ and TBATS (0.003, {0, 0}, 0.822, {<12, 5>}) were investigated. The performances of the two models were compared in terms of both simulation and prediction, and the results showed that the RMSE and MAPE measures of the TBATS (0.003, {0, 0}, 0.822, {<12, 5>}) model were lower than those of the SARIMA (2, 1, 2) (0, 1, 1)$_{[12]}$ model (Table 2). Therefore, the TBATS (0.003, {0, 0}, 0.822, {<12, 5>}) model worked better (Figure 5).

Based on the comparison of the above models, we found that the TBATS (0.003, {0, 0}, 0.822,{<12, 5>}) model had a better level of predictive accuracy, with incidence rates close to their expected levels in years. Therefore, this study used the new TBATS (0.002, {0, 0}, 0.801, {<12, 5>}) model from 2011 to 2019 to predict the incidence of scarlet fever during the 2020 COVID-19 pandemic. The final prediction model showed that the number of scarlet fever cases that were expected to occur in mainland China in 2020 was 89,354, whereas the actual number of cases was 17,206, with a total of 72,148 averted cases, showing an unprecedented decline. The actual number of cases that occurred in January 2020 showed the lowest relative decrease of only 11.47%, which was similar to the expected value (Table 3). The incidence of scarlet fever plummeted from February until May, when it dropped to the lowest level.

In Figure 6A, the expected incidence rate during the continuing spread of COVID-19 in 2020 differed significantly from the actual incidence rate trend, with the forecast showing a large fluctuating trend while the actual incidence rate showed a low and stable trend. Compared to the average number of cases in 2016–2019, the number of cases during the COVID-19 pandemic decreased by 76.83%, which is a much lower rate than the historical average incidence rate (Table 3). Surprisingly, there was a downward trend in the number of cases, wherein an increase should have occurred in March. Even in May and June, when scarlet fever was the most prevalent, the number of cases did not increase significantly, but instead decreased by ∼95% compared to the predicted value and showed

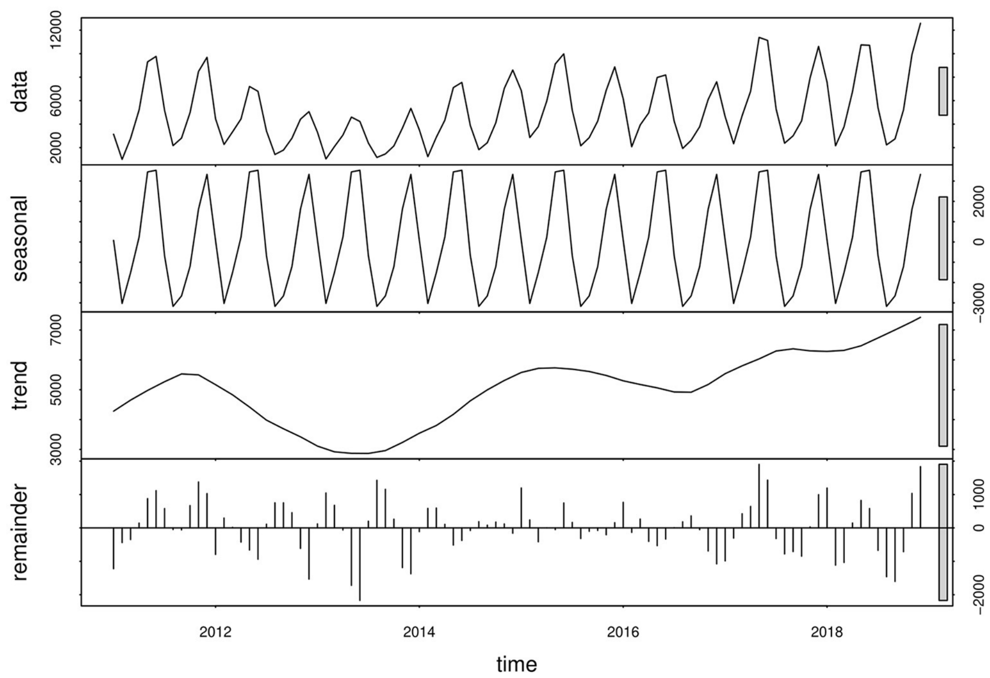

FIGURE 3
Monthly scarlet fever incidence and variations, from January 2011 to December 2018.

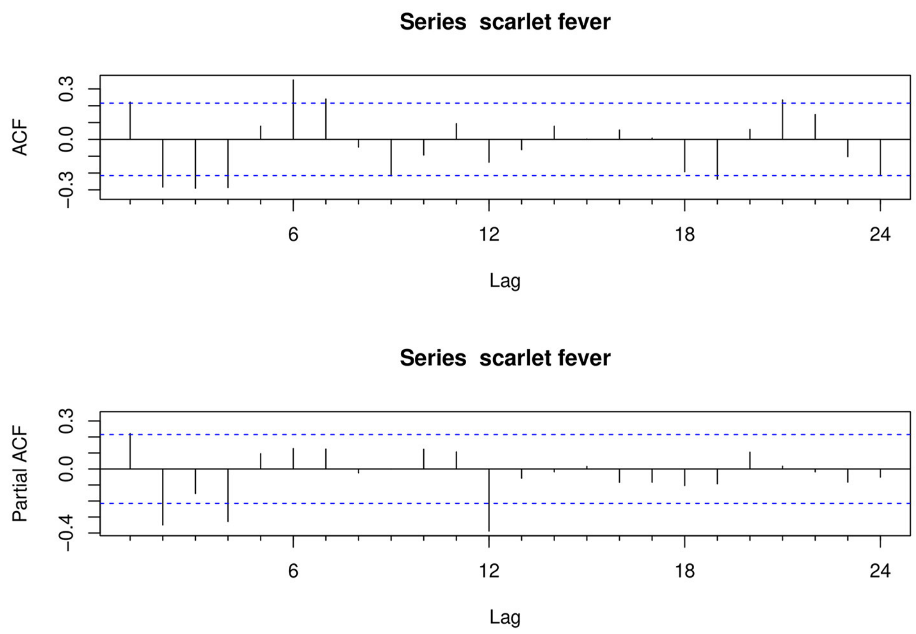

FIGURE 4
Autocorrelation and partial autocorrelation plots for the differenced scarlet fever time series.

a flat trend. We also found that the dual seasonality of scarlet fever during COVID-19 pandemic was no longer prominent, and the proportion of scarlet fever cases, although increasing again in November, remained below the expected level.

Figure 6B shows that the total annual incidence of scarlet fever in China showed a steady increase from 2011 to 2019 ($\beta 1 = 4396$, $P < 0.05$) and an immediate decrease in 2020 ($\beta 2 = -61526$, $P < 0.05$). The post-intervention change was not statistically significant (Table 4).

Table 5 shows a significant negative correlation between the number of scarlet fever episodes and each NPIs in mainland China ($P < 0.05$). By ridge regression analysis, the k-value in this study was 0.103, and ANOVA result was significant ($P < 0.05$).

TABLE 2 Comparison of the model fitting effect.

Model	RMSE	MAPE
TBATS	1,423.6	0.14
SARIMA	1,705.65	0.25

As seen in Table 6, among the eight NPIs, only cancellation of public events (c3) was statistically significant ($P = 0.045$).

4. Discussion

In brief, this study revealed the demographic and spatiotemporal distribution of the incidence of scarlet fever and patient characteristics in China from 2011 to 2017, with a fluctuating upward trend toward recent years. The comparison of the predicted and actual values of scarlet fever incidence in mainland China in 2020 also revealed an unprecedented downward trend, improving ∼80% of infections among the susceptible population. We confirmed that the comprehensive NPIs implemented during the COVID-19 pandemic led to a reduction in the number of scarlet fever cases; in particular, the cancellation of public events had the most significant effect.

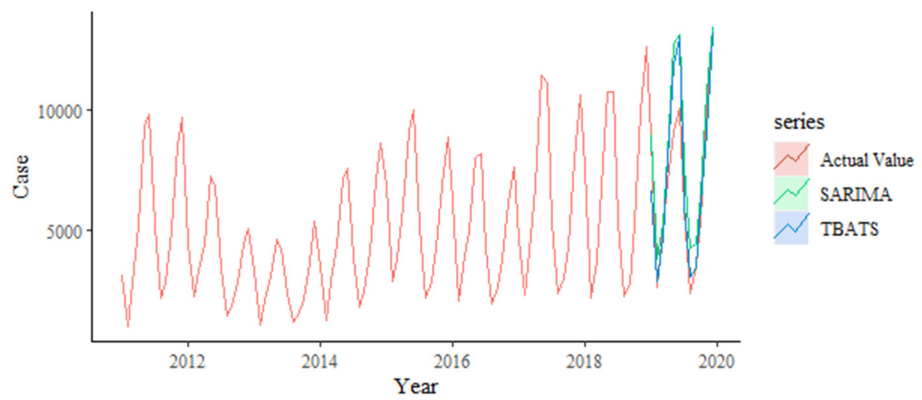

FIGURE 5
Comparison of SARIMA and TBATS models prediction fit.

TABLE 3 Comparison between actual and expected incidence in 2020, and the relative reduction in average incidence from 2016 to 2019.

Month	2020	Expect value	Relative reduction	2020	2016–2019	Relative reduction
January	6,352	7,175	11.47%	6,352	6,797	6.54%
February	580	3,002	80.68%	580	2,290	74.67%
March	444	4,822	90.79%	444	4,386	89.88%
April	442	8,239	94.63%	442	6,377	93.07%
May	562	11,687	95.19%	562	9,801	94.27%
June	677	13,018	94.80%	677	10,022	93.24%
July	789	6,167	87.21%	789	5,201	84.83%
August	763	3,047	74.96%	763	2,235	65.86%
September	877	3,455	74.61%	877	2,962	70.39%
October	1,102	6,117	81.98%	1,102	4,663	76.37%
November	1,925	9,264	79.22%	1,925	8,547	77.48%
December	2,693	13,362	79.85%	2,693	10,970	75.45%
Total	17,206	89,354	80.74%	17,206	74,248	76.83%

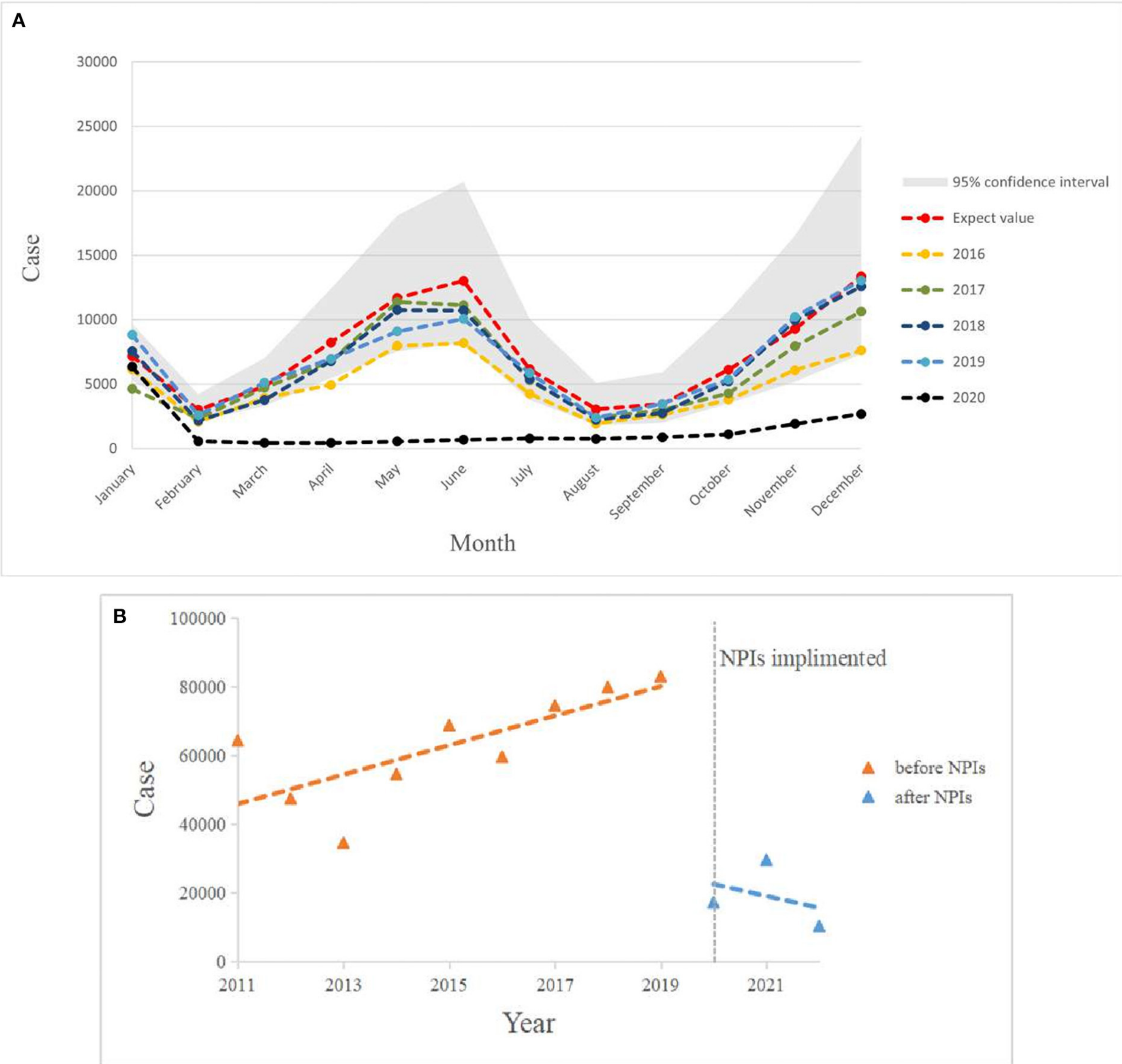

FIGURE 6
(A) Graph of monthly scarlet fever incidence trends in mainland China from 2016 to 2020 compared with expected values in 2020. **(B)** Incidence of scarlet fever before and after NPIs intervention in China, January 2011 to May 2022.

Based on the incidence of scarlet fever in mainland China from 2011 to 2017, the following conclusions can be drawn: scarlet fever is predominantly a childhood disease in China, and boys are more likely to contract scarlet fever than girls, which is consistent with the results of other studies (38). Children are prone to aggregate scarlet fever infection due to factors such as their weak resistance and high risk of exposure to the virus during school days. Furthermore, boys are associated with being more active than girls during the school year, thus increasing the risk of illness to some extent. That the incidence of scarlet fever reached a new peak in 2017 may be closely related to the effective implementation of the two-child policy (16).

In addition, scarlet fever has two seasonal peaks in mainland China each year, when children are in school, with cases decreasing during winter, and during summer holidays. The results of this study show that the incidence of scarlet fever varies significantly in different regions, which is consistent with other studies (5, 15). High incidence concentrations are mainly in the north, such as Shandong, Liaoning, Heilongjiang, Beijing, and Hebei, and previous studies have shown that this may be positively correlated with mean temperature and mean relative humidity (39). In addition, a study in Beijing showed that the incidence of scarlet fever was positively correlated with the number of hours of sunshine. The low incidence clusters are mainly in the south, such as Jiangxi, Guangxi, Guizhou, Hunan, and Hubei, and the incidence is especially low in winter, which may be related to the low sunshine during the rainy winter months. The causes of infectious diseases are complex and are not caused by a single meteorological factor, but are also closely related to social factors and pathogenetic characteristics (40). Therefore, school-based preventive and control measures are particularly important for preventing scarlet fever, such as paying attention to personal hygiene in schools, increasing the frequency of disinfection in schools, and strengthening exercises to enhance students' physical fitness. In addition, health departments should pay more attention to the surveillance, prevention, and control of infectious diseases; formulate scientific public health policies; and implement effective interventions to control infectious diseases and protect the children.

For the choice of the prediction model, the TBATS model was found to have higher predictive performance and was more suitable for predicting the incidence of scarlet fever in China.

TABLE 4 Interrupted time series analysis of the annual number of scarlet fever cases in mainland China from January 2011 to May 2022.

Series	Estimate	S.E.	*t*	*P*-value
Intercept	40,643	7,588	5.357	<0.001
Preintervention trend	4,396	1,355	3.245	0.012
Intervening variable	−61,526	12,946	−4.753	0.001
Postintervention	−7,981	8,081	0.988	0.352

Interestingly, we conclude that the expected incidence of scarlet fever in mainland China in 2020 showed an opposite trend to the actual incidence. Nearly 90,000 cases of scarlet fever were predicted to occur in mainland China in 2020, and the implementation of NPIs in the context of COVID-19 may have prevented more scarlet fever infections. Further exploration using ITSA showed a tendency toward a decrease trend in the total annual incidence of scarlet fever in China from January 2020 to May 2022, indicating that comprehensive NPIs achieved better results. This is largely due to the government's prevention and control policies as well as voluntary behavioral changes by individuals with reduced exposure risk, hospital visits, and exposure to counseling, which have greatly reduced the likelihood of disease transmission. For example, on January 20, 2020, the National Health and Wellness Commission included COVID-19 in the management of statutory category B infectious diseases, and in February, 2020, the State Council issued a notice on the prevention and control of COVID-19 in children and pregnant women. Therefore, this may be an important reason why scarlet fever incidence was not increased, but showed a downward trend in March, 2020. Thereafter, it did not show an increase in May and June, the strongest months of the season, in accordance with previous trends. This may be closely related to the importance of school closures in mitigating the spread of seasonal infections, similar to the findings of other related studies (41). Besides focusing on susceptible populations, it is also important to note that scarlet fever is an infectious disease that is prone to aggregate transmissions, and that, of the eight specific NPIs, the cancellation of public events had the most prominent impact in this study. In addition, a global study confirmed the cancellation of public events as an effective intervention to reduce COVID-19 infection rates (42). Therefore, in the absence of a vaccine or effective drugs for scarlet fever, reducing the risk of transmission and

TABLE 5 Correlation of the number of scarlet fever cases with each NPI from January 2011 to May 2022.

		Cases	c1	c2	c3	c4	c5	c6	c7	c8
Cases	*r*	1	−0.449**	−0.454**	−0.460**	−0.460**	−0.384**	−0.437**	−0.453**	−0.444**
c1	*r*	−0.449**	1	0.964**	0.978**	0.977**	0.838**	0.948**	0.974**	0.910**
c2	*r*	−0.454**	0.964**	1	0.982**	0.981**	0.836**	0.979**	0.986**	0.914**
c3	*r*	−0.460**	0.978**	0.982**	1	0.998**	0.838**	0.958**	0.989**	0.956**
c4	*r*	−0.460**	0.977**	0.981**	0.998**	1	0.836**	0.957**	0.986**	0.956**
c5	*r*	−0.384**	0.838**	0.836**	0.838**	0.836**	1	0.866**	0.859**	0.796**
c6	*r*	−0.437**	0.948**	0.979**	0.958**	0.957**	0.866**	1	0.970**	0.900**
c7	*r*	−0.453**	0.974**	0.986**	0.989**	0.986**	0.859**	0.970**	1	0.929**
c8	*r*	−0.444**	0.910**	0.914**	0.956**	0.956**	0.796**	0.900**	0.929**	1

Pearson correlation coefficient is "*r*".
** $P < 0.01$.
Eight specific NPIs in OxCGRT's containment and closure policy: school closures (c1), workplace closures (c2), cancellation of public events (c3), restrictions on public gatherings (c4), closures of public transport (c5), stay-at-home requirements (c6), restrictions on internal movements (c7), and international travel controls (c8).

TABLE 6 Ridge regression analysis between the number of scarlet fever cases and each NPI in mainland China from January 2011 to May 2022.

	Coeff	S.E.	*t*	*p*	Std. coef	VIF
c1	−497.895	731.038	−0.681	0.497	−0.060	1.309
c2	−670.791	582.133	−1.152	0.251	−0.078	0.777
c3	−638.506	315.099	−2.026	0.045	−0.085	0.297
c4	−609.591	368.837	−1.653	0.101	−0.081	0.404
c5	−67.180	1,025.133	−0.066	0.948	−0.006	1.628
c6	−83.115	758.895	−0.110	0.913	−0.010	1.316
c7	−410.545	498.746	−0.823	0.412	−0.052	0.676
c8	−742.939	843.410	−0.881	0.380	−0.087	1.641
Constant	5,241.198	916.078	5.721	0.000	0.000	0.000

Eight specific NPIs in OxCGRT's containment and closure policy: school closures (c1), workplace closures (c2), cancellation of public events (c3), restrictions on public gatherings (c4), closures of public transport (c5), stay-at-home requirements (c6), restrictions on internal movements (c7), and international travel controls (c8).

preventing infection may be the best way to reduce the number of scarlet fever cases. In the future, combination of vaccines, drug therapy, and NPIs should be considered as a most effective preventive measure.

Despite these findings, some limitations of our study should be mentioned. First, the data are not reported as individual case data, and daily data may be subject to error. Second, the decline in the age structure and regional distribution of scarlet fever due to COVID-19 was not explored because demographic and geographic distribution data were unavailable in 2020. Third, this study utilized two prediction models for scarlet fever, and their applicability to other diseases remains unexplored. In future studies, if daily scarlet fever data are available, it is necessary to conduct an in-depth analysis of the effectiveness of each NPI and further refine the model for the study of other diseases.

5. Conclusion

Scarlet fever poses a continuous threat to children in China, especially in the northern region, and it exhibits bimodal seasonal patterns. The TBATS model predicted a higher level of scarlet fever in China than the SARIMA model, showing that more than 80% of infections in susceptible populations was managed under the COVID-19 pandemic prevention policy. Strict NPIs have a positive impact on the prevention of scarlet fever, with the cancellation of public events having the most significant impact. This suggests that government policymakers need to maintain the use of different types of NPIs to prevent scarlet fever in the future, with a focus on vaccine development and drug treatment. In addition, data limitations suggest the need to still explore the impact of scarlet fever in different regions in the future.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.phsciencedata.cn/Share/index.jsp, http://www.nhc.gov.cn/wjw/index.shtml, https://ourworldindata.org/covid-stringency-index.

Author contributions

YM and SG devised the concept, formal analysis, and writing of the original draft. QW and HL were responsible for the funding acquisition and project administration. ZK, LS, BZ, YC, and LG were involved in the collection of resources to help write the manuscript. YL and LL designed the analyses framework. MJ was responsible for data analyses. YH, NN, and HS assisted with the writing of review and editing. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.923318/full#supplementary-material

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EDITED BY
Julio Elias Normey-Rico,
Federal University of Santa Catarina, Brazil

REVIEWED BY
Claudio Neidhöfer,
University Hospital Bonn, Germany
Akira Endo,
University of London, United Kingdom

*CORRESPONDENCE
Douglas E. Morrison
✉ demorrison@ucdavis.edu

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Modeling COVID-19 infection dynamics and mitigation strategies for in-person K-6 instruction

Douglas E. Morrison[1,2,3]*, Roch Nianogo[1,4], Vladimir Manuel[4,5], Onyebuchi A. Arah[1,4,6], Nathaniel Anderson[7], Tony Kuo[1,4,5] and Moira Inkelas[4,7]

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, United States, [2]Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, United States, [3]Department of Public Health Sciences, School of Medicine, University of California, Davis, Davis, CA, United States, [4]Clinical and Translational Science Institute, University of California, Los Angeles, Los Angeles, CA, United States, [5]Department of Family Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, United States, [6]Department of Statistics, College of Letters and Science, University of California, Los Angeles, Los Angeles, CA, United States, [7]Department of Health Policy and Management, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, United States

Background: U.S. school closures due to the coronavirus disease 2019 (COVID-19) pandemic led to extended periods of remote learning and social and economic impact on families. Uncertainty about virus dynamics made it difficult for school districts to develop mitigation plans that all stakeholders consider to be safe.

Methods: We developed an agent-based model of infection dynamics and preventive mitigation designed as a conceptual tool to give school districts basic insights into their options, and to provide optimal flexibility and computational ease as COVID-19 science rapidly evolved early in the pandemic. Elements included distancing, health behaviors, surveillance and symptomatic testing, daily symptom and exposure screening, quarantine policies, and vaccination. Model elements were designed to be updated as the pandemic and scientific knowledge evolve. An online interface enables school districts and their implementation partners to explore the effects of interventions on outcomes of interest to states and localities, under a variety of plausible epidemiological and policy assumptions.

Results: The model shows infection dynamics that school districts should consider. For example, under default assumptions, secondary infection rates and school attendance are substantially affected by surveillance testing protocols, vaccination rates, class sizes, and effectiveness of safety education.

Conclusions: Our model helps policymakers consider how mitigation options and the dynamics of school infection risks affect outcomes of interest. The model was designed in a period of considerable uncertainty and rapidly evolving science. It had practical use early in the pandemic to surface dynamics for school districts and to enable manipulation of parameters as well as rapid update in response to changes in epidemiological conditions and scientific information about COVID-19 transmission dynamics, testing and vaccination resources, and reliability of mitigation strategies.

KEYWORDS

COVID-19, school district, agent-based model, secondary transmission, K-6

1. Background

School closures due to the coronavirus disease 2019 (COVID-19) pandemic led to extended periods of remote learning, with potential harm for children's educational progress, psychosocial development, and mental and physical health (1–4). School closures also affect families, workplaces, and workforce participation (5). Since COVID-19 burden is often greater in socioeconomically disadvantaged communities, in-person instruction early in the pandemic was unavailable or inconsistent for the students who may need it the most, thereby increasing educational disparities for children in lower income families, communities of color, and households that include essential workers, contain multiple generations, experience crowded housing, and with members who have chronic conditions that put them at risk for severe COVID-19 (6, 7). Therefore, school districts need to find ways to bring all students back safely.

Recent studies suggest that secondary infection risk in schools is low when basic precautions are followed (8–10). Yet uncertainty surrounding the infectiousness of evolving viral variants and the management of pre- and asymptomatic populations slowed and disrupted school re-openings in the U.S. and has affected school attendance once re-opened. Maintaining in-person instruction, and consistent school attendance, during the pandemic means reducing infection hazard for susceptible children and adults who congregate daily for extended periods of time.

School districts sought to work with their public health authorities to understand and act upon risk in a dynamic environment, using the policy levers available to them. There is a need for practical models that inform planning for safer in-person instruction in K-6 settings. A practical model surfaces possible infection dynamics and is flexible in parameters and their values and is designed computationally to provide rapid results. Transparent flexible models could facilitate deeper understanding about levers of influence among local authorities tasked with responding to the pandemic on a day-to-day basis (11).

We designed a stochastic, agent-based model of resumed in-person instruction that includes representations of a variety of intervention levers, including screening for symptoms and exposures, biological testing, education to reduce transmission risks from socializing without distancing or masking, and vaccination. We developed this model while collaborating as a university science partner with a large urban school district to consider what would be necessary for safer resumption of this much needed face-to-face learning. Because the science of COVID-19 was evolving rapidly, we sought to create a model with parameters that end users could easily adjust as more information emerged regarding transmission dynamics and the impact of mitigation strategies. The model was flexible to accommodate different school structures and local environments.

This model was designed for adaptation; we implemented the model in the R statistical computing environment (v4.1.0) (12) and provide the source code at https://github.com/UCLA-PHP/school.epi.abm. We used the model to assess key outcomes of interest to school district stakeholders, and we provided an online user interface to the model as a practical tool to empower school districts and their implementation partners to explore how various combinations and variations of strategy components affect health and learning outcomes within different underlying epidemiological conditions that could arise in the real world. This user interface can be accessed at https://agent-based-models.shinyapps.io/RegionalCOVIDSchoolSimulation/. The purpose of this paper is to showcase the capabilities of this simulation model, not to make specific predictions for a particular school district or epidemiological scenario. We hope that this model will be helpful for policymakers both in future stages of the COVID-19 pandemic and for future epidemics.

2. Methods

2.1. Model design and scope

Here we describe the model in general terms; a detailed description of the implemented model is provided as Supplementary material.

2.1.1. Agents

The model contains two types of simulated individuals ("agents"): students and their associated household adults (two per student). We chose to include these agent types as they form the largest proportion of the school community. The model could be extended to include teachers and other school personnel as additional agents who interact with students and with one other. Each student is assigned to a particular school and classroom and has several "close classmates" within their class; close classmates have higher risks of transmission than other classmates.

2.1.2. Sources of infection

Infections in the model come from three sources: infectious classmates at school, infectious family members at home, and exogenous exposures outside of school and home.

On each day of the simulation, each currently infectious student who is currently in school has a chance to infect each other student in their class who is not yet infected. The risk of infection for a given student is $1 - (1 - p_C)^C(1 - p_D)^D$, where C is the number of infectious close classmates currently in attendance, p_C is the parameter for the risk of transmission to close classmates per infectious student (the "effective contact risk" for close classmates), D is the number of infectious contacts (including both close and distant classmates) currently in attendance, and p_D is the parameter of risk of transmission to distant classmates per infectious student. For example: if on a given day, a particular student has 2 infectious close classmates and 3 infectious distant contacts currently at school with them, then if $p_C = 0.01$ and $p_D = 0.005$, that student has a $[1 - (1 - 0.01)^2(1 - 0.005)^{2+3}] \times 100\% \approx 4.4\%$ chance of being infected in school on that day.

Infectious students have a chance to infect their household adults, and infectious household adults have a chance to infect their students and a chance to infect the other household adult (if not already infected). For easier interfacing with the available literature, the daily transmission risks are specified indirectly. The user interface provides parameters for the risk of transmission per infection. The risk per day is calculated based on this parameter and the duration-of-infectiousness parameters ("infection time-course"), as:

$$\textit{risk per infectious day} = 1 - (1 - \textit{risk per infection})^{1/\#\ \textit{days infectious}}.$$

Finally, each student has a daily exogenous risk of infection outside of school and home, which depends on whether they have received

COVID-19 safety education (as described in the Interventions section below). Each household adult also has a risk of exogenous infection.

2.1.3. Infection progression

Agents follow a susceptible-infected-recovered (SIR) framework in which they are initially either susceptible to infection, infected, or vaccinated or recovered (i.e. immune) (13). Susceptible individuals can become infected over the course of the simulation. Infected individuals then progress through a series of infection states. They first enter a latent period during which they are not yet infectious or symptomatic. Next, they become infectious but presymptomatic. Infectious presymptomatic individuals can become symptomatic or remain asymptomatic. Eventually, infected individuals recover and become immune.

2.1.4. Interventions

The model includes representations of several possible program components for resuming and maintaining in-person instruction. Not all these components may be implemented in some school districts, so the model has options for some of these components to be deactivated. For example, surveillance testing of non-symptomatic individuals can be eliminated by setting the "testing fraction" for surveillance testing to 0%. Thus, model users can modify parameters to exclude or alter some of the mitigation strategies to represent scenarios relevant to their environment.

One component is a daily symptom/exposure screening system through which students self-report if they have COVID-19 exposures or symptoms. This daily health screening may reduce the rates of infectious individuals coming onto campus; individuals reporting symptoms or suspected COVID-19 exposures could be diverted into quarantine protocols or receive other triage and follow-up. Such screenings have been implemented in workplaces, universities, and K-12 systems (14).

Another possible component of school-based mitigation strategies is outreach education of school community members. In such a program, school representatives might make phone calls to students' family members to provide information and guidance about safe behaviors that reduce their exposure to COVID-19 (e.g., social distancing, mask usage, and vaccination). In addition to influencing behavior, such engagement with students and their families may change the likelihood that individuals accurately report potential exposures and symptoms on the daily screen. The model includes a representation of this type of educational outreach.

Testing for COVID-19 infection is another possible component. Tests can be performed in response to reported COVID-19 symptoms or known exposure. Periodic surveillance testing can also be performed universally or in a random sample of non-symptomatic individuals to identify presymptomatic and asymptomatic cases. For the 2021–2022 school year, our partner district implemented weekly surveillance testing of 100% of their students. Both responsive and surveillance testing are represented in the model. The model can represent tests with different accuracy characteristics (specificity, sensitivity as a function of elapsed time since infection). In the analyses below, we assumed accuracy characteristics similar to PCR testing, but these parameters and testing frequency could be changed to represent antigen testing (15).

Other policies that can influence infection risks at school include defining and maintaining small groups in close proximity (e.g., classrooms, lunch groups) as well as using masks, physical space dividers, and other forms of physical barriers (16).

2.2. Model outcomes

We report the following model outcomes after 2 months of simulated full-time in-person school:

1. The cumulative percentage of enrolled students infected with COVID-19 since baseline.
2. The cumulative percentage of enrolled students infected with COVID-19 while at school.
3. The cumulative number of school days missed per student.
4. The percentage of schools with no in-school transmissions.
5. The percentage of schools with no detected infection clusters.

Other measured outcomes, such as infection rates among household adults, are not reported here in the interest of brevity but are provided in the online interface.

For each experimental scenario considered below, we simulated 10,000 schools in a single run of the model using the corresponding set of input parameter values. We calculated the five outcomes listed above for each school, and then combined results across the simulated schools to estimate outcome distribution summary statistics. For the student-level outcomes (#1-3), we report the means across the 10,000 simulated schools, as well as the 2.5 and 97.5% percentiles of these outcomes as 95% prediction intervals. For the school-level outcomes (#4-5) we report the event rates as percentages, as well as 95% exact binomial confidence intervals (percentiles and prediction intervals are not applicable for these outcomes).

2.3. Validation

Validation tests confirmed that the agent-initializing function produced the specified initial rates of current infection, prior infection, and COVID safety education characteristics among students at baseline for the default input parameter values. In the absence of school data when the model was developed, it was not feasible to calibrate this model. Methodological constraints make it difficult to compare the model output to actual experience of school districts; for example, few districts have reliable estimates of COVID-19 positivity from well-designed surveillance. For this paper, we assigned default parameter values based on the existing literature where possible and considered likely values for variables with considerable uncertainty (details in Supplementary material). To use the model to inform planning, policymakers should choose parameter values that reflect current conditions in their schools.

2.4. Example experiments

To demonstrate how the model can be used to explore the effects of interventions, we tested the effects of changes in four parameters that could be affected by school policies: class size, frequency of surveillance testing, fraction of students tested in each surveillance sample ("sampling fraction"), and proportion of household adults vaccinated (Tables 1–4). We started with the default parameter values and varied these four parameters to determine how the outcomes changed in response. We also considered a set of four scenarios examining interactions between surveillance testing and community education (Table 5).

2.5. Sensitivity analyses

In sensitivity analyses, we tested the effects of additional parameters: number of non-socially distanced classmates per student, test sensitivity and specificity, transmission risk from infectious students to non-socially-distanced classmates, exogenous infection risk, symptom/exposure reporting sensitivity and specificity prior to COVID-19 safety education outreach, receptiveness to COVID-19 safety education outreach, and effects of COVID safety education on accuracy of symptom/exposure reporting, and exogenous risk (Supplementary material). We created tornado plots as a simple, interpretable display; these plots assess the relative importance of these variables with respect to each outcome (17).

3. Results

In 10,000 schools simulated for 2 months of in-person instruction using the default parameter values except for class size, smaller class sizes resulted in fewer students infected in-school, more schools remaining transmission-free, and fewer school days missed (Table 1). With classes of 30 students each, an average of 4.53% of students became infected, 0.09% were infected in-school, 1.24 school days were missed per student, and 69.3% of schools remained transmission-free. With 10 students per class, these outcomes improved to 4.48% infected overall, 0.04% infected in-school, 1.21 school days missed per student, and 84.2% of schools remaining infection-free.

More surveillance testing resulted in lower transmission rates, but more school days missed (Table 2). With no surveillance testing, 4.49% of students became infected after baseline, 0.06% were infected at school, 1.18 school days were missed per student, and 79.2% of schools had no on-campus transmissions. Weekly surveillance testing with a randomly selected 25% of the student body tested in each week did not change these outcomes substantially. Daily testing of 25% of the student body produced small improvements in infection rates: 4.49% of students became infected overall, 0.04% were infected in school, and 84.2% of schools remained transmission-free; however, average school days missed increased to 1.30 days per student. Finally, daily testing of all students produced larger improvements in secondary infection rates: 4.48% of students were infected overall, 0.03% in school, and 87.3% of schools stayed transmission-free; however, school days missed rose to 1.59 days per student. The percentage of schools with no detected clusters had an opposite trend to the percentage of schools with no actual transmissions: with more surveillance testing of asymptomatic students, more schools had clusters detected.

The observed tradeoff between transmission and attendance occurred because increased testing increased the numbers of true positive cases, which are correctly isolated, but also the numbers of false positive cases, which are unnecessarily isolated: with no testing, students spent an average of 0.06 school days on-campus and infectious, vs. 0.03 school days with daily 100% testing; however, with 100% daily testing, students also averaged 1.41 school days quarantined and uninfectious, vs. 1.02 days with no surveillance testing (Table 3).

Higher levels of vaccination among household adults resulted in fewer infections overall and fewer school days missed, but no improvements in on-campus infections (Table 4). With no vaccinations, 4.50% of students became infected since baseline, 0.05% were infected while at school, 1.27% of students were infected by a household adult, 91.5% of students remained uninfected, 1.21 days were missed, and 80.2% of schools had no on-campus transmissions. With 75% of the adults vaccinated, only 3.58% of students became infected since baseline and 0.79 school days were missed per student; 0.06% of students were infected on campus, 0.34% were infected by a household adult, 92.4% remained uninfected, and 78.8% of schools had no on-campus transmissions. The decrease in the proportion of schools with no on-campus transmissions between the 0 and 75% adult vaccination scenarios was small (1.4 percentage points) but statistically significant (continuity-corrected chi-square test $p = 0.02$); as fewer students were being infected at home (0.34 vs. 1.27%), more remained uninfected and hence vulnerable to infection at school (92.4 vs. 91.5%).

In the scenarios examining interactions between surveillance testing and school community education, the "Education only," "Testing only," and "Testing + Education" scenarios all resulted in lower infection rates than the "No testing or education" scenario (Table 5). "Testing only" had better in-school infection rates than "Education only" but worse overall infection rates and average attendance rates. "Testing + Education" produced better infection rates than either strategy alone and a better average attendance rate than "Testing alone."

3.1. Sensitivity analyses

Detailed sensitivity analysis results are provided in the Supplementary material. Starting from our default assumptions, in-school infections were most affected by changes in risk per infectious classmate, exogenous infection risk, exposure and symptoms screening sensitivity and specificity, likelihood of symptoms if infected, class size, number of non-distanced classmates in school, and biological test specificity, while attendance rates were most affected by changes in symptoms/exposure screening specificity, exogenous infection risk, biological test specificity, and vaccination rate.

4. Discussion

Our model provides results in terms of health as well as attendance. Key findings are that (1) as expected, smaller class size resulted in less school transmission as well as fewer missed school days; (2) frequent testing leads to reduced transmission but increased school days missed due to positive students as well as students with false positive tests being in extended home isolation; and (3) vaccination of household members reduces the number of school days missed per student and total students becoming infected

TABLE 1 Mean-average outcomes after 2 months of in-person instruction, by class size.

Number of students per class	% of students infected since baseline (cumulative)*	% of students infected from school (cumulative)*	# School days quarantined per student (cumulative)*	% of schools with no on-campus transmissions so far**	% of schools with no detected infection clusters so far**
10	4.48 (2.62, 6.43)	0.04 (0.00, 0.24)	1.21 (0.91, 1.53)	84.2% (83.5, 84.9)	99.3% (99.1, 99.5)
15 (default)	4.50 (2.62, 6.67)	0.05 (0.00, 0.24)	1.21 (0.91, 1.53)	80.2% (79.4, 81.0)	99.0% (98.7, 99.1)
20	4.51 (2.62, 6.67)	0.06 (0.00, 0.48)	1.21 (0.92, 1.56)	76.9% (76.1, 77.7)	98.0% (97.7, 98.3)
30	4.53 (2.62, 6.67)	0.09 (0.00, 0.48)	1.24 (0.92, 1.83)	69.3% (68.4, 70.3)	94.8% (94.3, 95.2)

*2.5 and 97.5% percentiles (across the 10,000 simulated schools) are provided for student-level outcomes.
**95% exact binomial confidence intervals are provided for school-level outcomes.

TABLE 2 Mean-average outcomes after 2 months of in-person instruction, by surveillance testing frequency and sampling fraction.

Sampling fraction	Surveillance testing schedule	% of students infected since baseline (cumulative)*	% of students infected from school (cumulative)*	# School days quarantined per student (cumulative)*	% of schools with no on-campus transmissions so far**	% of schools with no detected infection clusters so far**
0%	No surveillance testing	4.49 (2.62, 6.67)	0.06 (0.00, 0.48)	1.18 (0.89, 1.49)	79.2% (78.4, 80.0)	99.5% (99.4, 99.7)
25%	Once a week (M) (default)	4.50 (2.62, 6.67)	0.05 (0.00, 0.24)	1.21 (0.91, 1.53)	80.2% (79.4, 81.0)	99.0% (98.7, 99.1)
	Twice a week (M/Th)	4.50 (2.62, 6.67)	0.05 (0.00, 0.24)	1.23 (0.94, 1.58)	81.3% (80.6, 82.1)	97.9% (97.6, 98.1)
	3x a week (MWF)	4.48 (2.62, 6.67)	0.05 (0.00, 0.24)	1.25 (0.95, 1.61)	83.0% (82.3, 83.8)	96.8% (96.4, 97.1)
	Every weekday (M-F)	4.49 (2.62, 6.67)	0.04 (0.00, 0.24)	1.30 (0.99, 1.68)	84.2% (83.5, 84.9)	94.5% (94.1, 95.0)
100%	Once a week (M)	4.49 (2.62, 6.67)	0.04 (0.00, 0.24)	1.28 (0.97, 1.65)	84.7% (84.0, 85.4)	95.7% (95.3, 96.1)
	Twice a week (M/Th)	4.48 (2.62, 6.43)	0.04 (0.00, 0.24)	1.35 (1.02, 1.78)	86.2% (85.5, 86.9)	90.5% (89.9, 91.0)
	3x a week (MWF)	4.47 (2.62, 6.43)	0.03 (0.00, 0.24)	1.43 (1.09, 1.90)	87.7% (87.0, 88.3)	83.9% (83.2, 84.6)
	Every weekday (M-F)	4.48 (2.62, 6.67)	0.03 (0.00, 0.24)	1.59 (1.20, 2.14)	87.3% (86.7, 88.0)	70.2% (69.3, 71.1)

*2.5 and 97.5% percentiles (across the 10,000 simulated schools) are provided for student-level outcomes.
**95% exact binomial confidence intervals are provided for school-level outcomes.

TABLE 3 Additional mean-average outcomes after 2 months of in-person instruction, by surveillance testing frequency and sampling fraction.

Sampling fraction	Surveillance testing schedule	# School days quarantined and uninfectious per student (cumulative)*	# School days quarantined and infectious per student (cumulative)*	# School days on-campus and infectious per student (cumulative)*
0%	No surveillance testing	1.02 (0.78, 1.29)	0.15 (0.07, 0.25)	0.06 (0.01, 0.12)
25%	Once a week (M) (default)	1.05 (0.80, 1.33)	0.16 (0.07, 0.25)	0.05 (0.01, 0.11)
	Twice a week (M/Th)	1.07 (0.82, 1.37)	0.16 (0.07, 0.26)	0.05 (0.01, 0.10)
	3x a week (MWF)	1.09 (0.84, 1.40)	0.16 (0.07, 0.26)	0.05 (0.01, 0.10)
	Every weekday (M-F)	1.13 (0.86, 1.47)	0.16 (0.07, 0.27)	0.04 (0.01, 0.09)
100%	Once a week (M)	1.11 (0.85, 1.43)	0.17 (0.08, 0.27)	0.04 (0.01, 0.08)
	Twice a week (M/Th)	1.18 (0.89, 1.57)	0.17 (0.08, 0.27)	0.04 (0.01, 0.07)
	3x a week (MWF)	1.26 (0.95, 1.69)	0.17 (0.08, 0.28)	0.03 (0.01, 0.06)
	Every weekday (M-F)	1.41 (1.06, 1.93)	0.18 (0.09, 0.28)	0.03 (0.01, 0.06)

*2.5 and 97.5% percentiles (across the 10,000 simulated schools) are provided for these student-level outcomes.

TABLE 4 Mean-average outcomes after 2 months of in-person instruction, by adult vaccination rate.

Percentage of household adults vaccinated	% of students infected since baseline (cumulative)*	% of students infected from school (cumulative)*	% of students infected by a household adult (cumulative)*	% of students not yet infected (cumulative)*	# School days quarantined per student (cumulative)*	% of schools with no on-campus transmissions so far**	% of schools with no detected infection clusters so far**
0% (default)	4.50 (2.62, 6.67)	0.05 (0.00, 0.24)	1.27 (0.24, 2.38)	91.5 (94.1, 88.6)	1.21 (0.91, 1.53)	80.2% (79.4, 81.0)	99.0% (98.7, 99.1)
25%	4.15 (2.38, 6.19)	0.06 (0.00, 0.48)	0.92 (0.24, 1.90)	91.9 (94.3, 89.3)	1.06 (0.79, 1.35)	79.5% (78.7, 80.3)	98.9% (98.6, 99.1)
50%	3.86 (2.14, 5.95)	0.05 (0.00, 0.48)	0.62 (0.00, 1.43)	92.1 (94.5, 89.5)	0.92 (0.69, 1.19)	80.0% (79.3, 80.8)	98.7% (98.5, 98.9)
75%	3.58 (1.91, 5.48)	0.06 (0.00, 0.48)	0.34 (0.00, 0.95)	92.4 (95.0, 89.8)	0.79 (0.59, 1.03)	78.8% (78.0, 79.6)	99.0% (98.7, 99.1)

*2.5 and 97.5% percentiles (across the 10,000 simulated schools) are provided for student-level outcomes.
**95% exact binomial confidence intervals are provided for school-level outcomes.

TABLE 5 Scenarios assessing the effects and interactions of surveillance testing and educational outreach to families.

Default parameter values	25% every Monday	50%	10%	4.50 (2.62, 6.67)	0.05 (0.00, 0.24)	1.21 (0.91, 1.53)	80.2% (79.4, 81.0)	99.0% (98.7, 99.1)
No testing or education	None	0%	50%	4.33 (2.62, 6.43)	0.05 (0.00, 0.48)	1.14 (0.85, 1.45)	80.4% (79.6, 81.2)	99.5% (99.3, 99.6)
Education only	None	100%	50%	4.10 (2.38, 6.19)	0.04 (0.00, 0.24)	1.08 (0.80, 1.38)	83.8% (83.1, 84.5)	99.7% (99.5, 99.8)
Testing only	100% every Monday	0%	50%	4.33 (2.38, 6.43)	0.04 (0.00, 0.24)	1.24 (0.94, 1.60)	84.9% (84.2, 85.6)	95.7% (95.3, 96.1)
Testing + education	100% every Monday	100%	50%	4.07 (2.38, 6.19)	0.03 (0.00, 0.24)	1.17 (0.89, 1.52)	88.3% (87.6, 88.9)	96.4% (96.0, 96.8)

*2.5 and 97.5% percentiles (across the 10,000 simulated schools) are provided for student-level outcomes.
**95% exact binomial confidence intervals are provided for school-level outcomes.

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but not school transmission. Comparing different combinations of mitigation strategies, with varying assumptions about the accuracy of parent-reported symptoms and exposures, produced results in school infection and attendance that were not additive, and show stakeholders how implementation integrity in combination with elected mitigation strategies could affect outcomes of interest.

Using parameters that reflect our best knowledge about COVID-19, the simulations show that no single program element or condition ensures safety and that some combinations have trade-offs between school infection and attendance. Our model reflects recent evidence that even without COVID-19 testing, on-campus infection control can reduce on-campus transmission, and high community prevalence does not necessarily lead to significant secondary infection if mitigation measures such as masking are implemented effectively (10), especially if vaccination rates are high.

Notably, the model illustrates the value of school districts measuring not just adoption of policy but the implementation quality of their mitigation strategies. For example, given the presymptomatic and asymptomatic features of COVID-19, particularly in children, the simulations help stakeholders appreciate the impact of accurate reporting of symptoms and exposures. School districts can see the potential impact of accurate parent and student reporting and therefore the potential need for effective design of the screening questions as well as ongoing education to improve the accuracy of reporting.

Public health credibility has been vital in the COVID-19 pandemic, and stakeholders need models that reflect the latest science so that district decisions are trusted. Our model is designed to be practical, transparent, and adaptable as mechanisms for transmission and mitigation and their interdependencies become known.

The model's structure and dynamics are not limited to COVID-19. With appropriate adjustment of the parameter values representing transmission risks and infection characteristics, this model could be used to represent any infectious disease and adapted for other congregate settings, such as residential facilities.

4.1. Limitations

This model was developed to surface dynamics that give stakeholders insights about mitigation strategies as the pandemic evolved. The model is not intended in its current form to make specific predictions or justify specific actions. Validation of the model's parameters and predictions with real data could increase its utility for accurately predicting policy outcomes. Notably, it is not possible to fully validate the model; most studies of COVID-19 prevalence and transmission in U.S. schools are limited by lack of systematic testing, incomplete contact tracing, and details about mitigation procedures as well as adherence to them and their timing (10, 18–20). Demonstrating the model in its current state provides a framework with outcomes that can improve how modelers provide and interpret results for school district stakeholders and provides a basis for future extensions.

In the simulation scenarios presented in this paper, we found that increasing vaccination rates for household adults resulted in improved student attendance rates (Table 4), but the size of this effect in practice will depend on the specific epidemiological, demographic, and policy factors that a particular school is currently experiencing. This model represents this context with a large number of modifiable input parameters, but there are inevitably additional dynamics which are not included in the model.

For example, characteristics of households of school community members that influence their exposure to COVID-19 include recurrent proximity to other household members (number in the household, and overcrowding), intermittent proximity to other individuals who do not live in the household (such as extended family/friends), density of neighborhood housing density (proxy for proximity), and ongoing potential workplace exposures such as essential or industrial workers in the household. Household behaviors include close physical contact, multiple caregivers of a child, and uses of facial coverings and other safety practices. Household health risks such as presence of individuals with chronic conditions, and/or older age, influences impact of household morbidity from any school-transmitted COVID-19 infection. None of these characteristics are implemented in the current model, for succinctness and due to limited resources for further extending the model, but they may play an important role in local transmission dynamics, particularly since these risk factors often co-occur with one another.

We also made a simplifying assumption that vaccination and recovery from infection each independently confer complete, long-term immunity from future infection. At the time when this model was being developed (Q4 2020), this assumption was plausible. Since that time, both scientific knowledge and the COVID-19 virus itself have evolved substantially, and the immunities conferred by vaccination or prior exposure are now understood to be incomplete, diminishing over time, and dependent on the specific type of vaccine received and on the variants of the COVID-19 virus that an individual has previously recovered from, compared to the one they are currently being exposed to. Immunity could be modeled with more nuance in future extensions of this model, as discussed below.

4.2. Future directions

There are three main avenues for further development of this work. First, the model could be extended, adding other agents such as teachers and other school personnel; incorporating more complicated social networks including sibling connections and asymmetric exposures; other interactions such as shared transportation (school buses and carpools) and after-school sports; compliance (reliability) in mitigation such as handwashing and mask-wearing; more nuanced dynamics for test sensitivity, for example having test sensitivity depend explicitly on symptomatic status rather than only days since infection; and imperfect and time-dependent immunity to infection after vaccination or recovery from prior infection. Second, the interactions between different input parameters could be explored, by simultaneously varying multiple parameters instead of only one at a time as we have primarily done in this paper. This is a more realistic use of the model and how we envision public health authorities and school systems making use of it. Readers are encouraged to access the model *via* the user interface at https://agent-based-models.shinyapps.io/RegionalCOVIDSchoolSimulation/ to explore other combinations of input values. Third, the user interface could be augmented by adding side-by-side comparisons of the outcomes for different combinations of input parameter values, narrative descriptions of individual runs of the simulation, and additional outcome time series.

5. Conclusions

Models enable stakeholders and researchers to consider infection dynamics and potential mitigation strategies in combination. Public health authorities and school systems can use insights from these models to establish operational needs for safer in-person instruction, such as accurate daily health checks and ongoing timely data on the reliability of mitigation strategies. Models can facilitate an iterative process by which understanding of the system is further deepened, which can in turn be used to reassure communities that schools can deliver in-person instruction without triggering large outbreaks. With future calibration, the model can ultimately have value for prediction, especially as the pandemic eventually becomes endemic, and new transmission and disease control scenarios arise (21, 22).

Given the availability of highly effective vaccines and the amount of community infection with COVID-19, the predictions of this model for a school district would be limited. However, the model continues to be useful in demonstrating key inputs to viral dynamics. It is also an example of a model that includes key inputs and that allows real-time change by users of key parameters and assumptions. We have published the source code for the model on GitHub (https://github.com/UCLA-PHP/school.epi.abm) so that other researchers can use and extend the model for districts in any location.

It is important for decision-making models in COVID-19 to be flexible given the rapid evolution of knowledge about how the virus operates, the rapid transmission dynamics of a disease that spreads through a population exponentially, and the rapidly changing landscape of testing features, costs, and operational burdens as what is being seen in the most recent wave of the Omicron variant infection (23, 24).

Public health authorities and school districts can make more meaningful choices about the welfare of K-6 students, their teachers, and their families if these decisions about in-person instruction are based on information from models that incorporate their local conditions and use the different elements available to them, especially those that reflect the COVID-19 situation in the real world. This study provides one such model, recognizing that not all possible elements may be politically or operationally feasible given the characteristics of a particular school community.

Preprint

This article was preprinted on medRxiv (25).

Data availability statement

Publicly available datasets were analyzed in this study. These data can be found at: https://github.com/UCLA-PHP/school.epi.abm.

Author contributions

DM, RN, VM, OA, NA, TK, and MI are members of a UCLA Clinical and Translational Science Institute (CTSI) science team tasked with developing a simulation model that can be used to inform scenarios under which K-6 school in-person instruction can be resumed safely during the COVID-19 pandemic. DM, RN, and VM conceptualized the original model design. DM, VM, NA, and MI performed iterative literature reviews to inform the model parametrization. DM and RN implemented and validated the model. VM and MI aligned the evolving model with pragmatic features based on school district collaborations. TK and OA advised on transmission dynamics parameterization and helped characterize the scenarios considered in the model building process. MI and TK facilitated team support from the Population Health Program at CTSI. All authors contributed to the interpretation of the data and provided substantial content to the text of the article.

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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.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.856940/full#supplementary-material

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