# PUBLIC HEALTH DATA CHALLENGES OF THE COVID-19 PANDEMIC

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# PUBLIC HEALTH DATA CHALLENGES OF THE COVID-19 PANDEMIC

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# Editorial: Public Health Data Challenges of the COVID-19 pandemic: A Sisyphean task!

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Editorial on the Research Topic
Public Health Data Challenges of the COVID-19 pandemic: A Sisyphean task!

In December 2019, a cluster of pneumonia cases was reported in Wuhan, China. Eventually it was identified, and the genetic sequence was thereafter disseminated, confirming a novel coronavirus infecting humans. Within just a few weeks, its rapid spread took on pandemic proportions, affecting people's lives and daily routines. As of May 2022, the COVID-19 pandemic is still raging on, posing challenges worldwide.

From its beginning, this pandemic has brought unexpected changes to health care systems and new challenges for public health, health monitoring, and health surveillance, namely in terms of the necessary data for clinical decisions, resource management, and policymaking. Moreover, health care systems had to maintain their non-COVID-19 activity while simultaneously the unrelenting impact of this new disease.

The scientific world, too, was taken by a hurricane, and witnessed an impressive number of COVID-19-related publications in record time. As of the end of April 2022, PubMed, one of the most well-known databases containing biomedical scientific literature, retrieved more than 255,000 citations with "COVID-19" as the search term. Of those, 72,587 records also included a reference to "data," revealing a large body of literature that likely involved the use of data to study COVID-19.

Projects like the Population Health Information Research Infrastructure (1) are, we believe, currently conducting literature reviews to better understand the uses, the pathways, and the needs of population health data in these pandemic times. It will take years, or even decades, to understand exactly what happened and what lessons we must assimilate to prepare for similar health crises and take with us into our new day-to-day.

The primary aim of our Research Topic *Public Health Data Challenges of the COVID-19 Pandemic* was to focus on public health data in the contexts of worrying data deficits, emergent problems, and innovative solutions originating from the COVID-19 pandemic crisis. Nevertheless, it was the secondary aim—a focus on the solutions and knowledge brought by the pandemic—that received the most contributions. Curiously, most articles presented creative ways of acquiring data, thus failing to let us know more about the issues we were addressing.

The COVID-19 pandemic has exposed gaps that need to be addressed for society to return to a new normal that is better than before. Therefore, coordinated efforts among health care providers and public health officials at different levels are necessary—for example, to catch up on vaccination in the United States (2). The rapid development of COVID-19 vaccines has demonstrated that, with extensive data sharing, it is possible for researchers who have the necessary resources and novel technologies to conduct and apply their research throughout the response to the COVID-19 pandemic (3). This worldwide response has shown the importance of vigilance and preparedness for any infectious disease.

Policy approaches can be a highly effective tool for preventing exposure to other communicable disease outbreaks and protecting the health of the public. Researchers and public health leaders can examine the bidirectional effects of laws and policies, which are important levers to improve health and wellbeing. It is also crucial to measure and monitor the effect of laws and policies on the health status of populations. In this regard, policy interventions and assessments should examine the degree to which such interventions achieve equity, contribute to the effectiveness of health promotion programs, and shape the behaviors of various sectors that influence population health (2, 4).

We also ended up with interesting new perspectives on the effects of COVID-19 on hospital activity, particularly the need to balance usual care with addressing the needs of the pandemic. As an example, Kalanj et al. discuss the considerable reduction in hospital admission rates for non-COVID-19 health concerns, including services related to cardiovascular and malignant diseases.

Many case studies in this Research Topic focused on strategies employed by the scientific community for sharing their experiences and challenges in dealing with the ongoing pandemic situation, as well as strategies for providing policy recommendations and advice to governments on the impact of the disease. Additionally, once the COVID-19 vaccine became available, we received literature describing the challenges of vaccination management and inequitable distribution in many different countries. The articles were related to policies and strategies concerning public health, health policy, and health planning, with a focus on local, regional, and national approaches. The articles also applied a range of different empirical and conceptual approaches to the topics they covered. They explored topics such as health policy on supporting the first-dose vaccination campaigns that prioritized administration in the elderly (Pontrelli et al.) and even the effects of a delay in vaccine acquisition that slowed down a national vaccination program with the potential to accelerate the spread of the virus and lead to a new lockdown (Kamran and Ali).

Public health strategies such as containment and mitigation were emphasized in several articles. These articles also stressed the importance of evaluating publications and using meta-analyses for recommendations, even during a pandemic (Boudesseul et al.); modeled the effects of public health measures during the COVID-19 pandemic (Qiu et al.); discussed the effects of epidemic prevention and control (Chen et al.); and supported with data the effects of some specific measures such as school closures (Chao et al.).

Several review articles also focused on the importance of equity. For instance, Ruiz-Hornillos et al. examined the equity guarantees and transparency in decision-making processes, and Haring et al. explored the concept of trust in current and future equitable relationship-building between communities and public-private interests.

Although the pandemic was a new and challenging health problem, the increase in scientific publications during this period is likely related to the fact that more than a few journals fast-tracked COVID-19 research (5). Even so, COVID-19 brought to light the need for more robust public health data: one of the top three medical subjects in these publications was public health (6). Nonetheless, evidence is still lacking on the efficiency of healthcare systems regarding their efforts to address the indirect impacts of the pandemic and maintain their regular level of services, including their responsiveness to the demand for both critical medical services and non-elective procedures (Kalanj et al.).

More research is needed to establish public health policy data devoted to an emergency during a pandemic, and also to support alert systems that may contribute to increased preparedness for future pandemics.

The challenge remains to reinforce the need for more analysis and exploration of the situations where public health data is not available for informing political decisions; where information systems run into ethical barriers; and where new and innovative solutions had to be created to overcome the data needs imposed by the unexpected challenges of COVID-19 that occurred at local, regional, national, and international levels.

But, most importantly, we cannot keep perpetually reinventing the wheel in terms of the use of data for research, for population health, for public health, or for health monitoring and surveillance. We need to start talking openly about data. We must be able to build on each other's efforts, to share and improve data. We are not doomed to start anew for every single study or challenge—research is not a Sisyphean task!

## Author contributions

CF, PN, RF-S, and AC have worked on the conceptualization, methodology, and writing. 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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POLICY BRIEF
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# Prioritizing the First Doses of SARS-CoV-2 Vaccine to Save the Elderly: The Case Study of Italy

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SARS-CoV-2 is currently causing hundreds of deaths every day in European countries, mostly in not yet vaccinated elderly. Vaccine shortage poses relevant challenges to health authorities, called to act promptly with a scarcity of data. We modeled the mortality reduction of the elderly according to a schedule of mRNA SARS-CoV-2 vaccine that prioritized first dose administration. For the case study of Italy, we show an increase in protected individuals up to 53.4% and a decrease in deaths up to 19.8% in the cohort of over 80's compared with the standard vaccine recalls after 3 or 4 weeks. This model supports the adoption of vaccination campaigns that prioritize the administration of the first doses in the elderly.

**Keywords: COVID-19, SARS-CoV-2, vaccination, elderly, prioritizing 1st dose**

## INTRODUCTION

Despite the restrictive measures adopted worldwide, the daily count of infections and deaths from COVID-19 remains high and unbearable. In western countries, the highest death toll has been paid by the elderly: in the case of Italy, of the ∼102.010 deaths due to the pandemic, 62% were over 80-years-old, according to the bulletin of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS), updated on March 17, 2021. The vaccination campaign has, therefore, prioritized this age group, whose immunization in Italy began on Monday, February 8, 2021 with difficulties due to various delays in the supply of the two approved mRNA vaccines (Pfizer/BNT Biotech and Moderna) initially dedicated to this cohort. The Italian strategic plan for anti-SARS-CoV-2/COVID-19 vaccination has been consequently adjusted several times (1).

The recommendation derived from registrative trials is that administration of the mRNA vaccines should be in two doses, spaced 3–4 weeks apart: the *efficacy* (protection assessed in clinical trials) of preventing symptomatic COVID-19 in clinical trials was 94.8 and 94.1% for Pfizer/BNT Biotech and Moderna, respectively (2, 3). However, when excluding cases of infection in the first 14 days after the first dose (the time needed for an effective immune response against the vaccine antigen), the same trial studies showed a good efficacy from the first dose alone: 92.6% (4) and 92.1% (3) for Pfizer/BNT Biotech and Moderna, respectively. A recent Israeli study also estimated first dose *effectiveness* (protection assessed in the real world, usually lower than efficacy) of 85% (95% CI 71–92) in reducing symptomatic COVID-19 cases (5). This data was confirmed in a study conducted in Scotland on healthcare workers (6). More recently, another study proved the efficacy of 57% (95% CI 50–63) from 14 to 20 days after the first dose and 66% (95% CI 57–73) from 21 to 27 days after the first dose (7). To date, the available data on vaccine efficacy against transmission is limited. However, an interim estimate of vaccine effectiveness of Pfizer/BNT Biotech and Moderna vaccines proved adjusted vaccine effectiveness against infection of 80% and 90%, respectively, 14 days after the first and second dose (8). What is well-known is that the vaccine reduces the symptomatic forms of COVID-19, thus also decreasing both the number of severely affected patients requiring admission to the ICU and deaths.

All these data refer to the short-term efficacy and effectiveness but show protection above the 50% threshold as considered by the European Medicines Agency (EMA) guidelines (9). Based on the epidemiological data and the scarcity of vaccine doses, the United Kingdom has adopted the strategy of postponing the administration of the second dose to 12 weeks after the first dose (10). The goal was self-evident: to protect as many people as possible as soon as possible, while waiting for a better supply of vaccines.

In Italy, the available doses of the two mRNA vaccines are much lower than those needed to immunize the entire population or even the over-80's in a short time. This situation is putting Italy, and other countries like the U.S., in front of a question similar to that faced by the United Kingdom: if the first objective is to save the greatest number of lives, why not delay the second doses until all high-risk subjects have been vaccinated with at least one dose?

Stanley Plotkin answers the question favorably (11), considering not only the apparent correlation between protection and low antibody levels after a single-dose administration of mRNA vaccine, as demonstrated in some studies, but also the relative efficacy of other vaccines, especially anti-hepatitis B, when administered at prolonged intervals (2, 12, 13). In addition, the study explains how memory B cells develop properly following the administration of mRNA vaccines, supporting the idea that further enhancement of antibody production is stimulated by a second dose of vaccine given up to 6 months after the first (14). Similarly, recent epidemiological modeling studies on SARS-CoV-2 showed the effectiveness of single dose vaccination strategy in containing the pandemic more rapidly (15). The debate is still ongoing among scientists and public health policymakers at both the national and international level (16, 17). The US CDC stated "There is no maximum interval between the first and second dose for either vaccine (Pfizer/BNT Biotech and Moderna). Therefore, if the second dose is administered >3 weeks after the first Pfizer-BioNTech vaccine dose or >1 month after the first Moderna vaccine dose, there is no need to restart the series" (18).

## METHODS AND RESULTS

In this article, we provide a computation of the expected benefits to support the choice of the best vaccination strategy. We focused on the analysis of the Italian cohort of 4,442,048 people over 80-years-old, who are the first category to be vaccinated, according to the current National Vaccination Plan (1).

We formulated a simple effective model that estimates the number of protected individuals and deaths during the early phase of the vaccination campaign, by using data on vaccine efficacy from clinical trials and effectiveness from observational studies. We modeled a scenario in which the effectiveness of the 1st dose after 14 days is $0.80 \pm 0.10$ (5, 9) and a more conservative scenario with lower effectiveness of $0.60 \pm 0.10$ (6).

We considered a 7-week period (the model was originally conceived in the period February 10–March 31), with a varying rate of weekly vaccine administrations. We counted protected individuals at week 9 (i.e., April 14) and deaths from week 3 to week 9 included (i.e., February 24 to April 14), discounting the 2-weeks period required for coverage activation. Protected individuals in a given week were obtained as the total individuals vaccinated with 1 or 2 doses at least 2 weeks earlier, each modulated for the effective coverage provided by the vaccine. Deaths at a given week were then obtained through the weekly mortality parameter applied to the susceptible population (the cohort) after subtracting the protected individuals. For model parameters and mathematical details, please refer to the section below.

The vaccination campaign for over-80's and fragile individuals was carried out using preferably mRNA vaccines (Pfizer/BNT Biotech and Moderna). On February 22, the AstraZeneca vaccine was also indicated by Italian authorities for people > 65 years; however, evidence on its efficacy on over-80's remains incomplete, planned supplies are late, and administration of this vaccine has been further delayed by the temporary suspension set up by the EMA last March after the report of cases of cerebral vein thrombosis occurring after the vaccination. All these factors resulted in a delay in implementing the vaccination using the AstraZeneca vaccine in the cohort of over-80's.

We considered two schedules of vaccine administration: a standard schedule of vaccine recall after 3 and 4 weeks, respectively, for Pfizer/BNT Biotech and Moderna, and an alternative schedule in which administration of the second dose begins after the whole cohort has received the first dose. In **Figure 1**, we report the pattern of vaccinated individuals under these two schedules over a 7 weeks period for only the Pfizer/BNT Biotech vaccine. The first 3 weeks are the same for both schedules. Afterward, under the standard schedule, the available doses will be reserved and used for the second vaccination of subjects who already been vaccinated, to the detriment of other individuals over 80-years-old not yet vaccinated, who will have to wait while remaining at risk.

Consider, for example, a scenario with 800,000 doses (about 18% of the cohort) of mRNA vaccine was administered each week in the considered cohort. Considering the latency of 2 weeks necessary to evoke an efficient immune response (and assuming a first dose effectiveness of 80%), with this strategy a total of 2,920,000 people will be protected at week 9 according to the model. If we assume a constant weekly mortality rate of $\sim$4 fatalities per 10,000 people in this age group [update as of March 10, 2021 (18)], there will be 7,061 deaths in the same cohort from

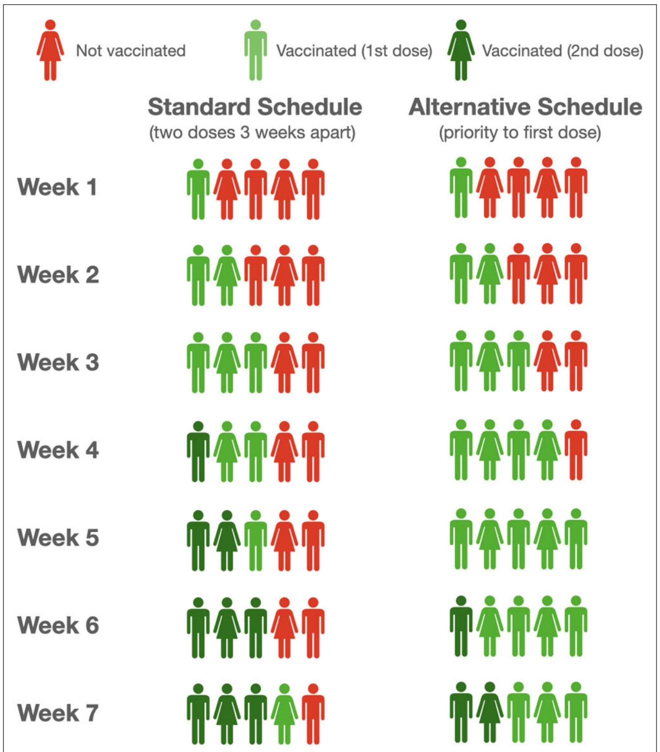


**FIGURE 1 |** Schematic illustration of standard and alternative schedule of vaccination.

week 3 to week 9. Conversely, following the alternative schedule (i.e., the strategy of prioritizing first doses to all individuals of the cohort before moving on to second doses), 3,727,330 people will be protected and a total of 5,664 deaths in the cohort are expected in the same time interval, i.e., a 27.6% increase of the protected and a 19.8% reduction of deaths, which notably is independent of the assumed mortality rate. The benefit is evident even when considering vaccine effectiveness of 60% and a different number of weekly vaccinations (refer to **Table 1** and **Figure 2**), the simple reason being the number of protected growing at a very different pace when the first doses or the second doses are administered.

As shown in **Figures 2A,B**, the alternative schedule increases protection and reduces the death in many more individuals than the standard one. The alternative schedule converges to the standard one, in terms of the number of protected individuals, only for about 1 million weekly administrations in this cohort, an extremely high and improbable number given the actual availability of doses; however, the advantage of the alternative schedule on the number of deaths is quite large at any time, because of the "advantage" in protection cumulated in the period covered by the model [see plot (C)]. Notably, in the plot (C), the number of protected individuals increases much more slowly over time with the standard schedule (red and orange line), plateauing at week 5 because second doses are being administered at that time. Instead, under the alternative schedule (blue and green lines), protected individuals increase linearly in time, with a possible bending when the number of weekly doses is so large that second doses administration start before week 7, as indicated by the black curve in the plot (D). Additionally, the plot (D) shows the sharp reduction in deaths with the alternative schedule, for both an 80% (purple line) and 60% (pink line) first dose vaccine effectiveness.

In addition, it is expected that the increase in protected individuals achieved by the alternative schedule would also reduce the number of hospitalizations in the ICU and in other inpatient units, thus alleviating the pressure on health structures and helping restore routine activities. Unfortunately, these indicators by age group are not reported in detail in Italian public reports as are the number of deaths, thus chosen as the study endpoint, however, they are estimated to be substantially higher (18).

It should also be noted that the strategy of temporarily postponing the second dose could be applied to other cohorts identified by the vaccination plan as priorities, for example extremely vulnerable individuals, as patients with chronic conditions that pose additional risk of death if infected, to obtain additional benefits, including patients in pediatric age, as Pfizer vaccine is authorized over 16 years of age. This benefit becomes even more evident in case of vaccine shortage, as mRNA vaccines would be then allocated to the fragile population they are meant for, independently from age, when applying this model. This study could be also implemented for other, younger ages and for estimating the impact on other important outcomes, such as ICU and hospital accesses.

Furthermore, as soon as vaccine supplies increase, the time interval between the two doses in the alternative schedule would be shortened, down to the recall times recommended by registrative trials. In any case, in the alternative schedule, the interval between the first and second doses is limited if the number of weekly vaccine administrations is high (<7.5 weeks if more than 600,000).

It may be argued that a delayed second dose facilitates the emergence of vaccine-resistant variants of the virus; however, the available data show that vaccines appear protective on variants now circulating in Europe, and the risk of this emergence is counterbalanced by the advantages of reducing viral circulation, by making more people non-susceptible to the virus in a shorter amount of time (6, 19–24).

## CONCLUSION

Many countries are facing high mortality caused by the circulation of SARS-CoV-2 among the elderly, who are not yet vaccinated. By prioritizing first dose administration, we estimated up to a 19.8% decrease in deaths in the cohort of over 80's, in case of effectiveness after the first dose of 80%, and a 6.9% decrease under the worst scenario of the effectiveness of 60%. This study has some limits. First, the data on vaccine efficacy was mainly derived from the total population, while this study focused on a cohort, namely the elderly, where the vaccination could be less effective. We proposed scenario 2 with low first dose effectiveness of 0.60 ± 0.10 to adjust for this

**TABLE 1 |** Comparison between standard and alternative schedule.

| | | Standard schedule: recall after 3-4 weeks | Alternative schedule: priority to first dose |
|---|---|---|---|
| Doses per week | | 400,000 (∼9.0% of cohort) | |
| Time between doses | | 3–4 weeks | 11 weeks |
| 1st dose effectiveness: 0.8 | Protected at 14/04 | 1,460,000 | 2,240,000 (+53.4%) |
| | Deaths 24/2–14/4 | 9,750 | 8,854 (−9.2%) |
| 1st dose effectiveness: 0.6 | Protected at 14/04 | 1,380,000 | 1,680,000 (+21.7%) |
| | Deaths 24/2–14/4 | 10,094 | 9,750 (−3.4%) |
| Doses per week | | 600,000 (∼13.5% of cohort) | |
| Time between doses | | 3–4 weeks | 7.5 weeks |
| 1st dose effectiveness: 0.8 | Protected at 14/04 | 2,190,000 | 3,360,000 (+53.4%) |
| | Deaths 24/2–14/4 | 8,406 | 7,062 (−16.0%) |
| 1st dose effectiveness: 0.6 | Protected at 14/04 | 2,070,000 | 2,520,000 (+21.7%) |
| | Deaths 24/2–14/4 | 8,923 | 8,406 (−5.8%) |
| Doses per week | | 800.000 (∼18.0% of cohort) | |
| Time between doses | | 3–4 weeks | 5.5 weeks |
| 1st dose effectiveness: 0.8 | Protected at 14/04 | 2,920,000 | 3,727,330 (+27.6%) |
| | Deaths 24/2–14/4 | 7,061 | 5,664 (−19.8%) |
| 1st dose effectiveness: 0.6 | Protected at 14/04 | 2,760,000 | 3,070,512 (+11.2%) |
| | Deaths 24/2–14/4 | 7,751 | 7,213 (−6.9%) |

aspect while still showing the usefulness of this model. Second, available data on efficacy and effectiveness mainly refer to a shorter time frame after the first dose, 4 weeks at most. In this model, we assumed a non-significant reduction of vaccine effectiveness at 11 weeks at most, as such a period may be required in case of vaccine shortages. Third, we do not embed this vaccination campaign into a formal susceptible-infected-recovered (SIR) based epidemiological model, as we assume the same virus circulation in the short time window considered when only the elderly are vaccinated. Such an embedding is a challenging task that would be likely be required to model longer time horizons and a population-wide vaccination coverage (25). Finally, we remark that this model focuses on the Italian scenario, which we consider as representative of other countries facing similar conditions in terms of infection rate, mortality, and vaccine supply, namely, the key parameters considered in this model. Overall, these findings suggest considering the vaccination option of prioritizing first doses in the elderly until the vaccine supplies are adequate.

## Model Formulation

Parameters:

- $\eta = 0.95$ (2, 3): effectiveness of second dose after 2 weeks
- $\xi$: effectiveness of first dose after 2 weeks:
  - Scenario 1: $0.80 \pm 0.10$ (5)
  - Scenario 2: $0.60 \pm 0.10$ (6)
- $\nu$: vaccine doses administered weekly (*)
- $z_P \simeq 0.87$ and $z_M \simeq 0.13$: ratio of available Pfizer/BNT Biotech and Moderna vaccines (1)
- $N = 4{,}442{,}048$ : cohort over 80 years of age
- $\mu = 0.0004 \pm 0.0000415$ (18) : weekly mortality rate (number of deaths on susceptible individuals) in over 80's in the week from 3 to 10 March 2021 in Italy

Standard schedule:

- Recall week: $T_P = 3$ (Pfizer/BNT Biotech) and $T_M = 4$ (Moderna)
- ${V_1}^X(t)$ and ${V_2}^X(t)$: vaccinated individuals with one or two doses of vaccine $X = \{P, M\}$ at week $t$:
  - ${V_1}^X(t) = \nu z_X t$ and ${V_2}^X(t) = 0$ if $t \leq T_x$
  - ${V_1}^X(t) = \nu z_X(2T_X - t)$ and ${V_2}^X(t) = \nu z_X(t - T_X)$ if $T_X \leq t < 2T_x$
  - ${V_1}^X(t) = \nu z_X(t - 2T_X)$ and ${V_2}^X(t) = \nu z_X T_X$ if $t > 2T_x$

Total vaccinated individuals with one or two doses: $V_1(t) = {V_1}^P(t) + {V_1}^M(t)$ and $V_2(t) = {V_2}^P(t) + {V_2}^M(t)$

Alternative schedule:

- Recall week: $T^* = N/\nu$ (for both Pfizer/BNT Biotech and Moderna)
- $V_1(t)$ and $V_2(t)$: vaccinated individuals with one or two doses of vaccine (either $\{P, M\}$) at week $t$ (expressions valid for $t \leq 2T^*$):
  - $V_1(t) = \min[\nu t, N] - V_2(t)$
  - $V_2(t) = \max[\nu t, N] - N$

Protected and deaths:

- Protected individuals at week $t$: $\Pi(t) = V_1(t-2)\,\xi + V_2(t-2)\,\eta$
- Deaths at week $t$: $M(t) \simeq \mu\,[N - \Pi(t)]$

(*) For Italy, using the full supply of vaccines for the first quarter of 2021 in the 4 weeks of the model would result in slightly over 1 million doses administered per week.

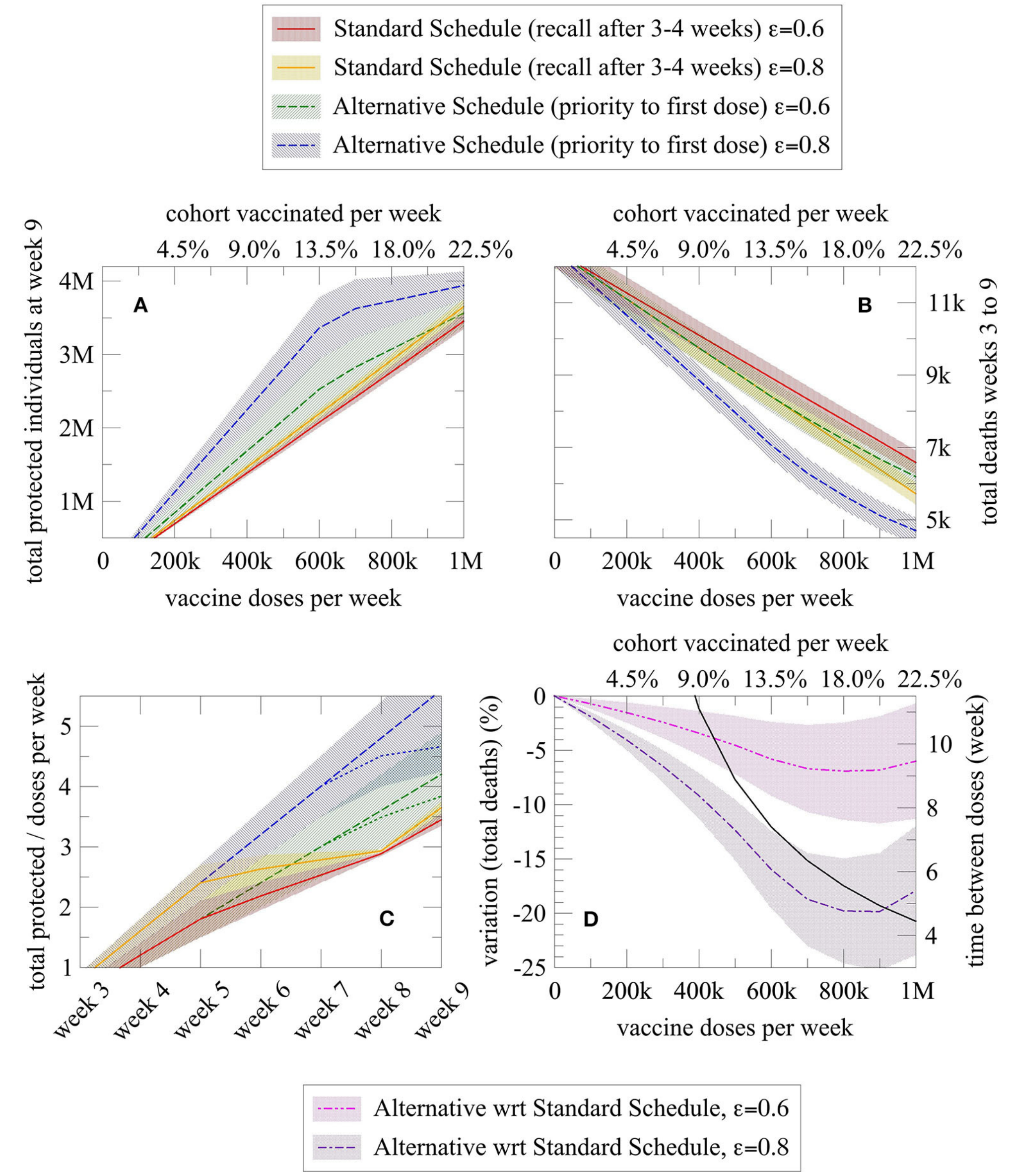


**FIGURE 2 |** Graphical representation of the number of protected and dead individuals as a function of different variables, for a given vaccination schedule (alternative vs. standard). Each schedule is represented by two lines, one for vaccine effectiveness of 80% (blue for alternative schedule and orange for the standard schedule) and one for vaccine effectiveness of 60% (green for alternative schedule and red for the standard schedule). **(A)** Total protected individuals at week 9 and **(B)** Total deaths from week 3 to 9 as a function of the number of doses administered per week (or equally expressed as the percentage of the cohort vaccinated each week); **(C)** Efficiency index (= protected individuals per doses administered over time) of the alternative and standard schedule as a function of the elapsed weeks (dashed sublines indicated a higher number of doses administered, namely 800,000 per week); and **(D)** Death reduction with the alternative schedule (purple line for an 80% vaccine effectiveness and pink line for a 60% vaccine effectiveness) compared with the standard schedule, and effective week in which administration of second doses begins in the alternative schedule after the entire cohort has received the first dose of vaccine (black line). In all plots, the shaded region denotes the confidence interval derived from the uncertainty associated with the effectiveness of the first dose and mortality rate.

## AUTHOR CONTRIBUTIONS

GP, GC, MR, AG, GS, and FS conceptualized, designed the article, and verified data. GP collected data. GP and GC analyzed data. GC created the tables and graphs. GP, GC, and MR drafted and wrote the manuscript. SB, FR, AS, CG, and PR reviewed the manuscript for important intellectual content. GP, GC, MR, AG, GS, SB, FR, AS, CG, PR, and FS revised the final manuscript. GP is guarantor for the article and expert in public health, clinical trials, and vaccine policy. MR is a medical doctor with expertise in scientific data collection, analysis, and scientific writing. GC, AG, GS, and FS are professors of Physics and experts in complex systems modeling. FR is a pharmacologist and expert in European regulatory affairs. 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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MINI REVIEW
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# Challenges and Strategies for Pakistan in the Third Wave of COVID-19: A Mini Review

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The world is currently gripped by the fear of the corona virus disease 2019 (COVID-19) pandemic. The causative agent of COVID-19 is a novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that attacks humans without prejudice, and primarily targets the respiratory system. Pakistan is a developing country with a large population and a weak economy. Currently, it is facing a major challenge to cope with the outbreak of the COVID-19 pandemic, especially the third wave. This fatal virus has increased its presence many folds in Pakistan. On average, 100 deaths per day were being recorded in the late spring of 2021. Delay in the acquisition of vaccine has slowed down the vaccination program for this disease. This in turn will accelerate the spreading of virus, and thus will lead to a lockdown situation.

**Keywords: pandemic, COVID-19, outbreak, death, lockdown**

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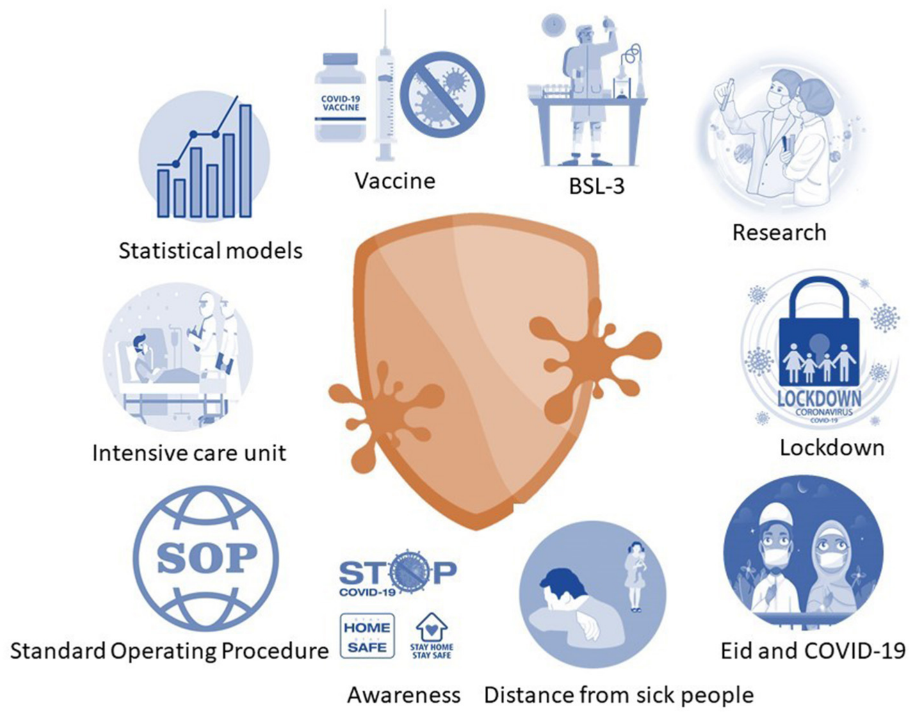
## ORIGIN AND HISTORY OF COVID-19 IN PAKISTAN

The first novel SARS-CoV-2 infected patient was reported in December 2019 (1), and the disease was shortly after named COVID-19 in January 2020 (2). The deadly disease has rapidly spread to around 215 countries since its origin from a seafood wholesale market in Wuhan, a central city in the People's Republic of China (PRC) (3). People would have never imagined that the situation shown in Steven Soderbergh's pandemic thriller movie Contagion (released in 2011) would become reality with the COIVD-19 pandemic (4). There has been considerable discussion on the multiple waves of this causative virus and its control measures.

Pakistan is an under-developed country with a population of about 220 million. It has five provinces: Balochistan, Sindh, Khyber Pakhtunkhwa (KPK), Punjab, and Gilgit Baltistan. The first case of COVID-19 was confirmed on 26th February 2020 by the Ministry of Health, Pakistan (5) and then a continuous spreading of this disease was observed across the country. This virus initially entered Pakistan through returning pilgrims from Iran (through the Taftan border), Saudi Arabia (6), and from Pakistanis who were trapped in other countries that were brought in on special flights (7). Pakistan is currently in a state of health emergency. A total of 1,024,737 tests were carried out with 672,931 (about 66%) confirmed cases of COVID-19 and more than 14,530 (about 2.1%) deaths, reported till late March 2021. Pakistan also experienced the recovery of 605,274 patients (about 90%) and the number of currently reported patients that are under treatment in the health sector is ∼53,127 (**Figures 1**, **2**). According to available data, about 300 medical workers in Pakistan are among the fatal victims of COVID-19. The provincial government of Sindh province was the first to implement a full lockdown, due to which the spread of this virus was reduced to some extent.




**GRAPHICAL ABSTRACT |** Possible potential approaches for decreasing the risks of COVID-19.

## FIRST AND SECOND WAVE OF COVID-19

Since its eruption, the first wave of the disease was very uncertain due to the unknown nature of the virus, its mechanism of infectivity, transmission, and possible treatment options. However, the rapid response of every country, including Pakistan, controlled the fatal prevalence of COVID-19. During the initial wave, Pakistan was very successful in managing the transmission of the disease. It was made possible due to implementation of partial and smart lockdown policies. In partial lockdown, limited time for movement was allowed to citizens after which free movement was strictly prohibited. In smart lockdown, specific areas within a city were sealed where COVID-19 positive cases were detected. Nevertheless, a second wave of the disease occurred, which was moderate in its transmission and pathogenicity. It could have been due to the progressive development in treatment and vaccinations.

## THE THIRD WAVE OF COVID-19

WHO had already warned the Pakistani government that the number of people infected with COVID-19 could exceed 0.2 million by mid-July, 2020 (8). However, no such expected infection rate was reported. A new variant of SARS-CoV-2 (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7) emerged from the United Kingdom (9), and has been detected in over 64 countries as of January 27, 2021, including Pakistan (10). This B.1.1.7 variant is associated with an increased risk of death compared to other variants with average deaths of 100 patients reported on a daily basis in Pakistan. Due to the arrival of this new variant, the 10 cities of Pakistan, Bahawalpur, Faisalabad, Hyderabad, Islamabad, Lahore, Multan, Muzaffarabad, Peshawar, Rawalpindi, and Swat, were put under stiff lockdown till April 11, 2021, where the provincial administration was directed to observe the strict implementation of SOPs.

One thing that was very common between the first and third wave was the time of onset i.e., Spring (from March till end of April). It may lead to the generation of a hypothesis that pollens have a significant role in the enhanced transmission of SARS-CoV-2 virus.

## COVID-19 AND COMORBIDITIES

It has been observed in several cases that COVID-19 patients develop certain additional comorbidities like typhoid, Myocarditis, blood coagulation, and the fatal attack of black fungus. The co-occurrence of these secondary disorders clearly indicate that SARS-CoV-2 provides a favorable condition for the growth of other microbes, however, its mechanism of action is still unexplored.

## DRUGS AND VACCINATION PROGRAMS

As of June 17, 2020, there was no vaccine available for COVID-19, but various drugs i.e., Tocilizumab, Bemsivir lyophilized, Ninavir lyophilized, Dexamethasone and Azithromycin, were used to

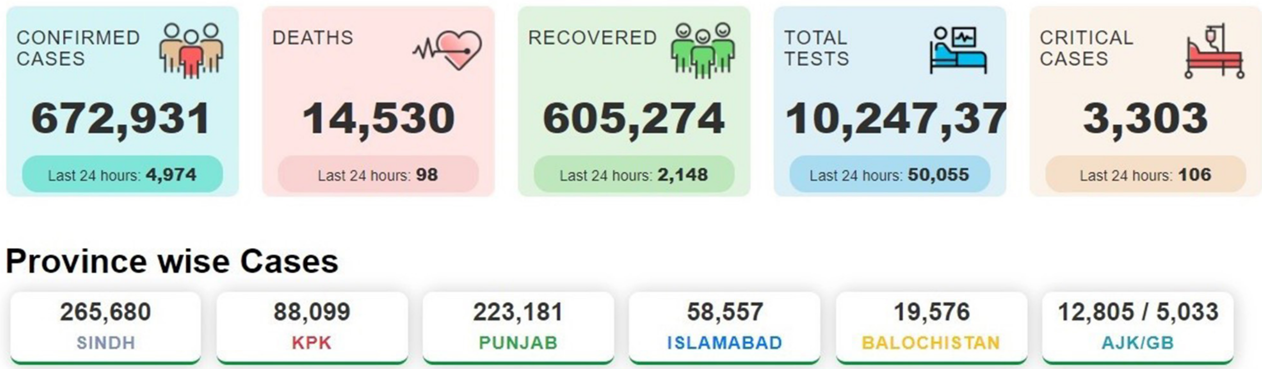



**FIGURE 1 |** COVID-19 status in Pakistan. The figure illustrates the deaths, confirmed cases, and tests performed from May 2020 to 31st March 2021 (The data were obtained from https://covid.gov.pk/).

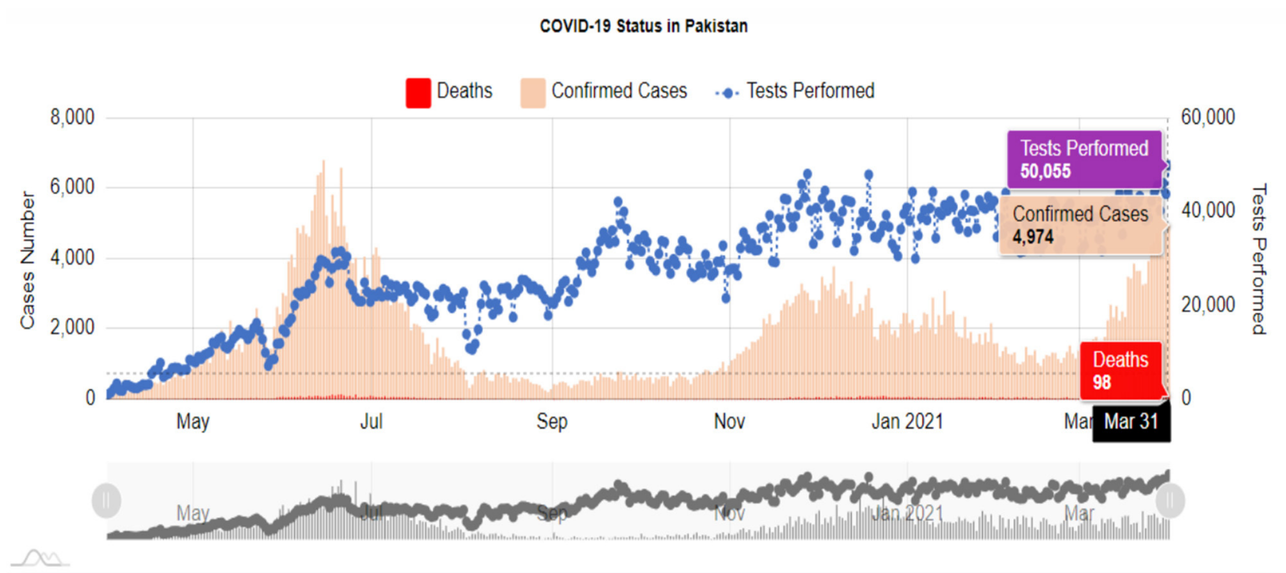



**FIGURE 2 |** Report of daily deaths due to Covid-19 during March 2021. Values show an exponential growth pattern since its outbreak on 26th February 2020 (data taken from the Pakistan statistics of NCOC, https://covid.gov.pk/).

treat the disease without proper regulation. Therefore, the only way to stop the spread of the virus was to observe self-isolation and social distancing from other people. The Drug Regulatory Authority of Pakistan (DRAP), after taking into account the set standards of quality and safety, approved hydroxychloroquine as the first medicine to treat COVID-19 patients. Later on, convalescent plasma therapy was also approved for the treatment of seriously affected COVID-19 patients. Then, a combination of the drugs chloroquine and azithromycin was also found to be effective in clinical trials against COVID-19 (11). Tocilizumab, an anti–interleukin-6 receptor monoclonal antibody, was also successful in a trial at Agha Khan Hospital, Karachi, Pakistan (12), however this method was not adopted by the Federal Government as a possible treatment to cure COVID-19 patients.

Today, vaccines are widely used to protect millions of people around the world from various infectious diseases. Therefore, it was expected that this pandemic would be controlled after the development of a corona vaccine. In this hope, Russia announced the first relevant vaccine (Sputnik-V) within just 15 weeks of the outbreak of the corona virus (13). Presently, DRAP has approved the four most promising vaccines: CanSino (CanSinoBIO, China), Sinopharm (Sinopharm Group Co., Ltd, China), Sputnik-V (Gamaleya Research Institute of Epidemiology and Microbiology, Russia), and Oxford-AstraZeneca (a joint adventure of the University of Oxford and Vaccitech Limited, United Kingdom). The vaccine developed by Pfizer was not approved due to its extreme low preservation temperature (i.e., −80°C) as Pakistan lacks such

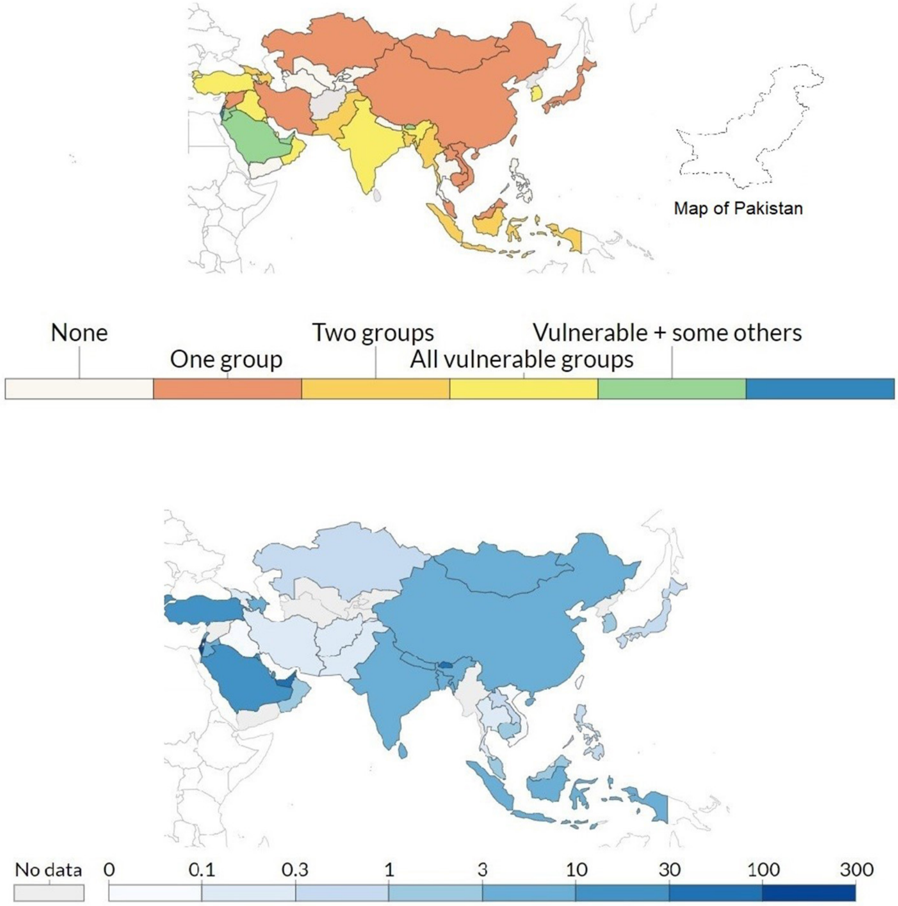



**FIGURE 3 | Top**: Metric records policies in Asian countries for vaccine delivery for three groups: (i) keyworkers, (ii) clinically vulnerable, and (iii) the elderly. Here one means to ensure the supply of the vaccine to one of the three groups, two means to ensure that two of three groups receive the vaccine, while three means ensuring that all groups receive the vaccine equally. **Bottom**: Metric record of the total number of vaccination doses administered per 100 people in the total population. This data counted as a single dose, even though people have received two doses of the vaccine (opensource: https://ourworldindata.org/).

facilities. The above stated four vaccines can be preserved around 0°C, which is quite easy to manage. Pakistan had received a donation of 3 million vaccine doses by mid- April, 2021 from CanSino. Pakistan will also receive 17 million doses of Oxford-AstraZeneca vaccine under the WHO-led COVAX program for developing countries (14). According to a Gallup Survey Poll of Pakistan, "*Sixty percent of Pakistanis said that they would get the COVID-19 vaccine if it became available, whereas 34% respondent were worried about the side effects and 22% are against the vaccine*" (15). The hallmarks of COVID-19 is that it has a higher mortality and pathogenicity in elderly people as compared to those younger than 18 (16). Currently, frontline health care workers and senior citizens (above 60 years) are receiving the Sinopharm vaccine (**Figure 3**) which consists of two doses and has been donated by China. The Federal Government has also issued licenses to pharmaceutical companies to purchase the Russian and Chinese vaccines and allowed them to sell to the private sector at a government approved price.

## FUNDAMENTAL CHALLENGES OF COVID-19 IN PAKISTAN

The current pandemic was not treated in Pakistan in the same way as other countries. Earlier predictive models suggested that the onset of summer may reduce the severity of the virus. However, the results of recently conducted research on COVID-19 does not support the earlier model and concluded that this virus is independent of weather conditions and climate change (17). A vast majority of the people did not follow the instructions and guidelines set by the Federal Government and subordinate departments (18) including the National Command Operation Center (NCOC), Ministry of Health, National Disaster Management Authority (NDMA), and the Drug Regulation Authority (DRA), which has resulted in the major spread of COVID-19 in Pakistan.

Despite various efforts made by NCOC to control COVID-19 transmission in Pakistan, some major shortcomings contributed to the deterioration of the corona situation. These include lack of public awareness at rural areas and a non-cooperative approach by the public toward free testing facilities provided by the government to avoid COIVD-19. The number of issues related to COVID-19 are continuously amplifying and getting more complicated each day, leading to the situation being seen as a catastrophic failure by the government (19).

## WORLD APPROACH DURING THE PANDEMIC

During the pandemic, the world has learned some important lessons. The first lesson was that health, economy, and human development are interlinked. It is necessary that these parameters be connected to achieve UN sustainable development goals in a coordinated manner (20, 21). It should be emphasized that public health is not an individual or government matter but it is the overall responsibility of a society (22). The third key point is the importance of the development of telemedicine training courses (23), forensic training (24), and patient referral systems (25) for medical professionals and health workers. Most developed countries have developed several statistical evidence based decision-making systems (26) and this should also be extended to under-developed and non-developed countries. It was also observed that the health care system of America collapsed during corona the pandemic despite being the best health care systems in the world. Each country must improve their current ability to deal with emergencies under normal circumstances (27).

## POSSIBLE POTENTIAL SOLUTIONS

The following strategic solutions are proposed to overcome the issue of COVID-19. These solutions are:

(i) Statistical model-based forecasting tools should be developed that may help in forecasting the spread, recoveries, and deaths from the current outbreak of COVID-19 (28).

(ii) The government must increase the capacity of intensive care units equipped with ventilators and related equipment. At present, only 1,500 ventilators are available throughout the country, which is not enough to cope with the emergent situation. Similarly, only one doctor is available for every 1,720 patients. This overburdens doctors who are treating COVID-19 patients in addition to their normal patients.

(iii) There is a need to develop consensus-based national standard operating procedures (SOPs) to control the COVID-19 situation following the guidelines of the World health organization (WHO) and Center of Disease Control (CDC).

(iv) A campaign should be launched to create more awareness among people regarding the use of face masks and hand wash (29), and avoiding close contact with infected people (30).

(v) The SOPs, recommended by the Government during the month of Ramadan and Eid, must be strictly followed (31).

(vi) Currently, only 20 biosafety laboratories are operational in Pakistan, and these have a testing capability of 60,000 tests per day. The existing number of biosafety containment level 3 laboratories (BSL-3) require an additional 15 laboratories in order to achieve a target of 100,000 tests daily.

(vii) The government must announce a price limit for corona vaccines for the private sector and it should be as low as possible. It may be pointed out that many developed countries have already fixed the price of the vaccine in their countries (32).

## CONCLUSION

The virus will continue to spread all over the world till a vaccine is available for each individual. Experts believe that the virus may remain within us for many years. The human race has never experienced such a situation before. All countries of the world should unite to adopt a common strategy under the umbrella of the United Nations platform to control the disease. We must create awareness among people to observe social distancing and lockdowns and wear face (in areas of high prevalence). Serious efforts should be made at the government level without any delay to acquire vaccines and make them available to each person.

## AUTHOR CONTRIBUTIONS

The topic was devised by KK under the conceptualization and supervision of AA. KK used PubMed for literature review. All authors have read and agreed to the published final version.

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# The Impact of COVID-19 on Hospital Admissions in Croatia

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**Background:** The COVID-19 pandemic disrupted hospital care, as hospitals had to deal with a highly infectious virus, while at the same time continuing to fulfill the ongoing health service needs of their communities. This study examines the direct effects of COVID-19 on the delivery of inpatient care in Croatia.

**Materials and Methods:** The research is a retrospective, comparative analysis of the hospital admission rate across all Diagnosis Related Group (DRG) classes before and during the pandemic. It is based on DRG data from all non-specialized acute hospitals in Croatia, which account for 96% of national inpatient activity. The study also used COVID-19 data from the Croatian Institute of Public Health (CIPH).

**Results:** The results show a 21% decrease in the total number of admissions [incident rate ratio (IRR) 0.8, $p < 0.0001$] across the hospital network during the pandemic in 2020, with the greatest drop occurring in April, when admissions plunged by 51%. The decrease in activity occurred in non-elective DRG classes such as cancers, stroke, major chest procedures, heart failure, and renal failure. Coinciding with this reduction however, there was a 37% increase (IRR 1.39, $p < 0.0001$) in case activity across six COVID-19 related DRG classes.

**Conclusions:** The reduction in hospital inpatient activity during 2020, can be attributed to a number of factors such as lock-downs and quarantining, reorganization of hospital operations, the rationing of the medical workforce, and the reluctance of people to seek hospital care. Further research is needed to examine the consequences of disruption to hospital care in Croatia. Our recommendation is to invest multidisciplinary effort in reviewing response procedures to emergencies such as COVID-19 with the aim of minimizing their impact on other, and equally important community health care needs.

**Keywords: COVID-19, pandemic, health system response, hospital admissions, AR-DRG, data transparency**



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## INTRODUCTION

The World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a Public Health Emergency of International Concern on 30 January 2020, and a Pandemic on 11 March 2020 (1). The spread of the virus caused disorder in health systems across the globe as countries attempted to deal with the contagion while at the same time maintaining the integrity of their health systems. Hospitals came under pressure to meet the ongoing health service needs of the community while responding to the additional COVID-19 case load and readjusted their care priorities. The Croatian response to COVID-19 essentially followed measures adopted by other European countries that included closing borders, limiting social interaction and creating COVID-19 isolation wards within hospitals (2).

As of the end of April 2021, Croatia reported some 332,183 COVID-19 cases and 1,997 COVID-19 caused deaths per million people, which is near the median point for European countries (3). The first COVID-19 case in Croatia was diagnosed on 25 February 2020. Three weeks later, and in the face of an increasing COVID-19 patient load and growing risk of contagion, the Croatian Government took steps to adapt hospital care delivery to the perceived needs of the pandemic. In Zagreb, the national capital, three hospitals were designated as COVID-19 centers and patients with COVID-19 related conditions requiring hospital care were admitted to those facilities. Four similar centers were established in the regions and in addition, most major hospitals established COVID-19 isolation wards. Under this reorganization, 15% of hospital beds in Croatia were designated as COVID-19 beds (3,599 beds out of a total of 23,597) (4).

Concurrently, hospital staffing schedules were reorganized, and the hospital workforce was divided into two groups, with each working in 2-week shifts. The aim of this strategy was to ensure that backup staff were available to replace potentially infected and COVID-19 positive workers. This workforce management measure was in place for a period of 6 weeks and ended at the beginning of May, once the perceived risk of COVID-19 infections among hospital staff diminished.

Under revised admission procedures, only patients who tested negative for COVID-19 were admitted to general wards for non-COVID-19 related conditions. Patients who needed immediate acute care and proved to be COVID-19 positive, were treated within COVID-19 isolation wards along with other patients who required hospital care due to COVID-19 infection. The realignment of hospital care delivery and reprioritization of needs resulted in the general post-ponement of elective procedures as priority was given to the treatment of COVID-19 admitted patients and urgent non-COVID-19 cases.

The introduction of shift work in hospitals also resulted in a reduction in hospital outpatient consulting hours which most likely had an impact on the admission rate, given that non-emergency admissions in Croatia are initiated by hospital-based specialists in an outpatient setting.

The aim of the study is to assess the direct effects of COVID-19 on inpatient care delivery in Croatia, to identify which types of cases were the most affected and to examine the potential reasons for such outcomes.

## METHODS

### Study Design and Data Sources

Information sources for the study are publicly available data from the Croatian Health Insurance Fund (CHIF) and the Croatian Institute of Public Health (CIPH). The CHIF data set comprised inpatient data grouped in accordance with Australian Refined Diagnosis Related Groups (AR-DRGs), for the period 1 January 2017 to 31 December 2020 (**Supplementary Table 1**) (5). The Croatian DRG system is based on a variant of the Australian AR-DRG system, utilizing a combination of the ICD-10AM and ICD-10 classifications for the coding of diagnosis, and Australian Classifications of Health Interventions (ACHI) for the coding of procedures. The DRG grouping algorithm is based on AR-DRG version 5.2 which assigns cases to 671 DRG classes (6).

The study examined data from all non-specialized acute hospitals in Croatia that serve a population of 4.2 million people, accounting for 96% of inpatient activity. The observed hospital network comprised 11 tertiary level hospitals and 22 secondary level hospitals.

The analysis compared the number of cases recorded in each DRG class. It focused on those DRG classes that were driven by either principal diagnoses or procedures that may have signaled admissions due to COVID-19, as well as those classes related to conditions such as cancers, cardiac and respiratory disease, and stroke.

The coding of principal diagnoses for cases with COVID-19 respiratory manifestations in Croatia was based on the International Classification of Diseases (ICD10 codes)[1] which resulted in DRG class grouping as either E62A, E62B or E62C (Respiratory Infections/Inflammatory Conditions). Otherwise, if COVID-19 patients required (invasive) ventilatory support the episode was grouped as either A06Z or E40Z (Respiratory System Diagnosis & Ventilator Support). If the case involved high flow oxygen therapy, it was classified as belonging to the E41Z (Respiratory System Diagnosis and Non-Invasive Ventilation) DRG class.

For the purpose of analyzing the effect of the COVID-19 pandemic on non-COVID-19 cases, we used DRG data reported in 23 Major Diagnostic Categories (MDC) which represent the grouping of patients based on their principal diagnoses which, according to DRG coding practice, is generally the main reason for admission (7). Each MDC corresponds to a single body system or etiology, and the system is harmonized with the ICD10 classification structure.

The study also utilized the COVID-19 data set provided by the CIPH and which incorporated information on reported national incidence of the COVID-19 virus, including the total number of COVID-19 related hospital admissions and the number of patients on ventilators (**Supplementary Table 2**) (8). The CIPH classified COVID-19 admissions as those cases that have a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It used WHO's COVID-19 coding guidelines as the standard for COVID-19 reporting by Croatian hospitals, and all admitted COVID-19 positive cases were identified by ICD10 code U07.1 (Covid-19, virus identified) as the secondary diagnosis.

Our study did not require informed consent nor ethical approval given that the data used were completely anonymized and publicly available from CHIF and the CIPH in compliance with Croatian data protection regulations.

[1] ICD10 codes: J01.-; J02.-; J03.-; J04.-; J05.-; J06.-; J12.-; J18.-; J20.-; J21.-; and J22.-.

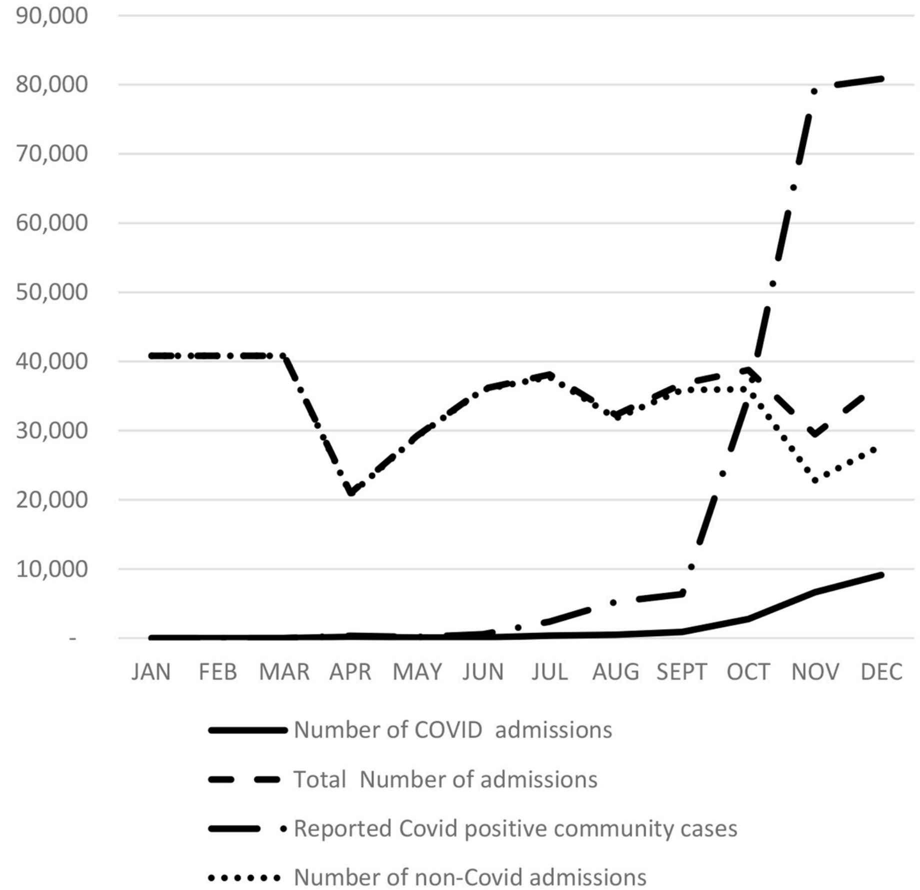


**FIGURE 1 |** Comparison of Total Monthly Admissions, COVID-19 Related and non-COVID-19 Admissions. Source: Monthly admission data from CHIF—January, February, March data is an average for the first quarter of 2020; Covid-19 admission data from PHI (PHI begun recording Covid-19 data on 14th April, 2020).

## Data and Statistical Analysis

As the first step of the data analysis we calculated changes in hospital admissions and compared the average number of acute inpatient cases over a 3-year period (2017–2019) with the number of cases over a 12-month period in 2020. We used DRG data grouped in MDCs in order to determine the extent to which, and for which conditions the onset of the pandemic altered the pre-COVID-19 casemix across the hospital network.

The next step of the analysis involved calculating changes to hospital admissions for six COVID-19 related DRG classes. Thereafter, we calculated changes in inpatient activity in non-COVID-19 related DRG classes for case groups that included cancer, cardiovascular diseases and stroke.

For each of the two time periods (2017–2019 and 2020) the incidence rate ratio for all MDCs, COVID-19 and cancer related DRGs classes was calculated as a number of events (inpatient admissions) divided by the total population during the two respective time periods (based on the Croatian Bureau of Statistics population estimates for 2017-2021).[2]

[2]https://www.dzs.hr/hrv/publication/StatisticsInLine.htm

The IRR was estimated as a ratio of the incidence rate for 2020 to that for 2017–2019. The 95% confidence interval limits for the IRR were estimated using the Wald method. Additionally, $p$-values of a Pearson chi-square test for the hypothesis of IRR being equal to one (i.e., the hospitalization incidence rate in 2020 being equal to that in 2017–19) were calculated. All statistical analyses were performed using SAS 9.4 with significance level set at $p < 0.05$. (SAS Institute Inc., Cary, NC, USA).

# RESULTS

The CIPH began reporting COVID-19 data on 14 April 2020. In 2020 it recorded 20,609 hospital admissions with a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For 2020, the total number of admissions compared to average admission for the previous 3 years decreased by 21% (an average of 532,860 cases between 2017 and 2019 to 420,890 cases in 2020). The decline in the number of admissions was similar in both tertiary and secondary level hospitals.

**Figure 1** shows monthly inpatient case activity for 2020 in the 33 hospitals covered in the study (based on CHIF data), along

**TABLE 1 |** Comparison of DRG case activity before, and during Covid 19 in 2020.

| Major diagnostic categories (diseases, disorders and other conditions) | DRG cases | | | | | | | | | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2017–19 Average tertiary hospitals | 2017–19 Average secondary hospitals | 2017–19 Average total hospitals | 2020 Total tertiary hospitals | 2020 Total secondary hospitals | 2020 All hospitals | % Change tertiary hospitals | % Change secondary hospitals | % Change total hospitals | |
| PRE - MDC | 3,388 | 1,544 | 4,932 | 3,636 | 1,609 | 5,245 | 7% | 4% | 6% | 0.0003 |
| 01-Nervous system | 23,241 | 17,383 | 40,624 | 18,056 | 13,722 | 31,778 | −22% | −21% | −22% | <0.0001 |
| 02-Eye | 13,223 | 6,245 | 19,468 | 7,329 | 3,096 | 10,425 | −45% | −50% | −46% | <0.0001 |
| 03-Ear, nose, mouth and throat | 13,204 | 7,646 | 20,850 | 8,286 | 4,495 | 12,781 | −37% | −41% | −39% | <0.0001 |
| 04-Respiratory system | 19,350 | 19,343 | 38,693 | 18,662 | 19,392 | 38,054 | −4% | 0% | −2% | 00.4321 |
| 05-Circulatory system | 38,036 | 24,537 | 62,573 | 30,132 | 18,885 | 49,017 | −21% | −23% | −22% | <0.0001 |
| 06-Digestive system | 28,526 | 22,420 | 50,946 | 23,422 | 16,900 | 40,322 | −18% | −25% | −21% | <0.0001 |
| 07-Hepatobiliary system and pancreas | 15,687 | 10,465 | 26,152 | 11,324 | 8,719 | 20,043 | −28% | −17% | −23% | <0.0001 |
| 08-Musculoskeletal system and connective tissue | 35,314 | 21,352 | 56,666 | 27,404 | 16,876 | 44,280 | −22% | −21% | −22% | <0.0001 |
| 09-Skin, subcutaneous tissue and breast | 12,542 | 7,298 | 19,840 | 8,338 | 5,090 | 13,428 | −34% | −30% | −32% | <0.0001 |
| 10-Endocrine, nutritional and metabolic diseases | 11,651 | 4,533 | 16,185 | 7,352 | 2,831 | 10,183 | −37% | −38% | −37% | <0.0001 |
| 11-Kidney and urinary tract | 14,933 | 11,697 | 26,630 | 11,852 | 9,183 | 21,035 | −21% | −21% | −21% | <0.0001 |
| 12- Male reproductive system | 5,093 | 3,010 | 8,103 | 3,719 | 1,931 | 5,650 | −27% | −36% | −30% | <0.0001 |
| 13- Female reproductive system | 12,590 | 7,758 | 20,348 | 9,062 | 5,920 | 14,982 | −28% | −24% | −26% | <0.0001 |
| 14-Pregnancy, childbirth and puerperium | 28,236 | 22,864 | 51,100 | 25,588 | 21,132 | 46,720 | −9% | −8% | −9% | <0.0001 |
| 15-Newborns and other neonates | 5,234 | 3,854 | 9,088 | 4,509 | 3,672 | 8,181 | −14% | −5% | −10% | <0.0001 |
| 16- Blood, blood forming organs, immunological | 3,268 | 2,323 | 5,591 | 2,428 | 1,910 | 4,338 | −26% | −18% | −22% | <0.0001 |
| 17- Hematological and solid neoplasms | 11,312 | 3,246 | 14,558 | 9,734 | 3,387 | 13,121 | −14% | 4% | −10% | <0.0001 |
| 18-Infectious and parasitic diseases | 5,726 | 5,915 | 11,641 | 4,745 | 5,371 | 10,116 | −17% | −9% | −13% | <0.0001 |
| 19-Mental diseases and disorders | 5,966 | 6,365 | 12,331 | 4,331 | 4,691 | 9,022 | −27% | −26% | −27% | <0.0001 |
| 20-Alcohol/drug use and induced disorders | 1,413 | 1,852 | 3,265 | 988 | 1,237 | 2,225 | −30% | −33% | −32% | <0.0001 |
| 21-Injuries, poisonings and toxic effects of drugs | 2,398 | 1,945 | 4,342 | 1,712 | 1,444 | 3,156 | −29% | −26% | −27% | <0.0001 |
| 22-Burns | 324 | 174 | 498 | 219 | 125 | 344 | −32% | −28% | −31% | <0.0001 |
| 23-Factors influencing health status | 5,629 | 1,181 | 6,811 | 4,384 | 1,022 | 5,406 | −22% | −13% | −21% | <0.0001 |
| ERROR DRG | 991 | 636 | 1,627 | 548 | 490 | 1,038 | −45% | −23% | −36% | <0.0001 |
| **Total** | **317,274** | **215,586** | **532,860** | **247,760** | **173,130** | **420,890** | **−22%** | **−20%** | **−21%** | **<0.0001** |

*Source: CHIF and authors calculation.*

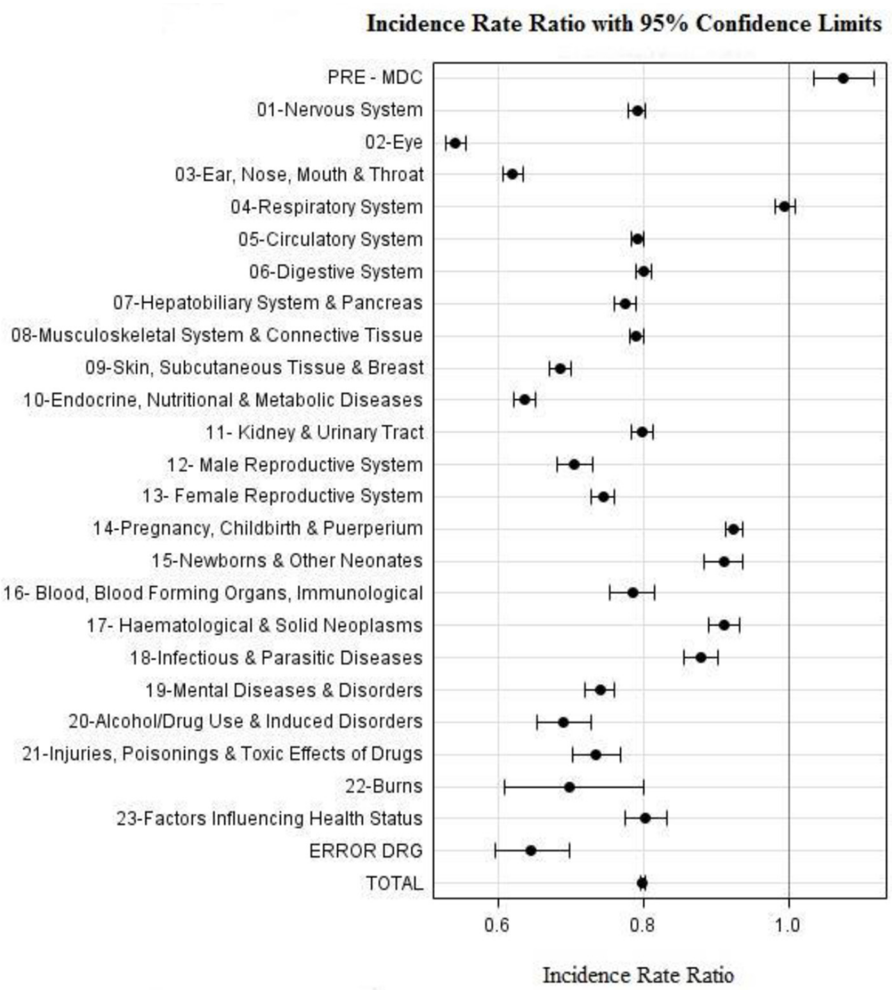


**FIGURE 2 |** Incidence Rate Ratio per MDC during 2020 as compared to period 2017–2019.

with the number of reported COVID-19 cases in the community and monthly admissions of patients with a COVID-19 diagnosis (based on CPHI data). The average monthly admission rate over the 3-year pre-COVID period was 44,400 cases, and it stood at an average of 40,810 cases for the first 3 months of 2020 (monthly DRG data was not available for the first 3 months of 2020). The first significant impact of COVID-19 on DRG activity was felt in April 2020 when admissions plunged by ~51% to 20,963 cases. This was the lowest monthly level of acute inpatient activity for 2020. Monthly admissions increased to 36,022 cases in June and oscillated at this level for the remainder of the year.

According to CIPH data, the COVID-19 hospital admission rate was relatively modest until September when the incidence of COVID-19 in the community begun to spike. The number of COVID-19 admissions grew dramatically from 888 cases in September to 9,120 cases in December 2020. During the same period, non-COVID related monthly case activity decreased by 36%, from 35,877 cases in September to a low of 22,822 in November, at a time when the incidence of COVID in the community was peaking.

**Table 1** compares the average 3-year (2017–2019) pre-COVID DRG case activity to that of 2020 expressed in MDCs. While the average decrease in activity was 21% ($p < 0.0001$), the MDCs in which the decrease in activity was considerably greater than the average included diseases and disorders related to: the Eye by 46% ($p < 0.0001$); Ear Nose and Throat by 39% ($p < 0.0001$); Skin, Subcutaneous Tissue and Breast by 32% ($p < 0.0001$); Endocrine, Nutritional and Metabolic by 37% ($p < 0.0001$); Male Reproductive System by 30% ($p < 0.0001$); Female Reproductive System by 26% ($p < 0.0001$); Mental Diseases and Disorders by 27% ($p < 0.0001$); Alcohol/Drug Use and Induced Disorders by 32% ($p < 0.0001$); Injuries, Poisonings and Toxic Effects of Drugs by 27% ($p < 0.0001$); and Burns by 31% ($p < 0.0001$). **Figure 2** shows corresponding IRRs calculated for every MDC.

MDCs for which the decrease in case activity was less than the average included medical conditions related to: Respiratory System decreasing by 2% ($p = 0.4321$); Pregnancy, Childbirth and Puerperium by 9% ($p < 0.0001$); Newborns and Other Neonates by 10% ($p < 0.0001$); Hematological and Solid Neoplasms by 10% ($p < .0001$); and Infectious and Parasitic Diseases by 13%

($p < 0.0001$). The only MDC experiencing an increase (6%) in activity was Pre-MDC which includes mechanical ventilation DRG (A06Z) episodes which are most likely associated with COVID-19 cases ($p = 0.0003$).

**Table 2** is based on CHIF data and shows the difference in case activity across six DRG respiratory classes attributable to COVID-19. The data shows an 37% increase in activity in this category, from an average of 17,875 cases over the 3-year pre-COVID period to 24,533 cases in 2020 ($p < 0.0001$). The increase was greater in tertiary level hospitals at 45%, compared to 31% in secondary level hospitals. An exception was DRG class E41Z Respiratory System Diagnosis with Non-Invasive Ventilation for which tertiary hospitals reported a 21% decrease in case activity, while secondary hospitals reported a 112% increase. As shown in **Figure 3**, we found that IRRs for all six respiratory DRG classes is >1.

**Table 3** shows case activity differences for DRG classes related to the treatment of cancers including DRG classes attributed to both malignancy and neoplastic conditions. Case numbers in these groups decreased by 14%, from an average of 44,206 in the 3 previous years, to 38,176 in 2020 ($p < 0.0001$). Tertiary hospitals experienced a decrease of 16% in cancer and neoplasm related admissions, while secondary level hospitals had a 6% decrease in such admissions. Cancer related DRG classes which experienced greatest reductions in activity were: Respiratory Neoplasms (28%; $p < 0.0001$); Malignancy in the Hepatobiliary System and Pancreas (27%; $p < 0.0001$); Malignancy Male Reproductive System (22%; $p < 0.0001$); and Malignancy Female Reproductive System (38%; $p < 0.0001$). DRG cancer classes in which reduction in activity was below the average included: ENT malignancy (3%; $p = 0.7115$); Procedures of Malignant Breast (7%; $p = 0.0130$); Malignant Breast Disorders (12%; $p = 0.0076$); and Lymphoma and Leukemia (12%; $p < 0.0001$). The only cancer related DRG class in which there was more activity during 2020, was Digestive Malignancy which increased by 11% ($p < 0.0001$). **Figure 4** shows IRR values for cancer related DRGs ($1 <$ IRRs $< 1$) which indicate that oncology case types were affected by the COVID-19 response in different ways.

In addition to cancers, activity data indicates decreases in admissions for the following non-elective DRG classes: Stroke (15%); Transitory Ischemic Attack (27%); Major Chest Procedures (31%); Chronic Obstructive Airway (55%); Coronary Bypass (24%); Procedures and Conditions related to Circulatory Disorders (27%); Heart Failure and Shock (13%); Coronary Atherosclerosis (38%); Hypertension (43%); Arrhythmia (26%); Rectal resection (17%); and Renal Failure (15%).

Notably, 2020 saw a 26% decrease in DRG classes attributed to endoscopic diagnostic procedures such as colonoscopies and gastroscopies, compared to the average for the previous 3 years.

## DISCUSSION

### Observations

General admissions in Croatian hospitals in 2020 fell by 112,000 (21%) over the study period despite the additional 20,609 COVID-19 related inpatient admissions reported by the CIPH. An initial dip in admissions occurred in April 2020, soon

**TABLE 2** | Difference in activity in Covid 19 related DRG classes before, and during Covid 19 in 2020.

| DRG no | DRG description | DRG cases | | | | | | | | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2017–19 Average tertiary hospitals | 2017–19 Average secondary hospitals | 2017–19 Average of all hospitals | 2020 Total tertiary hospitals | 2020 Total secondary hospitals | 2020 All hospitals | % Change tertiary hospitals | % Change secondary hospitals | % Change total hospitals | |
| A06Z | Tracheostomy or ventilation > 95 | 1,951 | 1,231 | 3,181 | 2,424 | 1,492 | 3,916 | 24% | 21% | 23% | <0.0001 |
| E40Z | Resp sys dx + ventilator suppt | 139 | 155 | 295 | 271 | 212 | 483 | 94% | 36% | 64% | <0.0001 |
| E41Z | Resp sys dx + non-invas ventiln | 573 | 122 | 695 | 454 | 259 | 713 | −21% | 112% | 3% | 0.4925 |
| E62A | Respiratory infectn/inflamm + ccc | 765 | 1,148 | 1,914 | 971 | 1,284 | 2,255 | 27% | 12% | 18% | <0.0001 |
| E62B | Respiratory infectn/inflam + smcc | 3,146 | 4,169 | 7,315 | 5,230 | 5,762 | 10,992 | 66% | 38% | 50% | <0.0001 |
| E62C | Respiratory infectn/inflamm-cc | 1,571 | 2,904 | 4,475 | 2,484 | 3,690 | 6,174 | 58% | 27% | 38% | <0.0001 |
| | **Total** | **8,146** | **9,730** | **17,875** | **11,834** | **12,699** | **24,533** | **45%** | **31%** | **37%** | **<0.0001** |

*Source: CHIF and authors calculation.*

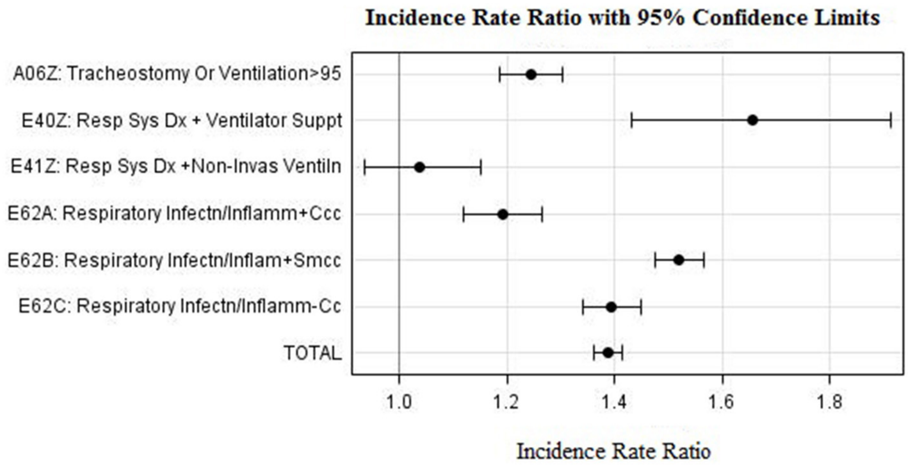


**FIGURE 3 |** Incidence Rate Ratio for COVID-19 related DRGs during 2020 as compared to period 2017–2019.

after the WHO declared COVID-19 a pandemic. In that period, Croatia experienced a 51% drop in hospital admissions, a trend also observed to varying degrees in other countries, across a number of medical specialties and emergency department visits (9–16).

An article by Willan, King et al. published in the British Medical Journal on 20th March 2020 at the onset of the pandemic, reflected that the UK government saw itself on war footing in its fight against the virus. The authors anticipated a need to reorganize hospital departments and to redeploy the hospital workforce in the face of an escalating COVID-19 patient load, while fewer staff are available due to infections. Importantly, they foresaw a situation where such pressures would impact adversely on the established standards of care to the extent that some patients may be harmed due shortcomings in treatment (17).

As the pandemic unfolded however, many countries reported a general decrease in hospital inpatient activity (14, 15, 18, 19) and our study shows that this was also the case in Croatia.

We show that Croatia experienced both a decrease in inpatient activity and decline in non-elective admissions for conditions which incidence is not related to the COVID-19 pandemic, but which otherwise pose a serious health risk if left untreated. In the case of cardiovascular diseases, we calculated a 26% decrease in cases over the study period. By comparison, various studies provide the following results: a United Kingdom (UK) study reported a 58% decrease in cardiovascular cases in March 2020 (9); an Italian study a decrease of 26% (11) during the same period; a US study a decrease of 45% (14); a German study reported a 13–28% decline in interventional treatments for heart failure and cardiac arrhythmias (20); and a multinational study of 12 EU countries showed a 30% reduction in acute coronary syndrome cases during the COVID-19 outbreak (21).

In the case of stroke, our study found that Croatia experienced a 15% decrease in stroke related DRG cases over the study period. In comparison, a UK study reported a 40% reduction in stroke cases over March and April of 2020 (22).

Our study also revealed a disruption in cancer care during the COVID study period. We found a 14% decline in admissions related to cancer and other neoplasms, with the greatest reductions occurring in DRGs attributable to Respiratory Neoplasms (28%) and Malignancy in the Hepatobiliary System (27%). This disruption in cancer treatment was also reported in other countries (23). In Germany, a study reported a 10–20% decrease in cancer related hospital admissions (20) and an Italian study reported a 32% drop in oncology related surgical procedures between March and June 2020 (16). Moreover, a UK study projected that delays in early diagnosis and treatment of cancers will, over a 5-year period, increase cancer mortality rates in the following categories: breast (9%), colorectal (16%), lungs (5%), and esophageal (6%) (24). Another UK study predicted that the cancer mortality rate may increase by 20% over a 12-month period, resulting in ∼6,000 additional deaths (25).

Though there does not appear to be a single reason for the general decline in inpatient activity in Croatia, contributing factors are likely to include: disruption within the hospital system given its reorganization to address the perceived requirements of the pandemic; the reluctance of people with healthcare needs to seek hospital care in the face of the perceived threat of acquiring a COVID-19 infection in a hospital setting; hospital staff shortages due to infection and illness among the health workforce; the reprioritization of elective procedures by hospitals; and a decrease in the non-emergency admission referral rate due to the reduction in outpatient hours.

There is however, evidence from international sources to support the argument that patient reluctance to attend hospitals could be a major contributing factor. For example, a number of studies on emergency department (ED) admissions during the COVID-19 pandemic report reductions in both daily attendances and surgical admissions through EDs, indicating that patients may not be presenting for needed care (10, 12, 13, 26). Such patient behavior was investigated in an Italian study (27)

**TABLE 3 |** Difference in case activity in cancer and neoplasm related DRG classes before, and during Covid 19 in 2020.

| DRG Names | DRG cases | | | | | | | | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2017–19 Average tertiary hospitals | 2017–19 Average secondary hospitals | 2017–19 Average of all hospitals | 2020 Total tertiary hospitals | 2020 Total secondary hospitals | 2020 All hospitals | % Change tertiary hospitals | % Change secondary hospitals | % Change total hospitals | |
| B66A, B66B - nervous system neoplasms | 1,113 | 822 | 1,936 | 913 | 679 | 1,592 | −18% | −17% | −18% | <0.0001 |
| D60A, D60B - ear nose mouth and throat malignancy | 907 | 237 | 1,144 | 907 | 207 | 1,114 | 0% | −13% | −3% | 0.7115 |
| E71A, E71B, E71C - respiratory neoplasms | 4,202 | 1,840 | 6,042 | 2,854 | 1,467 | 4,321 | −32% | −20% | −28% | <0.0001 |
| G60A, G60B - digestive malignancy | 5,728 | 1,872 | 7,600 | 6,405 | 2,061 | 8,466 | 12% | 10% | 11% | <0.0001 |
| H61A, H61B - malignancy in the hepatobiliary system | 4,659 | 1,195 | 5,854 | 2,782 | 1,499 | 4,281 | −40% | 25% | −27% | <0.0001 |
| J06A, J07A - procedures of malignant breast | 2,505 | 914 | 3,418 | 2,358 | 822 | 3,180 | −6% | −10% | −7% | 0.0130 |
| J62A, J62B - malignant breast disorders | 735 | 296 | 1,031 | 707 | 196 | 903 | −4% | −34% | −12% | 0.0076 |
| L03A, L03B - kidney, urinary tract neoplasm procedures | 1,085 | 295 | 1,380 | 932 | 219 | 1,151 | −14% | −26% | −17% | <0.0001 |
| L62A, L62B - kidney, urinary tract neoplasm conditions | 457 | 383 | 841 | 410 | 291 | 701 | −10% | −24% | −17% | 0.0008 |
| M60A. M60B - malignancy male reproductive system | 452 | 433 | 884 | 361 | 326 | 687 | −20% | −25% | −22% | <0.0001 |
| N60A, N60B - malignancy female reproductive system | 1,511 | 540 | 2,051 | 817 | 447 | 1,264 | −46% | −17% | −38% | <0.0001 |
| R01 to R04 - neoplastic procedures, lymphoma, leukemia, and other hematol. | 1,530 | 594 | 2,124 | 1,277 | 487 | 1,764 | −17% | −18% | −17% | <0.0001 |
| R60 to R62 - neoplastic conditions, lymphoma, leukemia, and other hematol. | 7,672 | 2,229 | 9,901 | 6,475 | 2,277 | 8,752 | −16% | 2% | −12% | <0.0001 |
| **Total** | **32,556** | **11,650** | **44,206** | **27,198** | **10,978** | **38,176** | **−16%** | **−6%** | **−14%** | **<0.0001** |

*Source: CHIF and authors calculation.*

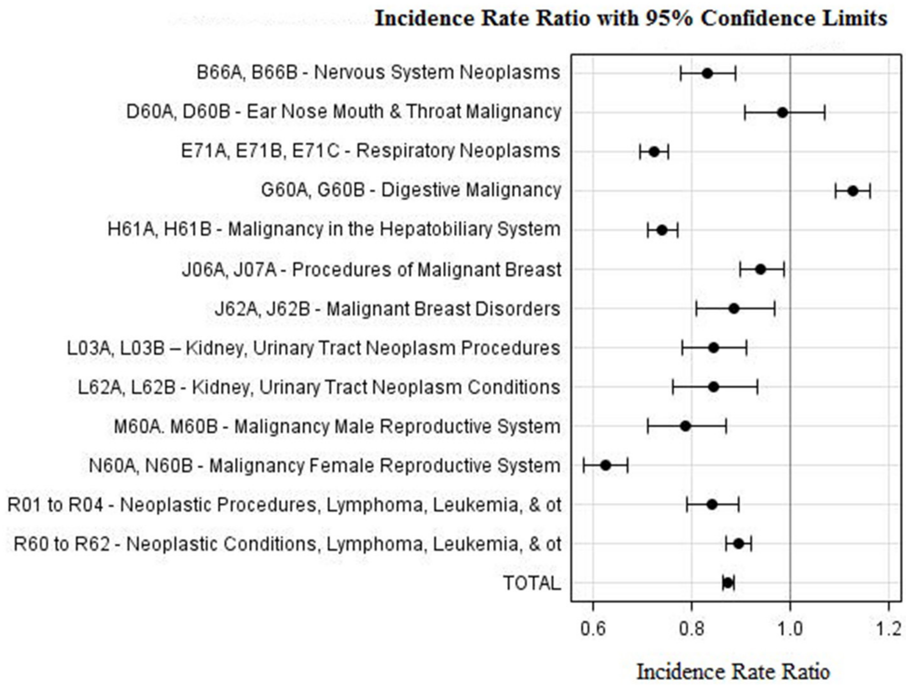


**FIGURE 4 |** Incidence Rate Ratio Cancer and Neoplasm related DRGs during 2020 as compared to period 2017–2019.

which found that 32% of the cohort surveyed, faced delays in scheduled services, 12% refused to attend scheduled services for fear of contagion, 6% avoided health services despite the onset of an acute issue, and 1.5% avoided EDs when in need. Deerberg-Wittram and Knothe propose that avoidance of care by patients in a situation such as the COVID-19 pandemic is an example of Dread Risk, which is a behavioral response in which rare and unexpected events like the pandemic, can trigger irrational risk evading responses such as avoiding hospitals due to the perceived risk of infection, while ignoring the risk that such behavior may result in more serious consequences for the person's health (26). Reichardta et al. provide further evidence of such behavior reporting that German states with increased incidence of COVID-19 experienced a greater decrease in hospital admissions (20).

Though post-poning elective interventions may be acceptable over the short term in order to deal with pressing needs at times of emergencies, such post-ponements are likely to exert pressure on hospitals in the longer term as they endeavor to address growing waitlists. According to data from the UK National Health Service (NHS), the waitlist of people awaiting treatment in England at the end of February 2021 was the highest since NHS records began in 2007 and stood at 4.7 million people, while the number of patients who were waiting more than 52 weeks for routine operations and procedures increased by 73% between December 2020 and February 2021 (28).

In summary, as in many other countries, the instinctive response of health authorities in Croatia to the sudden onset of COVID-19 was to address the perceived priority needs of COVID-19 patients. Analysis of DRG data reveals that, as the pandemic unfolded, this response resulted in a general reduction of hospital inpatient services, including the treatment of non-COVID-19 priority needs. The potential consequences of this drop in inpatient services in Croatia may result in increased mortality rates over the coming years for diseases such as cancer and heart conditions (11, 24).

Future studies using DRG data can reveal to what extent inpatient activity recovers over the coming years from the COVID-19 period. If the findings show, however, that the reduction in activity in certain DRG classes becomes more permanent over time, such studies may also include a re-evaluation of the historic need and clinical necessity of these types of admissions.

## Strengths and Limitations

The underlying strength of this study is the utilization of a full data set on inpatient activity for all non-specialist hospitals in Croatia which account for 96% of all acute impatient activity. It is also the first systematic attempt to describe the impact of SARS-CoV-2 pandemic on acute hospital admissions in Croatia.

The limitations of the study are two-fold. The first is related to the quality of DRG coding and the second concerns the COVID-19 admission data reporting standards.

We expect that the quality of the DRG data in Croatia is adequate for the calculation of inpatient activity given that it is audited by the CHIF and used for hospital payment purposes. Some anomalies may exist however, as in the case where our data shows a 21% decrease in activity in the DRG class E41Z in tertiary level hospitals, whereas secondary hospitals show a 112% increase in activity in the same class. While there may be other reasons for this unexpected result, a potential cause of the difference may be the incorrect coding by secondary hospitals of oxygen therapy as non-invasive ventilatory support. Nonetheless, anomalies such as this, should not have any bearing on the findings of this study.

The matter of COVID-19 admission data reporting standards relates to the question whether cases which were reported as COVID-19 were admitted in order to treat symptoms of COVID-19. CHIF's DRG data shows that there was an increase of 6,658 cases (from the average of 17,875 over the 3-year pre-COVID-19 period, to 24,533 cases in 2020), in the six DRG respiratory classes in which cases could be attributed to treatment for COVID-19. However, this finding does not correspond with CIPH data which reported that Croatian hospitals had 20,609 COVID-19 admissions in 2020. Though the reason for this difference requires further investigation, the variance may be due to the fact that admitted cases reported as COVID-19 by CIPH, may have included admissions for reasons other than respiratory manifestations due to COVID-19. The COVID-19 reporting protocol in use by the CIPH is that every patient seeking hospital care is tested at the point of admission and those who test positive are reported as COVID-19, even if they were asymptomatic.

## Conclusions

The regular and frequent publication of DRG activity data provides opportunities for timely decision making in responding to unfolding emergencies situations such as COVID-19. Moreover, an in-depth analysis of the DRG data set can provide insights into utilization patterns, epidemiology and care outcomes, including mortality rates (29).

Though it appears Croatia has responded comparatively well to the COVID-19 emergency, there is room for improvement. One lesson Croatia can draw from this experience is the need to develop strategies and processes whereby the response to pandemics is not necessarily at the expense of other and equally important community health care needs (30).

One area for improvement is that while the response should be timely, public health authorities need to react proportionally, taking into account the population-wide health risk as the pandemic evolves and inform the public accordingly. The strategy should include an evaluation of the consequences to population health if resources are moved from one care need to another. For hospitals, it would mean that their pandemic response is phased-in as well as possible in line with actual clinical need and organized around specialist task groups with the aim of minimizing disruption to the provision of other services. This approach however, would require the organization of hospitals to become more pliant in their ability to react to changing conditions, and to present as safe patient environments at times of contagion.

In addition, greater use of telemedicine would enhance access to care at a time when distancing measures are in place, and a well-targeted information campaign would educate the public of the deleterious consequences of not seeking care.

## 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

KKar, KKal, and SO led study design. KKar and RM were responsible for the statistical analyses. KKal wrote the first draft of the paper. All authors contributed to the development of the research question, study design in relation to the Croatian DRG hospital data, interpretation of the results, critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.720948/full#supplementary-material

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# Keeping Meta-Analyses Hygienic During the COVID-19 Pandemic

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Despite the massive distribution of different vaccines globally, the current pandemic has revealed the crucial need for an efficient treatment against COVID-19. Meta-analyses have historically been extremely useful to determine treatment efficacy but recent debates about the use of hydroxychloroquine for COVID-19 patients resulted in contradictory meta-analytical results. Different factors during the COVID-19 pandemic have impacted key features of conducting a good meta-analysis. Some meta-analyses did not evaluate or treat substantial heterogeneity ($I^2 > 75\%$); others did not include additional analysis for publication bias; none checked for evidence of *p*–hacking in the primary studies nor used recent methods (i.e., *p*-curve or *p*-uniform) to estimate the average population-size effect. These inconsistencies may contribute to contradictory results in the research evaluating COVID-19 treatments. A prominent example of this is the use of hydroxychloroquine, where some studies reported a large positive effect, whereas others indicated no significant effect or even increased mortality when hydroxychloroquine was used with the antibiotic azithromycin. In this paper, we first recall the benefits and fundamental steps of good quality meta-analysis. Then, we examine various meta-analyses on hydroxychloroquine treatments for COVID-19 patients that led to contradictory results and causes for this discrepancy. We then highlight recent tools that contribute to evaluate publication bias and p-hacking (i.e., *p*-curve, *p*-uniform) and conclude by making technical recommendations that meta-analyses should follow even during extreme global events such as a pandemic.

**Keywords: COVID−19, meta-analysis, heterogeneity, publication bias, hydroxychloroquine**

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## BACKGROUND

The 2020 COVID-19 pandemic has highlighted the urgent need for the development and administration of a new treatment for COVID-19. Despite the rollout of several different vaccines globally, the need to find treatment remains essential given the uncertainty and shortcomings with equal distribution of vaccines and vaccine availability. Meta-analyses have historically been used to establish the existence, size, and confidence of therapeutic effects or causes of particular diseases.

Meta-analysis is an important tool to determine the effectiveness of COVID-19 treatments, but it is essential that the strength of evidence be maintained by adhering to all components of the methodology. Various factors during the COVID-19 pandemic, including time pressure, have resulted in alterations and omissions of key aspects of meta-analysis that lower the quality of evidence. Some meta-analyses did not evaluate publication bias, nor treat substantial heterogeneity ($I^2 > 75\%$); none checked for evidence of *p*–hacking in the primary studies nor used recent techniques (i.e., *p*-curve or *p*-uniform) to estimate average population-size effect. Journals greatly favor publishing significant findings in comparison to non-significant findings, resulting in publication bias which can overestimate effect sizes (the strength of the relationship between two variables). These discrepancies may contribute to opposing results in the research evaluating COVID-19 treatments. A prominent example of this is the use of hydroxychloroquine (HCQ), where some studies reported a large protective effect, whereas others indicated no significant effect or even increased mortality when HCQ was administered with the antibiotic azithromycin.

In this paper, we first highlight the benefits and fundamental steps of meta-analytical studies. Then, we analyze examples of meta-analyses of HCQ treatments for COVID-19 patients that led to contradictory results and causes for this discrepancy. We conclude by making recommendations that meta-analyses should follow even during extreme global events such as a pandemic (see **Table 1**).

# METHODS

## Meta-Analysis: Principles and Procedures

Meta-analysis involves a set of statistical techniques to synthesize effect sizes of several studies on the same phenomenon (2, 3). Several benefits are expected from clinical meta-analyses:

- Identify, screen, select, and include studies based on systematic reviews of the literature (i.e., as recommend by the PRISMA Statement) (7).
- Compute the mean effect sizes across different studies (i.e., the average effect of a particular treatment on a specific condition).
- Evaluate the level of heterogeneity (i.e., the amount of variation in the outcomes detected by the different studies).
- Determine the impact of publication bias (i.e., the lack of publication of negative trials and underrepresentation of unpublished data, can lead to overestimated effect sizes).
- Run meta-regressions and subgroup analyses to control for the effects of studies' characteristics (e.g., design, procedure, measures) and sample (e.g., age/gender, BMI, clinical history).

Meta-analyses begins by identifying, screening, and evaluating potentially relevant studies, and ultimately collecting data from included studies and evaluating their quality (through PRISMA, for instance) (7). The mean and variance of the estimates is collected from every included study to compute a global weighted mean based on the inverse variance (2, 3). Some recent meta-analyses on the effect of HCQ in COVID-19 patients have omitted basic practices to assess publication bias (8), resulting in massive untreated heterogeneity (8) (i.e., $I^2 > 80\%$) or meta-analyzed small sets of studies [$k \leq 3$ implying low statistical power (9)]. None used recent tools to evaluate *p*-hacking and recent techniques for assessing the publication bias, possibly leading to an overall biased representation of the population-size effect.

## Gathering the Studies

The first step in conducting a meta-analysis is to search the literature for studies investigating a specific predefined question and using predetermined inclusion and exclusion criteria based on theoretical or methodological criteria (7) to determine eligibility. Several methods exist to assess and correct for publication bias among a set of studies (e.g., Egger or PET-PEESE tests, *p*-uniform, *p*-curve) (5, 10). A general issue is that studies likely differ significantly in design (e.g., randomized controlled trial vs. observational studies) and the specific questions they investigate (e.g., viral load, shedding, mortality/ICU events, mild symptoms). For instance, investigators must decide whether observational or quasi-experimental studies should be included alongside experimental studies. The lack of randomization inherent to observational or quasi-experimental studies is problematic as they are at risk of bias by uncontrolled confounding variables (11).

Recent advances in techniques question the reliance on estimates presented in the original studies for meta-analysis due to significant limitations (12). Systematic reviews and meta-analyses that use individual patient data (IPD) suggest collecting, validating, and reanalyzing the raw data from all clinical trials included in the meta-analysis. Following COCHRANE recommendations, IPD meta-analyses offer a multidisciplinary and cross-cultural perspective that decreases cultural and professional biases. IPD analyses also enable better assessment of moderator variable impact and improves statistical power (13). Integrating contextual variables helps ensure main effects are not explained by sample or country characteristics (or any other contextual factors). Limitations of including such variables are potential collinearity with other variables or insufficient precision in the measure. Although there are several advantages of conducting IPD meta-analyses, it also requires significant organization and coordination that can be challenging.

## Statistical Power

A major strength of meta-analysis is the relatively high statistical power associated with compiling several studies (i.e., independent RCTs may have few participants per group limiting their statistical power). The median number of studies in the Cochrane Database for Systematic Reviews is six, according to Borenstein et al. (2). This is a serious concern considering that (1) subgroup analysis and meta-regressions are routine procedures that require high levels of statistical power, and (2) many meta-analyses have high heterogeneity ($I^2 > 75\%$), which negatively affects precision and thus statistical

**Abbreviations:** AZ, Azithromycin; COVID-19, Coronavirus disease 2019; CQ, Chloroquine; EUA, Emergency-use authorization; FDA, Food and Drug Administration; HCQ, Hydroxychloroquine; HR, Hazard ratio; ICU, Intensive care unit; IPD, Individual patient data; OR, Odd ratio; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; RCT, Randomized controlled trial; RR, Risk ratio.

**TABLE 1 |** General recommendations for meta-analysis of clinical studies.

1. Include published and unpublished studies on the basis of inclusion/exclusion criteria (e.g., designs, measures, sample characteristics). Ideally, pre-register your meta-analysis on an accessible server (1) (e.g., PROSPERO database, Open Science Framework)
2. Systematically run heterogeneity tests ($Q$ statistic, the variance between studies ($\tau^2$), and the relationship between the real heterogeneity and the total variation observed, $I^2$). Some depend on the number of participants ($Q$) whereas other depends on the metric scale ($\tau^2$) so it is crucial to compare them to estimate true heterogeneity (2, 3)
3. In case of substantial heterogeneity (i.e., $I^2 > 75\%$), create homogenous subgroups based on theoretical or methodological justifications (4)
4. Estimate publication bias using funnel plots and inferential tests (i.e., Begg's/Egger's tests). In case of publication bias, run additional analysis comparing the main results with/without these studies (2, 3)
5. Evaluate *p*-hacking using *p*-curve. If H0 is true (no effect), the *p*-distribution must be uniform but right-skewed if there is an effect. In case of signs of *p*-hacking, exclude those studies and run again the analysis to compare the results (5)
6. Conduct separate analyses for observational, quasi-experimental, and experimental studies and evaluate the risk of bias for each study (6).

power. For example, the statistical power to detect a small effect size ($d = 0.2$) with 25 participants per group in 6 different studies using a random-effects model with moderate heterogeneity ($I^2 = 50\%$) and a 5% of type I error is only 26.7% (https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/power-calculator-tool.html).

## Assessing Heterogeneity

The objective of meta-analysis is not simply to calculate an average weighted effect estimate but also to make sense of the pattern of effects. An intervention that consistently reduces the risk of mortality by 30% in numerous studies is different from an intervention that reduces the risk of mortality by 30% on average, with a risk reduction ranging from 10 to 80% across studies. We must determine the true variance to provide different perspectives on the dispersion of the results based on the $Q$ statistic, the variance between studies ($\tau^2$), and the relationship between the real heterogeneity and the observed total variation ($I^2$).

## Publication Bias

Publication bias affects both researchers conducting meta-analyses and physicians searching for primary studies in a database. If the missing studies are a random subset of all studies, excluding them will result in less evidence, wider confidence intervals, and lower statistical power, but will not have a systematic influence on the effect size (2). However, whenever there are systematic differences in unpublished and published studies included in the meta-analysis, the weighted effect sizes are biased (e.g., a lack of studies reporting non-significant effects of HCQ in COVID-19 patients). Dickersin (14) found that statistically significant results are more likely to be published than non-significant findings, and thus when published studies are combined together, they may lead to overestimated effects. Also, for any given sample size, the result is more likely to be statistically significant if the effect size is large. Studies with inflated estimate effects are expected to be reported in the literature more frequently as a result (i.e., the first studies on HCQ likely reported large effects). This trend has the potential to produce large biases both on effect size estimates and significance testing (15).

Different techniques have been developed to detect publication bias (16). A widely used method—the funnel plot—consists of plotting effect sizes against their standard errors or precisions (the inverse of standard errors). A skewed funnel plot is usually an indication of the presence of publication bias. However, subjective visual examination as well as coding of the outcome, the choice of the metric, and the choice of the weight on the vertical axis all impact the appearance of the plot (17). Inferential tests such as Egger's regression test regress the standardized effect size on the corresponding precisions (the inverse of the within-study variance). Although widely used, the Egger test may suffer from an inflated type I error rate or low statistical power in certain conditions (16, 17).

# RESULTS

## Hydroxychloroquine and COVID-19 Meta-Analysis

HCQ and chloroquine (CQ) have been used for decades to manage and treat malaria and several autoimmune conditions. At the beginning of the pandemic, preliminary studies (18–20) suggested that HCQ might have a positive effect on the treatment of COVID-19 patients. This led the U.*S. Food and Drug Administration* (FDA) to issue an emergency-use (EUA) authorization on March 28, 2020 allowing for HCQ sulfate and CQ phosphate to be donated to the *Strategic National Stockpile* for use in hospitalized COVID-19 patients. Given its multiple antiviral effects, it is plausible that HCQ could be beneficial in COVID-19 patients (21). *In vitro* data have shown that HCQ/CQ blocks viral infection by inhibiting virus/cell fusion through increasing endosomal pH (22) and by reducing the production of inflammatory cytokines (23–25). Shortly after the EUA of HCQ/CQ, a group in France published a study describing viral load reduction/cure with HCQ (20). However, this study included a small sample size, was non-randomized, only reported viral load as an outcome, and excluded the most severely ill patients from the analysis. Numerous meta-analyses have already been published on the use of HCQ in COVID-19 patients, with some indicating a large protective effect for HCQ (8), and others reporting no effect (9) or increased mortality when HCQ was

**TABLE 2 |** Meta-analysis on the efficacy of hydroxychloroquine on COVID-19 patients published in peer-reviewed journals.

| References | *k/N* | Main results | Heterogeneity analysis | Publication bias analysis |
|---|---|---|---|---|
| Ayele Mega et al. (27) | 20/6,782 | HCQ group did not differed on the rate of virologic cure (OR = 0.78; 95% CI [0.39–1.56]) or the risk of mortality (OR = 1.26; 95% CI [0.66–2.39]) compared to control. | Some analysis revealed high heterogeneity (up to $I^2 = 95\%$). Subgroup analysis of observational vs. RCTs studies. | Cochrane risk of bias tool for RCTs. Newcastle-Ottawa Quality Assessment scale (NOS) for observational studies. Subgroup analysis with low biased studies. |
| Bignardi et al. (28) | 12/7,629 | HCQ (with or without AZ) was not associated with mortality (RR = 1.09, [0.98–1.20]). | Moderate heterogeneity ($I^2 \leq 54.6\%$). Subgroup analysis based on sensitivy analysis. | Egger test did not revealed sign of publication bias ($p > 0.05$). |
| Choudhuri et al. (29) | 14/12,455 | HCQ did not affect mortality compared to control group (RR = 1.003, [0.983–1.022]). | Low to high heterogeneity (up to $I^2 = 97.9\%$). No subgroup analysis. | Two authors independently evaluated within-study bias. |
| Das et al. (30) | 7/726 | HCQ did not affect the virological cure except after day 5 (OR = 9.33, [1.51–57.65]). | Null ($I^2 = 0\%$) to high heterogeneity ($I^2 = 96\%$) but small set of comparisons ($k = 2$). | Cochrane handbook to assess biased of RCTs (2 independent authors) and NOS for observational studies. ROBINS-I tool for non-randomised trials. |
| Ebina-Shibuya et al. (31) | 8/2,063 | HCQ was not associated with mortality (OR = 1.05, [0.53–2.09]). | $I^2$ varies between 0 (adverse event), 31% (all cause death), 57% (time to viral clearance) up to 74% (for viral clearance at 7 days). Subgroup analysis on study design (RCTs vs. observational). | Cochrane Risk of Bias tool for RCTs. |
| Elavarasi et al. (32) | 15/10,659 | No significant reduction in mortality in HCQ group (RR = 0.98, [0.66–1.46]), fever duration (mean difference – 0.54 days) or clinical deterioration (RR = 0.90, [0.47–1.71]). | High heterogeneity for mortatliy and clinical deterioration ($I^2 = 87\%$), virological clearance ($I^2 = 80\%$), time to fever remission ($I^2 = 72\%$). Subgroup analysis of RCTs vs Cohort studies. | Cochrane Risk of Bias Tool for RCTs/Newcastle Ottawa Scale revealed significant bias without additional analysis. |
| Elsawah et al. (33) | 6/609 | No significant effect on viral clearance, clinical progressions, or mortality (*p's* > 0.10). Significant improvement on radiological progression (risk difference −0.20 [−0.36, −0.03]). | Low ($I^2 = 0\%$) to high heterogeneity ($I^2 = 94\%$) without subgroup analysis. | Cochrane Risk of Bias Tool (2 independent authors). Sensitivity analysis after removing the low-quality studies. |
| Kashour et al. (34) | 21/20,979 | No effect of HCQ on mortality (OR = 1.05, [0.96–1.15]) and small increased mortality with HCQ/AZ combination on a subset of studies (OR = 1.32, [1.00–1.75]). | No heterogeneity for the HCQ group and moderate for the HCQ/AZ comparison ($I^2 = 68.1\%$). Sensitivy analysis excluded studies with high risk of bias. | Neither funnel plot nor Egger's regression test revealed signs of publication bias ($p = 0.276$) |
| Fiolet et al. (26) | 17/11,932 | No difference in mortality for all studies or RCT (OR = 0.83 and 1.09). | $I^2 = 84\%$ among non-RCTs with null heterogeneity for RCTs. | Funnel plot, Begg's and Egger's tests. |
| Ghazy et al. (35) | 14/12,821 | No difference between standard care en HCQ group (RR = 0.99, [0.61–1.59]). Mortality higher in HCQ/AZ comparison (RR = 1.8, [1.19–2.27]). | High heterogeneity was observed in different analysis ($0\% < I^2 < 98\%$). Subgroup analysis no revealed significant effect (e.g., mortality HCQ/AZ, RR = 2.23, [1.70–2.91]). | Publication bias assed by funnel plot. |
| Hussain et al. (36) | 6/381 | The risk of mortality in HCQ treated individuals is on average 2.5 times greater than in non-HCQ individuals (95% CI [1.07–6.03]). For moderate to mild symptoms, the rate of improvement was 1.2 higher compared to the control group (95% CI [0.77–1.89]). | These studies were perfectly homogeneous ($I^2/\tau^2 = 0$). | Marginal asymmetry on funnel plot. |
| Hong et al. (37) | 14/24,780 | No effet of HCQ alone or in combination on mortality (OR = 0.95, [0.72–1.26]). | Substantial heterogeneity in all analysis ($71\% \leq I^2 \leq 93\%$). Subgroup analysis of HCQ alone without effect (OR = 0.90, [0.60–1.34]). | Publication bias visible on funnel plot. Comparisons results with and without biased studies (no significant differences). |

*(Continued)*

**TABLE 2 |** Continued

| References | *k/N* | Main results | Heterogeneity analysis | Publication bias analysis |
|---|---|---|---|---|
| Lewis et al. (38) | 4/4,921 | HCQ group were not at fewer risks of developing COVID-19 (RR = 0.82, [0.65–1.04]), hospitalization (RR = 0.72, [0.34–1.50]) or mortality (RR = 3.26, [0.13–79.74]) compared to control but increased the risk of adverse events (RR = 2.76, [1.38–5.55]). | Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics (either 0 or 95%). Subgroup analysis based on (1) location contact with COVID-19, (2) dose of HCQ, and (3) pre- vs. post-exposure prophylaxis. No heterogeinty available for subgroups. | Funnel plot was not assessed giving the small number of studies. |
| Million et al. (8) | 20/105,040 | HCQ effective on cough, duration of fever clinical cure death and viral shedding (OR = 0.19, 0.11, 0.21, 0.32, and 0.43). | *Q*-test for the all set of studies ($Q = 51.8$, $p <$ 0.001). $I^2 \geq 75\%$ and significant *Q*-test for subset of studies when $k > 2$ studies (except for deaths, $I^2 = 0\%$, $p = 0.071$). No subset analysis based on heterogeneity. | None. |
| Patel et al. (39) | 6/2,908 | No difference between HCQ and control group on mortality (OR = 1.25, [0.65, 2.38]). Higher mortality in HCQ/AZ group compared to control (OR = 2.34, [1.63–3.34]). | There was significant heterogeneity in mortality outcome ($I^2 = 80\%$) for HCQ. Subgroup analysis based on sensitivity analysis. For the HCQ/AZ groups, there was perfect homogeneity ($I^2 = 0\%$). | Funnel plot was asymmetrical. Subgroup analysis based on homogeneous studies. |
| Pathak et al. (40) | 7/4,984 | No difference in outcome with/without hydroxychloroquine (OR = 1.11, [0.72, 1.69]). | Moderate heterogeneity ($32\% \leq I^2 \leq 44\%$). No subgroup analysis. | Funnel Plot and Egger regression asymmetry test (although not available in the paper). |
| Putman et al. (41) | 45/6693 | HCQ use was not significantly associated with mortality (HR = 1.41, [0.83, 2.42]). | Low heterogeneity ($I^2$ = 0–32%) but small set of studies ($k$ = 2 or 3). | Newcastle-Ottawa Scale for cohort studies and the Risk of Bias 2.0 tool for randomized controlled trials; case series assumed to be high risk by default. |
| Sarma et al. (9) | 7/1,358 | No differences on viral cure (OR = 2.37, [0.13–44.53]), death/clinical worsening (OR = 1.37, [1.37–21.97]) or safety (OR = 2.19, [0.59–8.18]). | Heterogeneity varies from null (for safety issues) to high ($I^2 = 72\%$, for virological cure). No subset analysis (except for the inclusion/exclusion of Gautret et al. [22]). | Cochrane/ROBINS-I/Newcastle Ottawa Scale (3 researchers). |
| Shamshirian et al. (42) | 37/45,913 | No difference on mortality in HCQ group (RR = 0.86, [0.71–1.03]) or HCQ/AZ comparison (RR = 1.28, [0.76–2.14]). | High heterogeneity ($I^2$ = 87–90%). Meta-regressions indicated significant effect of age ($p < 0.001$). | Moderate publication bias for mortality based on Egger's test ($p =$ 0.02). |
| Singh et al. (43) | 7/746 | No benefits of HCQ on viral clearance (RR, 1.05; 95% CI, 0.79 to 1.38; $p =$ 0.74). Significantly more deaths in the HCQ group compared to the control group (RR, 2.17; 95% 1.32 to 3.57; $p$ = 0.002). | Moderate heterogeneity in the clearance analysis ($I^2 = 61.7\%$, $p = 0.07$) and none in the death analysis ($I^2 = 0.0\%$, $p = 0.43$). No subset analysis based on heterogeneity. | Trim and fill adjustment, rank correlation, and Egger's tests. |
| Ullah et al. (44) | 12/3,912 | Higher mortality (OR = 2.23, [1.58–3.13]) and net adverse events (OR = 4.59, [1.73–12.20]) in HCQ group compared to control. | Moderate to high heterogeneity ($I^2$ = 54–94%) without subgroup analysis. | Funnel plot revealed minimal publication bias. |
| Yang et al. (45) | 9/4,112 | HCQ-azithromycin combination increased mortality in COVID-19 patients (OR = 2.34;, [1.63–3.36]) though it was also associated with benefits on viral clearance in patients (OR = 27.18, [1.29–574.32]). HCQ-alone did not reveal significant changes in mortality rate, clinical progression, viral clearance, and cardiac QT prolongation. | Null to high heterogeneity ($I^2 = 84\%$). Subsequent subgroup analysis showed that HCQ treatment could recuded mortality and severe illness in severely infected COVID-19 patients (OR = 0.27, [0.13–0.58]). | Funnel plot analysis did not reveal obvious publication bias. Possible bias due to lack of demographic and clinical data. |
| Zang et al. (46) | 7/851 | No difference in illness duration between the HCQ group and the standard treatment group (RR = 0.66, [0.18–2.43]). Death was higher in HCQ group compared to standard (RR = 1.92, [1.26–2.93]). | Moderate heterogeneity was observed ($41.2\% \leq I^2 \leq 72.1\%$) without subgroup analysis. | Cochrane Risk of Bias Tool for RCTs evaluated quality of studies (2 reviewers). Newcastle Ottawa Scale for observational studies and Egger test. |

*To date, 24 meta-analyses were published on April 11th, 2021. This table only described peer-reviewed meta-analyses evaluating HCQ efficacy on COVID-19 patients. We reported the number of studies (k) and participants (N) after exclusion/inclusion criteria.*

used with the antibiotic azithromycin (AZ) (26) (see a complete Table of HCQ/CQ meta-analysis and their bias on **Table 2**).

## Some Examples of Questionable Research Practices in Meta-Analysis Suggesting No-Effect or Effects of HCQ

Million et al. (8) published a meta-analysis containing 20 studies involving 105,040 patients of which 19,270 had been on chloroquine derivatives and found a positive effect of the drug on mortality and symptoms associated with COVID-19. On the other hand, Fiolet et al. (26) did not find any effect of HCQ/AZ in a meta-analysis of 29 studies including 11,932 patients. In both meta-analyses, the authors found large heterogeneity among the included studies ($I^2 = 75\%$ and $I^2 = 83\%$), which suggests the presence of confounders not being accounted for across studies, and neither study performed subgroup analysis to better explore the high heterogeneity. Study selection was problematic in both studies. For instance, Million and colleagues did not publish a flow diagram with the different phases of a systematic review as recommended by the PRISMA Statement (7). Several items, fundamental in the method of the PRISMA protocol, were not followed such as review protocol registration, detailed study selection criteria, data collection process, risk of bias within and across studies, and additional analyses. Million et al. (8) grouped "clinical" studies together (studies that had direct access to patients) and "observational big data" studies together (that may present conflicts of interest and show no effect of HCQ) instead of doing meta-regressions based on study designs (i.e., RCT vs. observational study). Fiolet et al. (26) excluded several studies because of critical risk of bias (i.e., lack of statistical information and the assignment of treatment, unknown timing between measures and confounders) with HCQ and AZ combination therapy (47–49).

Outcome selection is concerning, as Million et al. (8) reported positive effects on the duration of symptoms such as cough, fever, and clinical care with analysis of 1 to 7 small sample size studies (50). In Fiolet's et al. meta-analysis (26), the type of estimate used for effect sizes was inconsistent and not clearly reported. They did not make a distinction between Risk Ratios (RR), which are usually used in cohort studies, and Hazard Ratios (HR) and Odds Ratios (OR), which are used in case-control studies. This can influence the analysis because OR tend to overestimate effects compared to RR when the selected outcome occurs frequently (51). In both meta-analyses, the selection of included studies, the degree of heterogeneity in these analyses, and the calculations of effect sizes make the veracity of the estimates uncertain. Many of the meta-analyses published had low statistical power, untreated heterogeneity and none used tools to evaluate potential risks of *p*-hacking (13, 27–46, 52).

# DISCUSSION

## A Proposal for Conducting Meta-Analyses in Clinical Research

As discussed above, one potential bias in meta-analyses is "selection bias," which may lead to inaccurate estimation of effect sizes. An important question is whether to incorporate unpublished pre-print studies, especially when the field has limited studies and there is urgency for reliable data. An argument against this approach could be that unpublished studies might not be as rigorous as published studies. From this point of view, unpublished studies should not be included in meta-analyses because the inclusion of poorly conducted research also introduces bias. However, having access to published and unpublished studies helps decide which studies to include in a meta-analysis based on a priori inclusion criteria [through pre-registered meta-analyses for instance (1), see **Table 2**].

Readers typically focus on the forest plot, which depicts the quantitative effects and level of uncertainty for each study included in the meta-analysis. Forest plots are great tools to visually assess heterogeneity (coupled with quantitative index such as $I^2$ or *Q*-test) and pooled results (53). However, forest plots do not address publication bias and thus can mislead readers's conclusion if not presented with additional information such as a funnel plot.

One of the most widely used tools to assess publication bias is plotting the effect sizes for each study against an indicator for the precision to which each study estimated the effect size. In funnel-plots, studies will be plotted near the average effect size, while studies with low precision (e.g., small sample) will have effect estimates distributed on either side of the average effect, creating a funnel-shaped plot.

Although funnel plots are a widely used and reliable way to evaluate publication bias, another useful tool is the *p*-curve (5). The *p*-curve plots a proportion of observed *p*-values for each value of *p* in a set of studies. Because true effects are more likely to have smaller values of *p* (e.g., "$p < 0.01$") than values around the arbitrary significant threshold of $p < 0.05$, a flat *p*-curve or a *p*-curve indicating a higher proportion of *p*-values between 0.04 and 0.05 is more likely to be an indicator of questionable research practices, sometimes referred to as *p*-hacking. Van Assen et al. (4) propose the use of another tool, *p*-uniform, to estimate population effect size in the presence of small to moderate heterogeneity ($I^2 < 50\%$).

Conducting sub-group analyses for observational, quasi-experimental, and experimental studies will also help evaluate the risk of bias of each study design (6). In cases of substantial heterogeneity, researchers can generate a homogenous group of studies based on theoretical or methodological criteria and then use the *p*-curve and *p*-uniform to estimate the average population effect sizes for each subgroup analysis (4). Additional tools can be useful to determine publication bias. For instance, selection models can adjust for suspected selective publication; Rosenthal's fail-safe $N$ is used to estimate the number of unpublished studies necessary to overturn the significant results and Copas sensitivity approach uses regression models to evaluate publication bias (54).

The fact that statistically significant results are more likely to be published than non-significant results is a major source of publication bias. Additional sources of potential bias that should be addressed when possible include pipeline bias (non-significant results take longer to publish than significant results), subjective reporting bias (selective reporting of the results), duplicate reporting bias (results published in multiple sources), and language bias (non-native English speakers tend to publish non-significant findings in their native tongue) (54).

## CONCLUSION

Tensions over the use of HCQ for COVID-19 patients have unfortunately led some authors to disregard basic meta-analytical protocols. Concern over the quality of studies included in meta-analyses has also emerged in a recent comparative psychological study between meta-analytical findings and registered replication studies. The authors found that meta-analytical effect sizes significantly differed from the replication effect sizes for 12 of the 15 meta-replication pairs, and meta-analytic effect sizes were almost three times larger than the replication effect sizes (15). These inconsistencies call for caution when running and interpreting meta-analyses of new clinical studies.

## 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

JB and OZ contributed to the original idea and wrote the original manuscript. JB, OZ, and CR analyzed the relevant literature and updated the manuscript. JB, OZ, CR, and AH were all contributor in writing the final manuscript. All authors read and approved the final manuscript.

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# Response to the COVID-19 Pandemic: Comparison of Strategies in Six Countries

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**Objective:** This study aimed to examine the effectiveness of containment strategies and mitigation strategies to provide a reference for controlling the ongoing global spread of the pandemic.

**Methods:** We extracted publicly available data from various official websites between January 1 and December 31, 2020, summarized the strategies implemented in China, South Korea, Singapore, the United States, the United Kingdom, and France, and assessed the effectiveness of the prevention and control measures adopted by these countries with the daily new cases and mortality rate per 100,000 population.

**Results:** China, South Korea, and Singapore adopted containment strategies, which maintained a proactive approach by identifying and managing cases, tracking and isolating close contacts. China and Singapore had a similar epidemic curve and the new daily cases. As of December 31, 2020, the new daily cases of China and Singapore were below 100 with the mortality rates per 100,000 population of 0.3 and 0.5, respectively. But the new daily case of South Korea was as high as 1,029, with a mortality rate per 100,000 population of 1.8. In contrast, the United States, the United Kingdom, and France responded with mitigation strategies that focus on treating severe cases and those with underlying conditions. They had similar epidemic curves and mortality rates per 100,000 population. The United States had up to 234,133 new confirmed cases per day, and the mortality rate per 100,000 population was 107, while the United Kingdom had 56,029 new confirmed cases per day and the mortality rate per 100,000 population was 108, and France had 20,042 new cases per day, with a mortality rate per 100,000 population of 99.

**Conclusions:** China, Korea, and Singapore, which implemented strict containment measures, had significant outbreak control. Meanwhile, the successful practices in China, Singapore, and South Korea show that the containment strategies were practices that work especially at the individual level identifying and managing the infected patients and their close contacts. In the United States, the United Kingdom, and France, which implemented the mitigation policies, the effect of epidemic prevention and control was not significant that the epidemic continued or even increased epidemic relatively quickly.

**Keywords: COVID-19, containment strategy, mitigation strategy, countries comparison, public health**

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# INTRODUCTION

The coronavirus disease 2019 (COVID-19) is continuing to spread worldwide. As of Feb 23, 2021, the COVID-19 outbreak has caused 112,222,860 confirmed cases and 2,483,930 death cases. The number of new cases outside China exceeded 290,000, the total of confirmed cases was more than 110 million, and the total number of death cases was more than 2.47 million (1). However, fortunately, in the past year, at least 186 countries have implemented varying degrees of restrictions on population movement to slow the spread of the severe acute respiratory syndrome coronavirus (SARS-CoV) and prevent health systems from becoming overwhelmed. These restrictions have amounted to lockdowns in 82 countries, resulting in a retreat in new cases and the mortality rate (2, 3).

In response to the COVID-19 epidemic that is ravaging the world, countries have employed various strategies for controlling the pandemic based on their different economic, cultural, and health system situations. These epidemic control strategies can be divided into two types: one type is a containment strategy, and the other is a mitigation strategy. A containment strategy focuses on disease prevention and the control of infectious diseases from three aspects: infectious sources, transmission routes, and susceptible populations (4). It aimed to break the chain of transmission through a combination of aggressive test-and-isolate policy (identify and isolate all infectious persons, including those with mild illness) and social distancing measures (5). Furthermore, the containment strategy abided by "five early's" principles (early detection, early report, early investigation, early isolation, and early treatment). The confirmed cases and suspected cases were treated in intensive until the medical observation period was complete (4).

Whereas, a mitigation strategy focuses on reducing the transmission rate, asserting that the spread of COVID-19 cannot be completely interrupted and can only be slowed when the population forms an adequate immune barrier and the intensity of the epidemic decreases to become a seasonal infection, such as influenza (4). It aimed to reduce death tolls by focusing on the medical care of severe cases while relying on social distancing to flatten the curve of epidemic impact on healthcare systems (5). Moreover, the mitigation strategy prioritizes hospitalization for severe cases or those with the underlying disease rather than early detection of all cases, isolates and treats mild cases, or screens and manages close contacts (6).

In order to compare the effects of different types of non-pharmaceutical interventions, this study selected China, South Korea, and Singapore of Asia with earlier epidemics, these countries implemented containment strategies to successfully contain COVID-19 with cases and close-contact identification and management. Meanwhile, we also selected the United States, the United Kingdom, and France, these countries implemented mitigation strategies that tried to control the COVID-19 by actively treating severe cases or those with underlying diseases but were experiencing a severe outbreak of COVID-19. We hoped that our findings would provide a policy reference for the countries experiencing the impact of the COVID-19.

# METHODS

## Data Collection

The epidemiological data are extracted from official websites and updating in real-time, including the National Health Commission of the People's Republic of China, Johns Hopkins University & Medicine Coronavirus Resource Center, and Worldometer, which has synthesized data from government websites of countries (7–9). Data indicators include national population, totally confirmed cases, daily new cases, total deaths, and daily new deaths. We calculated the mortality rate per 100,000 population using the national population and the total deaths.

## Policy Information

Information on the control strategies, policies, and measures of six countries were searched from national documents and government webpages of various countries, such as media announcements and governmental decrees between January 1 and December 31, 2020. The control strategies, policies, and measures were categorized into containment and surveillance, healthcare, border control, and community and society measures.

Finally, we selected epidemiological data and policy information from January 1 to December 31, 2020, and assessed the effectiveness of the COVID-19 strategies adopted by these countries by combining the strategies of the six countries with the daily new cases and mortality rate per 100,000 population.

# RESULTS

## The National Response to the COVID-19 Pandemic

### China, South Korea, and Singapore Containment Strategies

China was the first country to report the COVID-19 infection. South Korea and Singapore were the following rapidly hit countries after China. At the beginning of the COVID-19 outbreak, with no immediate vaccines and antiviral medication for COVID-19, China being the epicenter of the outbreak swiftly swung into action in managing the epidemic. Typical measures include the use of existing traditional public health epidemic containment strategies of lockdown infectious areas, testing, isolation, quarantine, expanding the number of beds, physical distancing, and community containment (10).

Similarly, South Korea and Singapore, the next two hit COVID-19 outbreak countries after China, fully utilized their experience from the Middle East respiratory syndrome (MERS) outbreak in 2015 and the severe acute respiratory syndrome (SARS) outbreak in 2003, respectively, in responding to COVID-19. Based on the three core principles of openness, transparency, and creative innovation, South Korea was able to effectively implement the strategy of 3Ts of testing, tracing, and treatment (11). However, the Singapore government had constructed a three-pronged approach which includes travel, healthcare, and community measures to curb the spread of COVID-19. The major measures taken for COVID-19 in China, South Korea,

**TABLE 1 |** The major measures taken for COVID-19 in China, South Korea, and Singapore.

| Measures | China | South Korea | Singapore |
|---|---|---|---|
| Containment and surveillance measures | Implementing strictly the "Four early's" measures of early detection, early reporting, early isolation, and early treatment.<br>(1) Early detection: performing community screening, setting up temperature testing points in neighborhoods, companies, shopping malls and other public places, and conducting nucleic acid testing screening for people with clinical symptoms, close contacts of confirmed cases, and people returning from epidemic areas.<br>(2) Early reporting: individual initiative reporting, unit uniform reporting, pharmacy discovery reporting, medical institution reporting, joint prevention, and control reporting.<br>(3) Early isolation/quarantine: self-quarantine at home, centralized medical isolation, and centralized hospital for observation.<br>(4) Early treatment: clearly diagnose and transfer to a designated hospital as soon as possible. | "Three Ts" measures of fast Testing, meticulous Tracing, and appropriate Treatment.<br>(1) Fast testing, the Korean government granted emergency use authorization for testing kits which helped to build a foundation for large-scale testing. And the introduction of drive-through and walk-through screening stations for sample collection coupled with fast and aggressive testing allowed early detection of confirmed cases in communities.<br>(2) Meticulous Tracing: the time needed for epidemiological investigations was also significantly reduced thanks to the utilization of ICT.<br>(3) Appropriate treatment: confirmed cases are first categorized by severity for access to appropriate treatment. | (1) At healthcare facilities or through contact tracing confirmed cases were based on clinical and epidemiological criteria, and continuously update as change of the COVID-19 situation. Doctors were also allowed to test patients who are suspected for clinical or epidemiological reasons.<br>(2) All suspected and confirmed cases were immediately isolated in hospital. Asymptomatic close contacts were required to quarantine for 14 days. Also, the government launched the "TraceTogether" APP to trace close contacts.<br>(3) All public hospital laboratories offer PCR testing for COVID-19 to increase national diagnostic capacity. |
| Healthcare measures | (1) Pairing assistance, mobilizing 29 provinces to assist different cities in Hubei province. From January 24 to March 8, 2020, a total 346 medical teams and 42,600 medical personnel were mobilized to support Hubei province.<br>(2) Makeshift hospitals, establishing Huoshenshan hospital, Leishenshan hospital, and 16 Fangcang shelter hospitals in Hubei province, these hospitals treated more than 12,000 COVID-19 patients.<br>(3) Classifying management of "four categories of personnel". All confirmed cases were transferred to the hospitals for centralized treatment, suspected cases, febrile cases who might be carriers, and close contacts were sent to designated venues for isolation and medical observation. | (1) Whether public hospitals or private hospitals were committed to responding to the COVID-19 outbreak.<br>(2) Launching Community Treatment Centers (CTCs), from March 2 to March 26, 2020, a total of 3,292 patients were admitted to 17 CTCs.<br>(3) Case categorization by severity: asymptomatic, mild, severe, and critical. Asymptomatic patients and patients with mild symptoms were isolated at Residential Treatment Centers or self-quarantine, patients with moderate symptoms were hospitalized at Dedicated Infectious Disease Hospitals, patients with severe symptoms or extremely severe symptoms were hospitalized at Government-designated Isolation Hospitals. | (1) Activating the National Center for Infectious Diseases (NCID) for isolation and treatment of confirmed cases.<br>(2) Implementing the "Public Health Preparedness Clinics program" –activated more than 800 fever clinics to treat fever patients and provide subsidies for citizens.<br>(3) The Big Box at Jurong Mall was transformed into a community care facility, accepting mainly mild patients for treatment and isolation.<br>(4) Mild and undifferentiated persons were instructed to self-isolation at home. Those with persistent or worsening symptoms are advised to return to the same doctor for evaluation and referral for testing. |
| Border control measures | (1) In the Guidelines on Novel Coronavirus Diagnosis and Treatment emphasized on the elements of the port health quarantine, increased the epidemiological history of travel or residence in countries and regions with serious outbreaks abroad.<br>(2) Nucleic acid testing were required to all travelers or returning residents entering from all ports of entry. They will be released from quarantine if they do not present with symptoms and are tested negative for SARS-CoV-2 after 14 days of quarantine.<br>(3) Implementing the health declaration system for people exit and entry, strictly carrying out entry health quarantine, and suspending the entry of foreigners with valid Chinese visas and residence permits. | (1) Adopted monitoring measures such as special entry procedures and mandatory installation of a Self-Check Mobile App to keep track and monitor the health of inbound travelers after arrival.<br>(2) Introduced mandatory COVID-19 testing and 2-week quarantine for all inbound travelers regardless of their port of departure.<br>(3) Visa-free entry and visa-waiver programs were also suspended, with in addition to countries that had not imposed entry bans on Korean travelers.<br>(4) In late June, the Korean government introduced country-specific restrictions, temporarily suspending visa issuance and non-scheduled flights and requiring submission of negative PCR-test results for issuing Korea-bound flight tickets. | Escalating border control measures:<br>(1) Since Jan 3, 2020, temperature and health screening of incoming travelers from Wuhan and extended to all travelers since Jan 29, is in place at all ports of entry.<br>(2) Since Feb 1, Singapore imposed entry restrictions on visitors from China; returning residents and long-term pass holders are subject to a 14-days quarantine.<br>(3) Since March 24, prohibiting short-term visitors and cruise ship stops.<br>(4) Since March 27, everyone who enters Singapore without a Stay Home Notice at a designated facility must wear an electronic tracker. |

*(Continued)*

**TABLE 1** | Continued

| Measures | China | South Korea | Singapore |
|---|---|---|---|
| Community and social measures | (1) Lockdown infection areas: from Jan 23 to April 7, 2020, lockdown Wuhan city. Also, the different varying degrees of blockade were imposed nationwide.<br>(2) In China, all provinces have activated the highest-level public health emergency response. Subsequently, many tourist attractions were temporarily closed, suspending nationwide tour operations and overseas group travel and free-travel operations.<br>(3) School closures, postponed school opening or online classes, extended Spring Festival holidays or working from home to reduce population moving. | (1) No areas have been locked down.<br>(2) Social Distancing—Isolation/Quarantine, Stay-at-home advisory, Closure of<br>(3) Schools, Postpone School Opening or Online Classes, Restriction on using group facilities, Restriction on group events, and Curfew by district. | (1) No areas have been locked down.<br>(2) Before April 5, 2020, the Singapore government took standing community and social measures: focused on health education, limited recreational restrictions, moratorium on large events, implementation of leave orders and home quarantine orders for different populations, temperature testing.<br>(3) After April 5, 2020, the government introduced strict measures: suspending work, school, and working from home. |

and Singapore are summarized in **Table 1** from containment, healthcare, border, and community and society.

## The United States, the United Kingdom, and France Mitigation Strategies

Compared with China, South Korea, and Singapore, where the COVID-19 infections occurred earlier, the United States, the United Kingdom, and France seemed slow to respond to the COVID-19 outbreak and preferred to adopt mitigation strategies. The aggressive measures of the US federal government could date back to a national emergency declaration on March 13, 2020. Since then, the United States has adopted a combination of "containment" and "mitigation" strategies, with multiple channels and means of response and increasing support for prevention and control.

The government did not take more measures to control the COVID-19 epidemic before mid-March, 2020. However, the British government began implementing the mitigation strategies based on the theory of "herd immunity" until the outbreak in Italy and Spain were nearly out of control in March due to the confirmed cases of Italy was exceeded 5,000 per day, and total deaths exceeded 1,000; and the confirmed cases of Spain was nearly 10,000 per day, and total deaths exceeded 1,000 (12, 13). Subsequently, the government further implemented more stringent measures, such as city lockdown, school closures, and entertainment closures to stop the virus from spreading more widely (14). Similarly, France practiced loose mitigation strategies until mid-March. The French government was alerted only when the COVID-19 epidemic was raging, with the number of confirmed cases and deaths increased dramatically. After that, a strict mandatory stay at home was imposed, and a state of national emergency was declared (15). The major measures taken for COVID-19 in the United States, the United Kingdom, and France are summarized in **Table 2** from containment, healthcare, border, and community and society.

## Epidemiological Trends and Population Mortality Rates of COVID-19 in Six Countries

As shown in **Figures 1–3**, China, South Korea, and Singapore experienced large COVID-19 outbreaks and contained the COVID-19 outbreak with a containment strategy, especially in China and Singapore. China and Singapore had a similar epidemic curve and the number of new confirmed COVID-19 cases by December 31, 2020. In terms of mortality rate per 100,000 population, the rates of China, South Korea, and Singapore were 0.3, 1.8, and 0.5, respectively. As of December 31, 2020, especially in China and Singapore, which maintained a low mortality rate per 100,000 population no more than 1.0, new confirmed cases per day were only 87 and 30, respectively. However, new confirmed cases per day in South Korea were as high as 1,029 due to the infections linked to hospitals, nursing homes, churches, prisons, and family gatherings during the holidays.

**Figures 4–6** showed that the United States, the United Kingdom, and France, which responded with a mitigation strategy when the COVID-19 pandemics emerged, had similar epidemic curves and mortality rates per 100,000 population by December 31, 2020. The daily new cases of these three countries were decreased between May and July with the mitigation strategies. However, with economic recovery and restrictions relaxing, these three countries were experiencing the second wave of the epidemic, with a doubling in daily new cases compared with the first wave. As of December 31, 2020, the United States had up to 234,133 new confirmed cases per day, and the mortality rate per 100,000 population was 107, while the United Kingdom had 56,029 new confirmed cases per day and the mortality rate per 100,000 population was 108. France had 20,042 new cases per day, with a mortality rate per 100,000 population of 99.

Whether in the new confirmed cases per day, or the mortality rate per 100,000 population, the difference is significantly remarkable between China, South Korea, and Singapore, which

**TABLE 2 |** The major measures taken for COVID-19 in the United States, the United Kingdom, and France.

| Measures | United States | United Kingdom | France |
|---|---|---|---|
| Containment and surveillance measures | The United States had a slow start in widespread SARS-CoV-2 testing.<br>(1) The Trump administration announced a campaign to conduct tests in retail store parking lots across the country, but this was not widely implemented.<br>(2) The NIH launched a new rapid test development program on April 29, 2020, Rapid Acceleration of Diagnostics.<br>(3) As of July 1, 2020, only four states are using contact tracing apps as part of their state-level strategies to control transmission.<br>(4) As of August 2020, the FDA had granted Emergency Use Authorizations to over 200 tests for detecting current or past infection. | (1) The United Kingdom incorporated COVID-19 testing for severe acute respiratory illness (SARI) and ILI surveillances. Starting in early June, mass antibody testing was conducted.<br>(2) Individuals with suspected mild symptoms of COVID-19 (new continuous cough, fever or anosmia) and all members of their households to self-isolate for 7 and 14 days, respectively, and call NHS111 if required. Patients with persistent and severe symptoms were advised to contact their general practitioner (GP) ] or call emergency services.<br>(3) On May 18, 2020, the NHS Testing and Tracing Service was launched, whereby anyone in the UK with symptoms can request an antigen test via a dedicated website. | (1) French surveillance system: according to the COVID-19 surveillance protocol, physicians suspecting a COVID-19 case have to contact immediately either the emergency hotline (SAMU-Centre 15), if the patient is seeking medical attention from a general practitioner, or a referring infectious diseases specialist at hospital level.<br>(2) Possible cases have to be hospitalized, isolated and cared for in one of the 38 French referral hospitals designated by the Ministry of Health.<br>(3) Setting up case definition and update with the situation of the COVID-19. Contacts are traced from the date of onset of clinical symptoms in a case. |
| Healthcare measures | (1) Establishing temporary hospitals: the first temporary hospital in New York was completed on March 28, 2020.<br>(2) Expanding the number of beds: on March 28, 2020, the U.S. medical ship "Mercy" docked in Los Angeles, which can provide 1,000 beds.<br>(3) Appropriate treatment: on August 23, 2020, the FDA approved the use of plasma from recovered individuals to treat patients with severe COVID-19.<br>(4) From early 2020, five or six operating primarily in the U.S. began vaccine research, and COVID-19 vaccine were administered from December 14. | (1) Established temporary critical care hospitals: capacity was upgraded at Belfast City Hospital in Northern Ireland, NHS Louisa Jordan was established in Scotland, temporary critical care NHS Nightingale hospitals were built across England, and the Dragon's Heart Hospital was set up in Cardiff, Wales.<br>(2) Primary care practitioners were advised to avoid face-to-face assessment of suspected cases. Instead, patients should be immediately isolated and referred to the local health authorities *via* a hotline. | (1) Relying on the military to reinforce medical forces. A field hospital was established in the Milus region of Alsace with a total of 30 intensive care beds on March 25, 2020. Also, France activated a medical high speed train, Air Force A330 and navy helicopters to transport critically ill patients in the east to areas with less severe outbreaks.<br>(2) Launching the White Plan and Blue Plan to coordinate all medical resources, including hospitals, clinics, and social security agencies. Also, retired health care workers and medical students have also been mobilized to join the fight against the epidemic. |
| Border control measures | (1) Public health screening at Major Airport on January 22, 2020, and 11 Airports added to Screening Watch List.<br>(2) Suspension of access to the United States: beginning March 21, 2020, U.S. border crossings closed to travel other than "core essential travel."<br>(3) On March 13, 2020, the federal government escalated from a public health to a national emergency, and since March 16 all states had declared a state of emergency or a public health emergency. | (1) In March 2020, the UK went into lockdown. The government banned all non-essential travel.<br>(2) Travelers entering the UK would have to self-isolate for 14 days upon arrival to help slow the spread of COVID-19.<br>(3) From October onwards, varying levels of lockdown were imposed in England. | (1) The France government announced a lockdown period from March 17 to May 11, 2020: ban on all travel except relating to professional activity, buying essential goods, health or family reasons or brief individual exercise.<br>(2) From March 17, France closed its borders for 30 days. The government advised long-term residents who have lived abroad to avoid international travel or return to France for the next 30 days.<br>(3) The government addressed that France entered a second nationwide lockdown from October 30, 2020. |
| Community and social measures | (1) Many additional mitigation policies have been enacted at the state level: school closures, large gathering bans, non-essential business closures, stay-at-home orders, bar/restaurant limits, and primary election postponements.<br>(2) Lockdown infection areas: on December 3, 2020, locked down the city of Los Angeles, USA.<br>(3) Mask mandates have been implemented: as of early August, just over half of states require individuals to wear a mask in public, although in some states without a statewide mandate local authorities have mask wearing ordinances. | (1) Implementing a series of TV, radio and social media campaigns and recommendations for behavior change in the general public.<br>(2) The stringency of containment measures escalated: the closure of non-essential services on March 16, follow by a lockdown on March 23.<br>(3) Closures and restrictions: schools closure, non-essential activities were prohibited. Individuals were required to stay at home and work from home where possible, with only an hour of exercise, trips for food shopping and medication allowed per day, and a social distancing measure of 2 m.<br>(4) Mask mandates have been implemented when people take public vehicles. | (1) The first nationwide lockdown: bans on gatherings, closure of most public establishments, and closure of schools and institutes of higher education.<br>(2) Progressive lifting of lockdown restrictions: all gatherings, meetings, activities, travel and usage of public transport were required to respect social distancing rules.<br>(3) Masks made mandatory in an extended range of public places.<br>(4) Curfews and second national lockdown: with similar restrictions to the first national lockdown except that primary- and secondary school children can still attend school. |

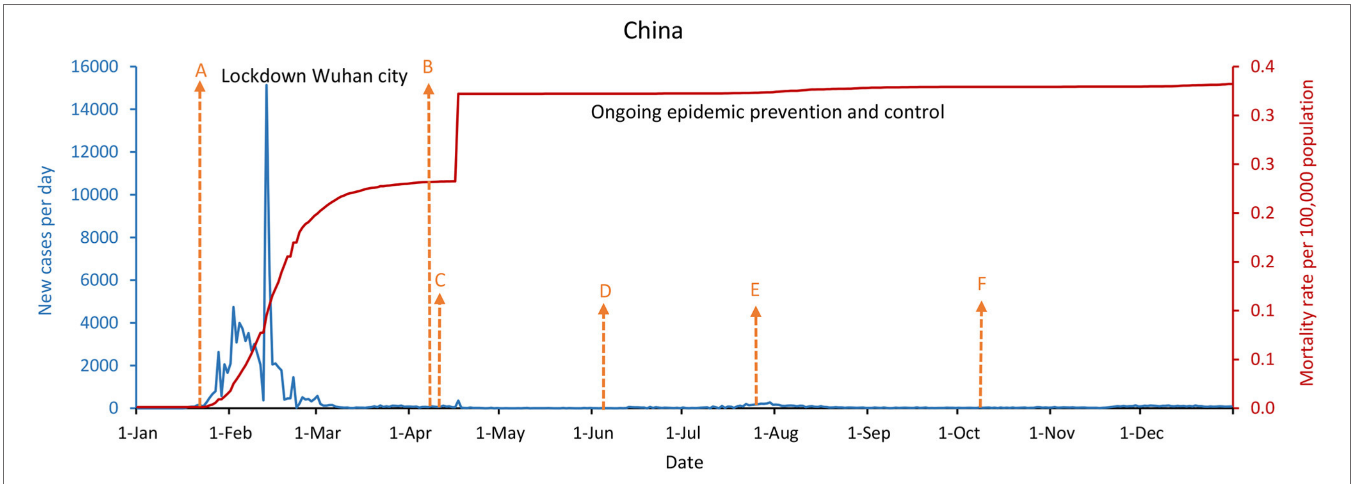


**FIGURE 1 |** China's coronavirus disease 2019 (COVID-19) epidemic curves and population mortality rate (between January 1 and December 31, 2020). **(A)** Beginning of January 23, 2020, lockdown Wuhan city, all provinces or regions initiated a Class 1 Response Public Health Emergency. **(B)** Beginning of April 8, lifting lockdown of Wuhan city, and entering the phase of ongoing epidemic prevention and control. **(C)** On April 9, a COVID-19 cluster was detected in Heilongjiang Province. **(D)** On June 4, a COVID-19 cluster emerged at Xinfadi Market in Beijing. **(E)** On July 26, COVID-19 cases were mostly from outbreaks in Xinjiang and Liaoning. **(F)** On October 11, a COVID-19 cluster appeared in Qingdao.

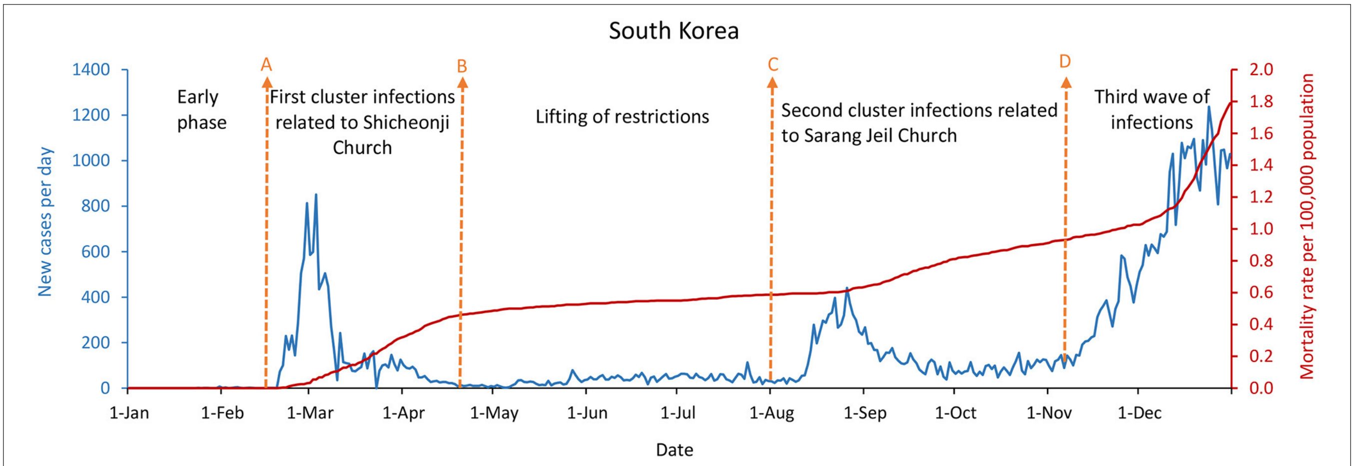


**FIGURE 2 |** South Korea's COVID-19 epidemic curves and population mortality rate (between January 1 and December 31, 2020). **(A)** Starting on February 19, 2020, canceling mass gatherings, and various measures were taken to mass testing. **(B)** Starting on April 22, lifting restrictions of stores, restaurants, gyms, cram schools, bars, and religious services. **(C)** Starting in August, authorities ordered 12 high-risk business categories, including nightclubs, karaoke bars, buffet restaurants, and museums to cease operations; banned gatherings; imposed distancing rules; and wearing masks continued to be in place. **(D)** Starting on November 9, escalating the social distancing level.

implemented the containment strategies, and the United States, the United Kingdom, and France, which took the mitigation strategies. **Figures 2**, **4–6** showed that South Korea, the United States, the United Kingdom, and France all had a similar epidemic curve by December 31, 2020. Nevertheless, South Korea had a case fatality rate of ∼1% of countries adopting a mitigation strategy (South Korea: 1.8 vs. the United States: 107; United Kingdom: 108; and France: 99, by December 31, 2020).

## DISCUSSION

There are differences in healthcare workers, health systems, health authority model, political systems, and cultural customs among China, South Korea, Singapore, the United States, the United Kingdom, and France, so their prevention and control strategies combat the COVID-19 outbreak differ. China, South Korea, and Singapore have maintained a proactive approach in responding to the COVID-19 outbreak by identifying and managing cases, tracking and isolating close contacts, and strictly restricting or controlling population movement when feasible and appropriate. Although no large-scale embargoes were implemented in Singapore and South Korea, and the outbreak rebounded in South Korea, these three countries have adopted a containment strategy based on the nature of prevention and control policies. In contrast, the United States, the United Kingdom, and France have implemented nationwide

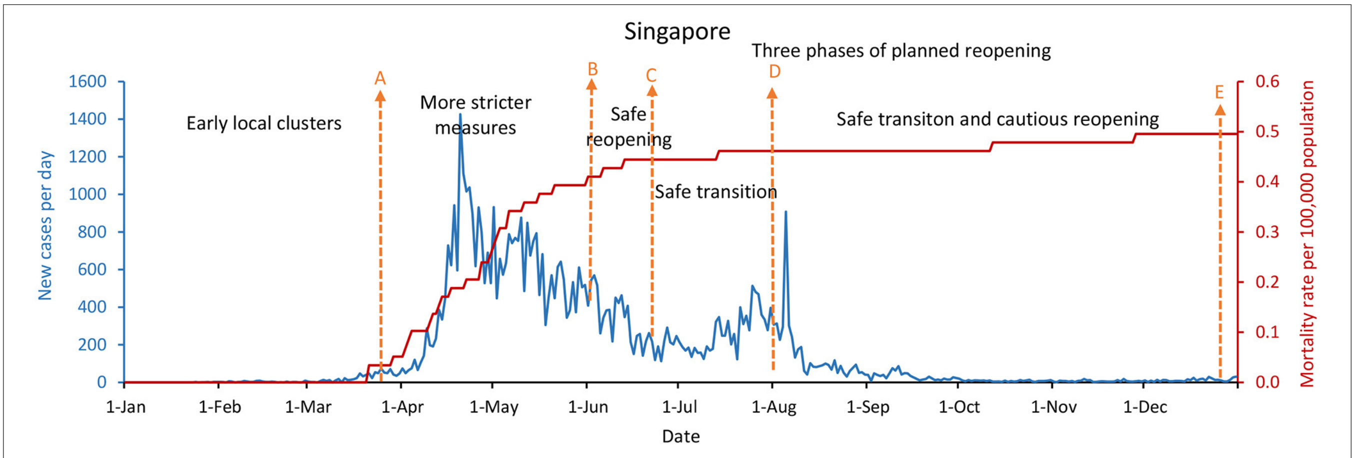


**FIGURE 3 |** Singapore's COVID-19 epidemic curves and population mortality rate (between January 1 and December 31, 2020). **(A)** On March 24, 2020, the Multi-Ministry Task Force announced stricter measures. **(B)** Starting on June 2, relaxing measures and implementing "Safe Reopening." **(C)** Starting on June 19, implementing "Safe Transition." **(D)** Starting in August, continuously implementing "safe transition," and cautious reopening. **(E)** Starting on December 28, implementing "Safe Nation."

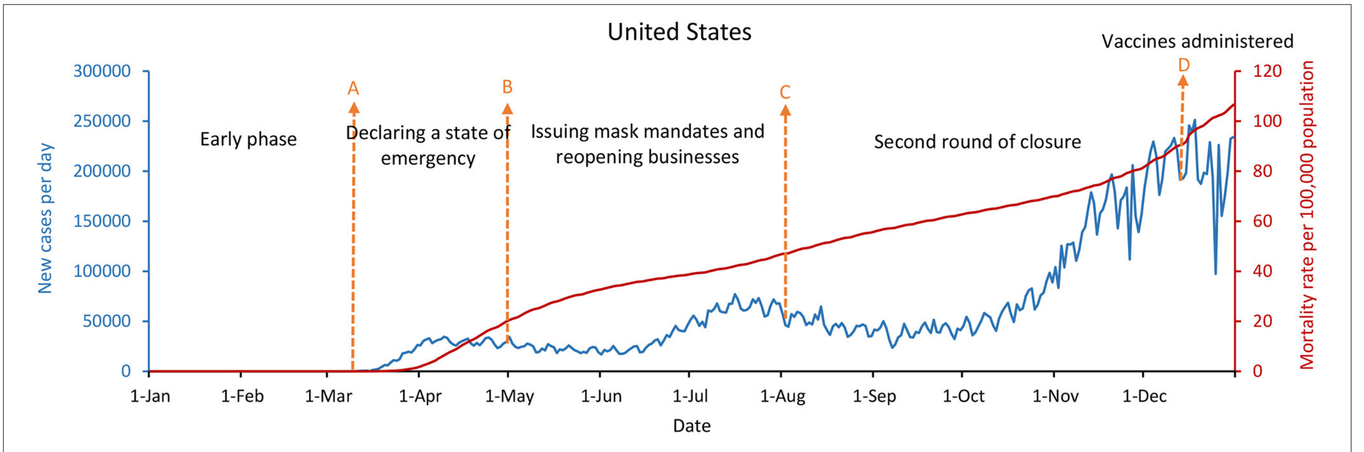


**FIGURE 4 |** The United States' COVID-19 epidemic curves and population mortality rate (between January 1 and December 31, 2020). **(A)** By March 13, 2020, the federal government escalated from public health to a national emergency, and by March 16, all the states had declared a state of emergency or a public health emergency. **(B)** Starting in May, reopening of businesses and restaurants, and masks mandate for everyone in public spaces. **(C)** Starting in August, the second round of closure. **(D)** Starting on December 14, the first doses of the COVID-19 vaccine were administered.

lockdown; however, these three countries focus on treating the severe cases and those with underlying conditions, and they have implemented measures that are essentially mitigation strategies.

## Containment Strategy

China's experience with SARS exposed weaknesses in the public health system and prompted a rethink of epidemic prevention policies. The government subsequently invested 6.8 billion RMB (US$850 million) to establish a new three-level network of disease control and prevention systems (16). Meanwhile, after decades of exploration and improvement, China has gradually constructed a public health system with medical institutions and medical administrative institutions (17). Wuhan experienced the problem of insufficient healthcare workers in the early stage, but the integration of the public health system and national power successfully transferred to "health care to all" (18). During combating the COVID-19 epidemic, the public health system of China mobilized the government and all sectors of society, unified command, tracked the overall situation of the epidemic, and scrambled to adapt to the development of the epidemic. For example, given the Chinese Spring Festival approaching, the national population flow would reach the peak, in order to control the continued export of infected patients in Wuhan, to avoid the nationwide spread of the epidemic, Wuhan must be locked down. After Wuhan city lockdown, responding to a dramatic increase in cases and inadequate health resources, mobilizing healthcare workers from other provinces to support Hubei, erecting Huoshenshan hospital, Leishenshan hospital, and 16 Fangcang shelter hospitals. Moreover, to interrupt the chain of transmission of the epidemic, a series of strict

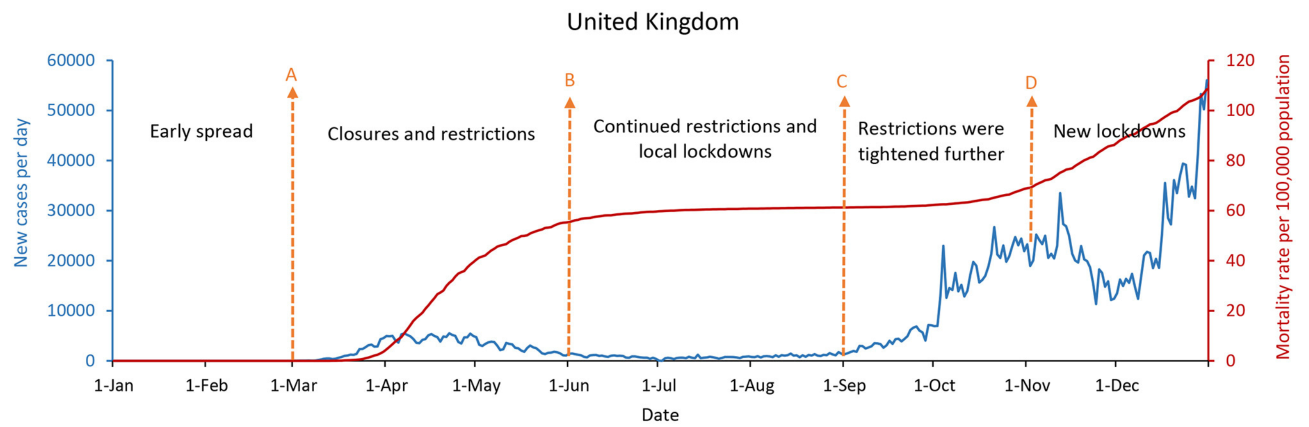


**FIGURE 5 |** The United Kingdom's COVID-19 epidemic curves and population mortality rate (between January 1 and December 31, 2020). **(A)** Starting in March 2020, closures and restrictions. Closures and cancelations in March, lockdown continues in April, and lockdown easing begins. **(B)** Starting in June 2020, continued restrictions and local lockdowns. Requiring individuals to self-isolate for 14 days upon arrival, making face masks compulsory on all public transport, and delaying lockdown restrictions. **(C)** Starting in September, the restrictions were tightened further. **(D)** Starting in November, new lockdowns.

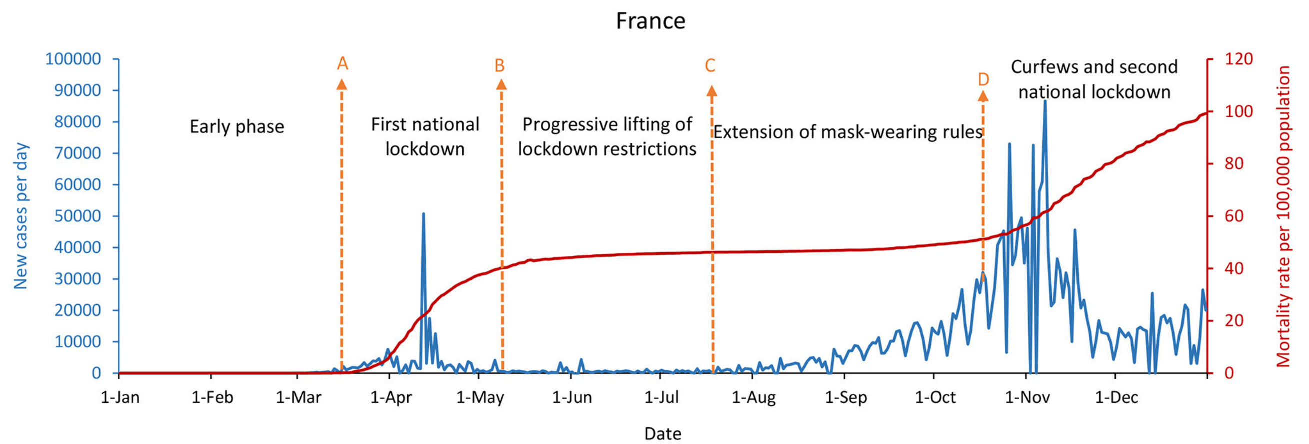


**FIGURE 6 |** France's COVID-19 epidemic curves and population mortality rate (between January 1 and December 31, 2020). **(A)** Beginning of March 17, 2020, first national lockdown. **(B)** Beginning of May 11, progressive lifting of lockdown restrictions. **(C)** Beginning of July 20, an extension of mask-wearing rules. **(D)** Beginning of October 17, curfews and a second national lockdown.

containment strategies were imposed in communities, screening and classifying management of "four categories of personnel," and implementing "four early's" measures (early detection, early diagnosis, early isolation, and early treatment) to the community, even to individuals. After the battle of Wuhan, the subsequent outbreaks of sporadic epidemics and even localized clusters in Harbin of Heilongjiang, Shulan of Jilin, Xinfadi of Beijing, and Qingdao of Shandong, all proved to be the most valuable window of time for China's full-scale nucleic acid testing (19).

Similar to China, after the SARS epidemic in 2003, Singapore invested a lot of resources in improving its epidemic prevention system, establishing an interdepartmental working group pre-planning system that can be activated immediately when it encounters a public health crisis and operates in a whole-of-government manner. It has also established a public health system that includes community general clinics, public hospitals, and the National Centre for Infectious Diseases (20). Singapore, a city-state and global travel hub in Southeast Asia faced a significant risk of imported cases and implemented strict travel-related measures that all travel restrictions and quarantine orders are capped at the standard 14 days based on the COVID-19 incubation period (21, 22). Since limited community transmission emerged, Singapore implemented strict surveillance and smart tracking measures using TraceTogether, the Ministry of Health raised public awareness on the importance of personal hygiene, tracking investigation combined with early isolation, early treatment, and other means effectively control the spread of the virus in the community. With a large number of migrant workers in Singapore, there was a surge in confirmed cases in early April 2020 when multiple clusters of foreign worker dormitories were discovered. A task force was formed to contain the spread in the dormitories and ensure the welfare of the workers. The task force sealed off dormitories with infection clusters, isolated those with symptoms, and moved some workers to new accommodations. Strict sanitation, hygiene treatment, and security isolation measures were implemented. Medical support was deployed to these quarters for early and extensive testing, isolation, and treatment (22).

South Korea experienced a public health crisis caused by MERS in 2015, which exposed a weakness in the national health disaster response system. Since then, improvements have been made at all levels and throughout the public and private health sectors to protect society from the threat of emerging infectious diseases (23, 24). After 5 years, the COVID-19 pandemic occurred. Without the stringent control measures adopted by most countries, Korea was very successful in rapidly smoothing the epidemic curve in the early stages of the epidemic by scaling up testing to detect cases as early as possible (25). Such as establishing more than 600 screening sites that are capable of performing SARS-CoV-2 nucleic acid tests, including public healthcare clinics, drive-through centers, and walk-in screening sites. Other measures include school closures, locking down areas with severe outbreaks, and banning gatherings (6). In late April 2020, the daily new cases reached their lowest level (<10 cases). However, since the lifting of strict restrictions, such as keeping social distance in early May, community transmission with unknown sources of infection and influx of foreign cases have continued. In addition, a series of outbreaks occurred at several large-scale gatherings and spread to local cities (24).

## Mitigation Strategy

The United States is a wealthy country and has a well-developed healthcare system, but it has relatively poor health status and healthcare coverage and does not provide its population with the best and most equitable healthcare treatment. The US insurance system is primarily based on private employers, and individual coverage is voluntary (25). Based on these characteristics, the United States is armed with numerous high technological and biological tools to fight the COVID-19 outbreak (10). However, the initial United States response to the pandemic was otherwise slow, in terms of preparing the healthcare system, stopping other travel, and testing. Meanwhile, the leader still remained optimistic (26). With the COVID-19 cases confirmed in all 50 states of the United States, the country has begun to implement a series of mitigation measures, including all the states that had declared a state of emergency or a public health emergency, school closures, extensive gathering bans, non-essential business closures, stay-at-home orders, bar/restaurant limits, primary election postponements, and mask-wearing ordinances. Unfortunately, the lack of national leadership and a patchwork of state and local government responses but perhaps most detrimental is the division of society along partisan lines (27, 28). In addition, there is also a primary issue in the United States: the poor coordination of testing efforts and the inability to test at scale to provide comprehensive national (or even state) surveillance (25). These reasons had led to the highest number of cases and deaths in the United States, globally.

The United Kingdom has a well-established and respected universal healthcare system (NHS) that invests heavily in public health, but the shortage of personal protective equipment (PPE) and the deaths of healthcare workers in the early phases of pandemic posed a significant risk to the patients and healthcare workers (29). Meanwhile, the United Kingdom declared the COVID-19 epidemic as influenza in the early stage, emphasizing that COVID-19 was unlikely to be interrupted completely and focused mainly on treating severe cases, most of which had mild symptoms. Matters worsened when Vallance initially rejected "eye-catching measures," such as stopping mass gatherings or closing schools. To widespread criticism, he floated an approach to "build up some degree of herd immunity" founded on an erroneous view that the vast majority of cases would be mild, such as influenza (30). With Italy, Spain, and France had taken firm public health action and was in complete lockdown, and the UK was also starting to work on preventing the disease. The policies were to be based on science, with an initial focus on containment, involving identifying people infected with SARS-CoV-2, contact tracing, and isolation of people with proven exposure (31). In addition, a package of intensive interventions was put in place including physical distancing, with a particular impact on leisure activities; workers being required to work from home where possible; shielding of both older individuals (70 years) and people in high-risk groups of all ages; school closures; and self-isolation of symptomatic individuals (32).

France benefits from its universal health insurance system, relatively large number of healthcare professionals and hospital beds, but the French system is complex, and the notoriously weak coordination between the different parts of the care system makes it more difficult for primary and social care providers and hospitals to mount a joint response. In addition, France experienced months-long protests and strikes by healthcare workers before the COVID-19 outbreak coming (33). In fact, the COVID-19 epidemic did not have a significant impact on France at the beginning of the outbreak. Subsequently, with the dramatic increase in new COVID-19 cases, France implemented strict intervention strategies in March 2020, such as implementing strict national lockdown, improving the COVID-19 detection, fully protecting the medical workforce, and strengthening research and clinical treatment methods for COVID-19. However, early dissemination of the government was intended to reassure the population that the probability of the virus spreading in France was low. Moreover, following the rapid spread of the virus in France toward the end of February, the government, totally unprepared for a pandemic (33). This was one reason for the poor control of the epidemic in France, the sharp increase in daily COVID-19 cases, and the high mortality rate per 100,000 population (as of December 31, 2020, the mortality rate per 100,000 population was 99).

## Containment vs. Mitigation Strategy

This study found that each country has implemented a series of non-pharmaceutical interventions at four levels of the epidemic: containment and surveillance, healthcare, border control, and community and society, but the effectiveness of the prevention and control measures were different among these six countries. China, South Korea, and Singapore, due to their experience with previous MERS and SARS epidemics, responding quickly, implementing strict interventions, and control the spread of the epidemic to keep the daily new cases and mortality rate per 100,000 population low. However, there are differences in the group behaviors of social people, such as community closure, home isolation, and social behavior self-discipline. In China, when a COVID-19 case was confirmed in a region, the community was immediately put under strict control or even lockdown, and large-scale nucleic acid testing of residents in the community, as well as tracing and home quarantine of close contacts. In addition, criminal detention will be imposed on those who conceal their travel and hinder the prevention and control of the epidemic. Also, people must wear masks to take public transports or to enter public places.

In Singapore, mask-wearing continues to be mandatory in public transport and all public places (34). In addition to the many violators who have been fined for not abiding by safe distances and gathering in excess of the maximum number of people, some restaurants, bars, and other businesses have been ordered to close and face fines for continuing safety violations. However, there are community cases of those who continue to go out and participate in activities after developing respiratory symptoms, and large-scale virus interdiction measures, such as those in the first wave of the outbreak have been relaxed (35). Furthermore, some users of TraceTogether even switched off their apps or left their tokens at home in protest (34). In South Korea, under the revised anti-infectious disease law, violators can face up to a year in prison, a 10 million won fine, or in the case of foreign passport holders deportation. However, it was only in May 2020 that the Seoul government began requiring people to wear masks on public transport and in taxis, and the weak awareness of the public not to comply with the quarantine regulations has caused mass cluster infections (36).

In contrast, the United States, the United Kingdom, and France, due to their lenient approach at the beginning of the epidemic, made the subsequent fight against the epidemic more difficult. Although a series of non-pharmaceutical interventions were implemented, and these countries have initiated vaccination programs for COVID-19, the results seem to be less than satisfactory. Of course, there are some reasons why implementing a strict containment strategy is simply not possible in the United States, the United Kingdom, and France. There are at least two reasons for this. The primary reason is that these are homes of intense liberal democratic norms, and the government cannot simply impose any type of lockdown. In Sweden, it is even constitutionally forbidden to impose lockdown unless there is a war (37). There were many violent protests, and people were even beaten or killed in the United States and France over simply mask mandates during the COVID-19 pandemic (38–40). Also, the United States is a federal system, and the United Kingdom is actually many countries combined into one, meaning that it is not possible for the central government to take over all decisions for the lower-level political units.

This study compared prevention and control strategies among China, Singapore, South Korea, the United States, the United Kingdom, and France, and examined the effectiveness of containment strategies and mitigation strategies. However, this study also has limitations that need to be considered. Other studies should be developed in order to confirm what has been achieved. Such as we can further work on the population-based epidemiological studies, respectively, in these six countries to improve non-pharmaceutical interventions.

## CONCLUSION

Based on this study it seems that China, Korea, and Singapore, which implemented strict containment measures, had significant outbreak control. In the United States, the United Kingdom, and France, which implemented mitigation policies, the effect of epidemic prevention and control was not significant that the epidemic continued or even increased relatively quickly. However, until the vaccine is globally available and effective, countries still need to address the current COVID-19 epidemic with non-pharmacological measures to avoid further damage. Meanwhile, the successful practices in China, Singapore, and South Korea show that containment strategies were practices that work especially at the individual level identifying and managing infected patients and their close contacts.

## DATA AVAILABILITY STATEMENT

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

## AUTHOR CONTRIBUTIONS

HC and GS conceived the paper and study guarantors. HC, YZ, XW, MY, and JJ collected the data. HC drafted the manuscript. LS, YZ, XW, MY, and JJ revised the manuscript. GS contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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# Bioethical Concerns During the COVID-19 Pandemic: What Did Healthcare Ethics Committees and Institutions State in Spain?

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**Objectives:** Each new wave of the COVID-19 pandemic invites the possible obligation to prioritize individuals' access to vital resources, and thereby leads to unresolved and important bioethical concerns. Governments have to make decisions to protect access to the health system with equity. The prioritization criteria during a pandemic are both a clinical and legal-administrative decision with ethical repercussion. We aim to analyse the prioritization protocols used in Spain during the pandemic which, in many cases, have not been updated.

**Method:** We carried out a narrative review of 27 protocols of prioritization proposed by healthcare ethics committees, scientific societies and institutions in Spain for this study. The review evaluated shared aspects and unique differences and proffered a bioethical reflection.

**Results:** The research questions explored patient prioritization, the criteria applied and the relative weight assigned to each criterion. There was a need to use several indicators, being morbidity and mortality scales the most commonly used, followed by facets pertaining to disease severity and functional status. Although age was initially considered in some protocols, it cannot be the sole criterion used when assigning care resources.

**Conclusions:** In COVID-19 pandemic there is a need for a unified set of criteria that guarantees equity and transparency in decision-making processes. Establishing treatment indications is not the aim of such criteria, but instead prioritizing access to care resources. In protocols of prioritization, the principle of efficiency must vary according to the principle of equity and the criteria used to guarantee such equity.

**Keywords: equity, morbidity, mortality, prioritization, triage, healthcare ethics committees, COVID-19**

## INTRODUCTION

The COVID-19 pandemic has posed many ethical questions to healthcare professionals worldwide (1–3). One concern, in particular, has arisen due to the shortage of human and material resources within an epidemiologic setting. Indeed, as a result of such a circumstance and despite the efforts undertaken, global health systems have been pushed to their limits. The shortfall—whether temporary or for an extended time—has needed prioritization criteria for accessing to such resources.

Each new wave of the COVID-19 pandemic invites the possible obligation to prioritize individuals' access to vital resources everywhere, and for which some hospitals and institutions have drafted documents that should be analyzed and re-evaluated continually.

Governments have to make decisions to protect access to the health system with equity (4). The prioritization criteria during a pandemic are both a clinical and legal-administrative decision with ethical repercussion. The criteria proposed by European scientific societies differ in some aspects from the recommendations of bioethics committees (5).

Prioritization policies could differ depending on the health system of each country. Most of them emphasized the need to save the greatest number of lives, but they had different approaches on how to achieve it, different clinical criteria to use and ethical principles to defend (6). In Spain, each attempt tried to give an answer to these questions, the scientific societies, the healthcare ethics committees (HECs), so a retrospective analysis of all of them is necessary, providing a bioethical approach. This preliminary work can be the basis to compare priorization policies in other countries, since it is conceivable that in a few years there will be corresponding documents at EU level.

The pandemic in Spain had a considerable impact, so that during the first wave there were more than 2,000 daily hospitalizations for more than 2 weeks, becoming the eighth country with the highest number of cases and a mortality rate that reached being the fifth in the world (60.7/100,000), which meant an overload of the health system (7, 8). In these circumstances, some hospitals, HECs, and institutions were forced to develop documents in which the prioritization of people's access to vital resources was recommended. These documents generated in a situation of exceptionality are still in place in some centers, so a reevaluation and exhaustive analysis of them is necessary to be able to update them to current circumstances.

The pandemic may have revealed the scarce bioethical resources available in our health systems (9). Our aim is to analyse the prioritization protocols used in Spain during the COVID-19 pandemic. Yet, as the current set of prioritization criteria continues presenting several, difficult-to-respond matters, perhaps it is time to reflect on what was proposed and include an ethical vision when considering efficient resource management (10).

## METHODS

In an attempt to provide such clarification, we carried out a narrative review of the protocols and documents prepared in Spain by different HECs, scientific societies, and other institutions that have responded to various ethical matters related to the pandemic and scarcity of resources. The search was diversified into documents elaborating by HECs, Hospitals, Universities, Scientific Societies, Regional Institutions and Nacional Institutions, We collected public documents those available on the intranet of these institutions and in hospitals' HEC network, as well as those internal documents sent directly to researchers from this project. The documents were analyzed by the authors, experts in bioethics. We reviewed 85 documents, discarding 58. The main exclusion criterion used was the absence of the prioritization issue in the documents analyzed. 27 documents were selected for a final analysis (11). Fifteen of the documents had been prepared by HECs 3 by Regional Institutions, three by Scientific Societies, three by Hospitals, two by Nacional Institutions, and one by a University. The data to be extracted from the documents were agreed in order to evaluate the answers given to the dilemmas raised by the researchers. So the questions were: Who decides which criteria to use to prioritize individuals?, What should be prioritized: lives / years of life / quality of life?, What criteria should be used?, Is it enough to recommend some scales or is it convenient to prioritize some criteria and set "cut-off points?," Can an age limit be set for resource access?, Should the use of resources be limited to patients with disabilities?, Should patients with COVID-19 be given higher priority than those without COVID-19?, Is it ethical to prioritize by order of arrival?, Can healthcare professionals be prioritized?, Who makes decisions for each patient? What is the role of HECs in establishing resources access?, Is a discussion on legal regulations necessary to prioritize resources? The answers to these questions were evaluated and. a critical assessment was made from the ethical and/or administrative legal point of view. Below the results obtained for each question are described, with the common points and differences. The summary of the results is presented in **Table 1**.

## RESULTS

### Q1. Who Decides Which Criteria to Use to Prioritize Individuals?

To know how these decisions were made in the pandemic, it is necessary to remember the sequence of events.The first case of COVID-19 in Spain was on 31 January 2020 (7). On 1 March, 83 cases had been confirmed, and the spread of the virus became widespread throughout the national territory. On 10 March, more than 1,500 were already infected, whilst on 11 March, 2020, the World Health Organization (WHO) considered that COVID-19 had to be characterized as a pandemic. On 12 March, RD 6/2020 was approved, empowering the State Health Administration to act in the event of a shortage of medicines, health products, or any product necessary to protect health (12). However, it was not until April 2 when the Ministry of Health issued its first report on ethical aspects in pandemic situations (13). At this time, there were more than 120,000 infected and 11,700 deaths. The absence of centralized guidelines had, however, led many HECs and institutions to prepare their

**TABLE 1 |** Main data of the analyzed documents.

| | Publication date | Scope of action | Objective in *triage*. | How many criteria were used? | Were fundtional situation criteria used? (Which?) | Were severity criteria used? (Which?) | Were Prognostic criteria used? (Which?) | Were age criterion used? | Was the age limit for access to resources specified? | Were quality of life criteria used? | Was it prioritized in order of arrival? | Were some criteria prioritized over others? | Were non-covid patients taken into account? | Was health care prioritized? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. DBC del H.U. Infanta Elena (Valdemoro, Madrid) | 10-3-20 | EC | N°L | 4 | Yes (Barthel) | Yes (SOFA) | Yes (Charlson) | Yes | No *R(a) | No | No | Yes (F > S > P) | YES | No |
| 2. CEAS H.U. La PriNDesa (Madrid) | 13-3-20 | EC | N°L > N°Y | 5 | Yes (NS) | Yes (Apache) | Yes (NS) | Yes | yes, <80 años | No | Yes | No | Yes | No |
| 3. CEAS H. Clínico San Carlos. (Madrid) | 16-3-20 | EC | N°L | 5 | Yes (NS) | Yes (SOFA y Apache) | Yes (NS) | Yes | yes, <80 años | Yes (NS) | No | No | Yes | No |
| 4. CEAS HUF Alcorcón. (Madrid) | 16-3-20 | EC | N°L > N°Y | 3 | Yes (Barthel) | No | Yes (Charlson) | Yes | No | No | No | Yes (P > F > A) | No | No |
| 5. CEAS H. Severo Ochoa. (Madrid) | 17-3-20 | EC | N°L | 4 | No | Yes (SOFA y Berlin) | Yes (Charlson) | Yes | No | No | R | No | Yes | No |
| 6. CEAS Getafe. (Madrid) | 18-3-20 | EC | N°L > N°Y | 4 | Yes (Barthel) | Yes (NS) | Yes (Charlson y Profund) | Yes | No * R(a) | No | No | Yes (S>P>A) | Yes | No |
| 7. Grupo bioética SEMICYUC | 20-3-20 | SS | N°L > AC | 4 | Yes (NS) | Yes (SOFA) | Yes (NECPAL) | Yes | yes, <80 años | Yes (NS) | R | Yes (S > P > A) | Yes | No |
| 8. CEAS H. U. La Paz. (Madrid) | 22-3-20 | EC | N°L | 2 | Yes (NS) | No | Yes (NS) | Yes | No * R(a) | No | No | No | No | No |
| 9. CEAS H.U. Cruces. (Barakaldo, Bizcaia) | 23-3-20 | EC | NS | 2 | No | Yes (NS) | No | No | No | Yes (NS) | No | No | No | No |
| 10. UCI Osakidetza. País Vasco | 23-3-20 | RI | N°L > N°Y | 4 | Yes (Barthel) | Yes (SOFA) | Yes (Por patologías) | Yes | yes, <80 años | No | No | Yes (S > P > A) | No | No |
| 11. Comité de Bioética de España | 23-3-20 | NI | N°L | NS | No | No | No | Yes | No * R(a) | No | R | No | Yes | Yes |
| 12. CEAS C.H.U. de Badajoz. | 24-3-20 | EC | N°L | 3 | Yes (NS) | Yes (NS) | Yes (NS) | Yes | No * R(a) | No | No | Yes (F/P) | Yes | No |
| 13. Comité de Bioética de Cataluña | 24-3-20 | RI | N°L > N°Y > QL | 3 | Yes (NS) | Yes (SOFA) | Yes (NS) | Yes | No | Yes (NS) | No | Yes(S = P = A) | No | No |
| 14. CEAS H.G.U. José María Morales Meseguer (Murcia) | 24-3-20 | EC | N°L | 5 | Yes (Barthel) | Yes (SOFA) | Yes (Profund o NECPAL) | No | No | Yes (ECOG) | No | Yes (S > P/Q) | No | No |
| 15. CEAS H. U. Clinic Barcelona. | 26-3-20 | EC | NS | 4 | Yes (NS) | Yes (SOFA) | Yes (MACA o PCC) | Yes | yes, <80 años | Yes (NS) | R | Yes (F > P > A) | No | No |
| 16. Observatorio de Bioética Y Derecho de la Universidad de Barcelona. | 30-3-20 | RI | N°L > QL | 5 | Yes (Barthel) | Yes (SOFA o Apache) | Yes (MACA o PCC) | Yes | yes, <80 años | Yes (NS) | No | No | No | No |
| 17. Comisión Asesora de Bioética Del PriNDipado de Asturias CABEPA. | 31-3-20 | EC | N°L | NS | Yes (NS) | No | No | No | No * R(a) | No | R | Yes (F) | Yes | No |

*(Continued)*

**TABLE 1** | Continued

| | Publication date | Scope of action | Objective in *triage*. | How many criteria were used? | Were fundtional situation criteria used? (Which?) | Were severity criteria used? (Which?) | Were Prognostic criteria used? (Which?) | Were age criterion used? | Was the age limit for access to resources specified? | Were quality of life criteria used? | Was it prioritized in order of arrival? | Were some criteria prioritized over others? | Were non-covid patients taken into account? | Was health care prioritized? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18. Ministerio de Sanidad. | 3-4-20 | NI | N°L | NS | No | No | No | No | No * R(a) | No | R | No | Yes | No |
| 19. H. Ernest Lluch de Calatayud (Zaragoza) | 16-4-20 | H | NS | 2 | No | Yes (NS) | Yes (NS) | No | No | No | No | No | No | No |
| 20. Cátedra de Cuidados Paliativos, U. de Vic (UVIC-UCC), | abr-20 | U | NS | 2 | Yes (Frágil-VIG o CFS) | No | Yes (MACA, PCC o NECPAL) | No | No * R(a) | No | No | No | No | No |
| 21. Sociedad de Geriatría y Gerontología | 4-5-20 | SS | NS | 3 | Yes (NS) | Yes (NS) | Yes (NS) | No | No | No | No | No | No | No |
| 22. Sociedad Cardiología Geriátrica | 11-6-20 | SS | N°L | 2 | Yes (NS) | No | Yes (NS) | No | No * R(a) | No | No | No | No | No |
| 23. CEAS H.U Donostia | ND | EC | N°L > N°Y | 3 | No | Yes (NS) | Yes (NS) | Yes | No * R(a) | No | R | No | Yes | Yes |
| 24. CEAS H.M. Hospitales. Triaje | ND | EC | N°L | 3 | No | Yes (NS) | Yes (NS) | Yes | No * R(a) | No | No | No | Yes | No |
| 25. H. U. Puerta de Hierro | ND | H | N°L | 3 | Yes (NS) | Yes (SOFA) | Yes (NS) | Yes | No * R(a) | No | No | Yes (F > P) | No | No |
| 26. CEAS de Segovia. | ND | EC | N°L > QL | 3 | No | Yes (NS) | Yes (NS) | Yes | No * R(a) | No | R | No | No | No |
| 27. Medicina Intensiva del H. Vall d'Hebron (Barcelona) | ND | H | NS | 5 | Yes (NS) | Yes (NS) | Yes (NS) | Yes | yes, <80 años | Yes (NS) | No | Yes (A > P) | No | No |

*ND, No data; EC, Ethics Committees; H, Hospital; RI, Regional Institution; NI, Nacional Institution; SS, Scientific Society; U, Universidad; N°L, To save as many lives as possible; N°Y, To maximize the number of years of life saved or increase the chances of living longer; QL, To prioritize the quality of life; NS, Not specified; *R(a), Explicit refusal to use age as the sole criterion to limit access to a resource: R, Rejects it as a criterion; F, Fundtional; S, Severity; P, Pronostic: A, Age; Q, quality of life.*

own documents with recommendations on prioritization prior. The first of these documents was published on 10 March, 2020, by the Department of Bioethics at Infanta Elena University Hospital (14). Since then, and until the dissemination of the Ministry of Health's recommendations, on 2 April, 2020, another 16 documents were identified including the critical document from the Bioethics Committee of Spain, on March 25, about ethical aspects of priorization in health resources (15).

## Q2. What Should Be Prioritized: Lives/Years of Life/Quality of Life?

Another concern issue is to determine the objective in prioritization, as several approaches are possible (16–18):

- To save as many lives as possible.
- To maximize the number of years of life saved or increase the chances of living longer.
- To prioritize the quality of life, i.e., disability-free survival over isolated survival (to maximize the number of QALYs, quality-adjusted life years).

When analyzing the documents, 12 of 27 (44.4%) stated that the objective was to save the greatest number of lives. Another six (22.2%) proposed a combination of the first two points, and four (14.8%) proposed integrating quality of life in the objectives. The remaining documents (18.5%) did not explicitly comment on this objective.

## Q3.What Criteria Should Be Used?

Most of the documents reviewed (88.9%) recommended certain criteria to take into account during prioritization (**Table 1**). All recommended to use a combination of several criteria, between 2 and 5, with a median of four.

The criteria used can be divided into:

- Criteria related to the clinical situation or severity of the patient, collected in 20 (74.1%) documents. The SOFA scale was the most used, followed by APACHE.
- Prognostic criteria for morbidity and mortality in 23 (85.2%) documents. The most recommended criteria included the Charlson scale, MACA, PPC, PROFUND and NECPAL. The majority did not, however, specify the scales to be used (51.8%).
- Age criterion, collected in 19 (70.4%) documents, which is analyzed later.
- Functional situation of the patient (recommended in 19 (70.4%) documents), with the Barthel scale being the most used.
- The patient's quality of life of the patient was recommended in eight (29.6%) documents, amongst which only one specified the ECOG scale.

## Q4. Is It Enough to Recommend Some Scales or Is It Convenient to Prioritize Some Criteria and Set "Cut-Off Points"?

The levels of recommendation varied: in some cases, the clinical or functional situation of the patients was recommended to be taken into account, whilst in other instances, the use of certain scales, such as the aforementioned Brathel, SOFA, etc., was proposed. Only some (44.4%) ranked some criteria: six prioritized severity and prognosis criteria, whilst five the patient's functional situation.

## Q5. Can Age Limit Be Set for Resource Access?

The document presented by the Ministry of Health in 2 April 2020 (13) shows that the age criterion cannot be used to deny or limit health care and the use of certain measures. It maintains "the absolute ban on criteria based on discrimination for any reason to prioritize patients within those contexts... excluding patients from access to certain resources (e.g., applying said limitation to anyone aged >80 years) is contrary, by discrimination, to the fundamentals dictated by our rule of law" (Article 14 of the Spanish Constitution).

Previously, the Bioethics Committee of Spain (15) had already established that the age criterion could not be used to deny or limit health care and the use of certain life support measures.

However, the age criterion was included as a priority criterion in six of the protocols that were published previously to the Ministry of Health document, namely limiting access to intensive care to those aged >80 years. The Semicyuc document (19) recommended that patients with similar characteristics prioritize the person with the longest QALY. In the remaining protocols, age was included as one more criterion to consider when prioritizing, e.g., in the Charlson scale, age effectively influences the clinical prognosis. Non-etheless, 12 (44.4%) documents reflect an explicit refusal to use age as the sole criterion to limit access to a resource.

## Q6. Should the Use of Resources Be Limited to Patients With Disabilities?

The presence of the recommendation to prioritize disability-free survival over isolated survival in the Semicyuc protocol (19) of 23 March motivated the Directorate General for Disability Policies of the Ministry of Social Rights and Agenda 2,030 to consult with the Bioethics Committee of Spain. The latter indicated in its report (15) that the criteria used must respect the dignity of the person, as well as the equity and protection against those vulnerable; The document published by the Ministry of Health (13) also recommends avoiding discrimination based on disability, explaining that the only valid reasons for prioritization would be the patient's clinical situation and objective survival expectations.

## Q7. Should Patients With COVID-19 Be Given Higher Priority Than Those Without COVID-19?

In this sense, 11 (40.7%) documents do reveal the need to allocate resources to patients with non-COVID-19 pathologies to avoid discrimination. Some documents explain that prioritization criteria must be the same for all pathologies, even prioritizing patients without COVID-19 due to the known resource efficiency in these cases.

## Q8. Is It Ethical to Prioritize by Order of Arrival?

The criterion "first to arrive, first to be admitted", was considered as a possibility in only one case; eight (28.6%) explicitly rejected it. Several documents also criticized this principle (20), since the use of a resource may imply that it is denied to another person who could benefit more or could unfairly be detrimental to those who become ill later (3). In this sense, the Bioethics Committee of Spain clarifies in its document that this criterion would not respect the principles of equality and justice (15).

## Q9. Can Healthcare Professionals Be Prioritized?

None of the documents raised the possibility of prioritizing care to healthcare professionals with respect to resource allocation. The document presented by the Bioethics Committee of Spain (15) does address it, suggesting it could be ethically acceptable per the principle of justice to prioritize individuals who have placed their health at a greater risk. Similarly, by virtue of the ethical principle of reciprocity, society must support people who accept a disproportionate burden or risk to protect the public good.

## Q10. Who Makes Decisions for Each Patient? What Is the Role of HECs in Establishing Resources?

Caring for patients with and without COVID-19 raises the question of who should make the decision regarding prioritization. Should it be the medical team, critical services, ethics committees or a group of experts created ad hoc? On one hand, decision-making by people outside the supervising medical team, be it the HECs or a group of experts, could improve impartiality and reduce emotional overload for the aforementioned team. On the other hand, HECs have been suggested as not being designed for this type of decision-making processes. It seems clearer then, that the decision be based on a clinical assessment made by the supervising medical team that personalizes protocols to a patient's specific situation.

In this respect, the document presented by the Ministry of Health is unambiguous in that decisions will be made by the supervising medical team, so that a third party is unsuitable to impose criteria unless such party be involved in the patient's care. However, the Ministry also recommends the benefit of requesting or receiving guidance from reference HECs when made possible by time availability or from other physicians with more experience.

# DISCUSSION

Q1. In an attempt to answer this question, we should consider that prioritizing people does not merely comprise establishing scientific-medical criteria to select patients who will benefit the most from a certain resource. Prioritization, in fact, alludes to restricting or suspending a constitutional right to health protection due to the scarcity of resources. In other occasions, however, such prioritization would not be carried out otherwise, given that adaptation of therapeutic efforts for the benefit of the individual and not due to a lack of resources.

Establishing prioritization criteria is both a clinical and legal-administrative decision, for which the report by the Bioethics Committee of Spain (15) urged the Ministry of Health to lead and coordinate the development of common, unique criteria for the entire national territory (13, 21). During the pandemic there can be collisions of rights and governments have to make decisions to guarantee access for all people to available health resources (4). Neither professionals nor scientific societies set health priorities with respect to the application of new treatments, vaccinations, etc. The health authority should set prioritization criteria; the hospital management bodies should agree on a protocol, as it concerns applying these criteria; and the medical team should make a decision that is in accordance with a patient's specific situation. In this way, the healthcare provider will prudently apply criteria that have previously been adopted by the authority, whilst considering the context and particularities of a patient.

Unfortunately, this procedure was not that followed during the first wave of the pandemic. But from this learning, the prioritization of vaccines was carried out with a more logical sequence in Spain. The Ministry of Health proposed a technical committee made up of lawyers, scientists and ethicists and they established recommendations to prioritize vaccines in people with a higher risk of serious disease, so as to guarantee equity at the national level. The criteria were communicated transparently and assumed by all regional institutions and hospitals. In addition, they were periodically reviewed to adapt to events (22).

Q2. This is an essential question because its consequences are decisive in establishing prioritization criteria. Choosing the first criterion considers the equal value of all human life. It would not, therefore, be possible to make distinctions between individuals on other factors except for the probability of survival. On the other hand, adopting the second criterion would make it possible to deny older people access to resources if other younger people or people with underlying pathologies that decrease life expectancy were in need of such. If the third criterion receives priority, access to health resources could be denied to people with disabilities, chronic diseases, dependents, etc.

The document presented by the Ministry of Health (13) states that the objective should be the maximum benefit conferred when saving possible lives, a criterion recommended by the WHO (23) and the only one that conforms to the Spanish Constitution.

Q3. We were facing a disease, in which evolution and treatment response were unknown, or at least, not as much as in other pathologies. It was not often possible to know which patients did or did not benefit more from a resource. Compounding this was the possibility that there were no resources for all those who could benefit from such.

The use of several criteria in most of the protocolsmay indicate that no value is in itself sufficient to determine which patients should receive scarce resources. It further underlies an apparent consideration by all documents, namely the use of multiple values was necessary to make a fair decision on resource allocation and it was, therefore, adaptable to the context of the patient (3).

Q4. The first approach that does not establish clear recommendations incurs the risk of being ambiguous; however, if the criteria established is too narrow, the professional loses the flexibility needed when evaluating each patient. Retrospective studies assessing results obtained with the different scales are warranted to establish more precise recommendations.

Q5. The introduction of the age criterion may have to do with a possible erroneous approach to prioritization objectives. If it is intended exclusively to maximize the use of healthcare resources, that objective will lead to the adoption of criteria that are discriminatory from a constitutional point of view. A priority objective could be to guarantee equitable access to the constitutional right to health protection, as established by the Oviedo Convention and the Universal Declaration of Bioethics and Human Rights. Efficiency alone should, therefore, not be taken into account without the integration of the principle of equity (21).

Q6. Prejudice against people with disabilities should be avoided. Doing otherwise would be incompatible with the International Convention on the Rights of Persons with Disabilities, which was ratified by Spain in 2008.

Q7. There is a risk of allocating most resources to patients with COVID-19 during the pandemic at the expense of patients with other pathologies. Similarly, on some occasions, the effectiveness, and efficiency whilst using resources in the former group may not be as clearly defined as in patients with other intensive pathologies such as stroke, acute myocardial infarction, multiple trauma or in cases of oncological surgeries. Therefore, resource distribution should be fair, and proportioned in such scenarios.

Q10. The criterion of adopting prioritization decisions through healthcare professional groups has also been proposed in other countries. For example, a document prepared by the German Society for Intensive Care (24) suggests the intervention of two intensive care physicians, a representative from the nursing staff and a person with other training, such as clinical ethics.

### Q11. Is a Discussion on Legal Regulations Necessary to Prioritize Resources?

As indicated at the beginning of the document, common prioritization criteria should be established throughout the national territory by those who have the powers to complete such actions, which in this case, is the Ministry of Health. Within the inter-territorial council, it must urge the creation of a task force and the elaboration of a document that provides a framework for decision-making processes in line with constitutional order and recommendations generated by national and international bioethics committees within the last, few months. Such an action has been undertaken in the case of prioritization of vaccine administration (17).

## CONCLUSIONS

Prioritizing people's access to vital resources has generated several concerns that have led various HECs and institutions to try to resolve them differently This has been reflected in the great heterogeneity of the different prioritization documents. Unifying criteria would be necessary to guarantee fairness and transparency in decision-making processes. The report by the Ministry of Health on the ethical aspects in pandemic situations can be a model framework; however, a document at a national level that specifies certain aspects is necessary. It is not a matter of whether to establish an indication or not for a resource; rather, it is about the prioritization of access to resources. The principle of efficiency and prioritization criteria pertaining to such principle (which was the first response given from the HECs, in general) must be modulated by the principle of equity and the introduction of prioritization criteria that guarantee the prior. An update and adaptation of initial protocols to the healthcare practices of each hospital are necessary. In this respect, HECs have an important role in the participation of multidisciplinary teams that help professionals who request such guidance during decision-making processes.

## AUTHOR CONTRIBUTIONS

JR-H, ÍM, MH, and PP-M: conceived and designed the revision of the protocols. PH, JR-H, JM, and MN: reviewed the protocols. JR-H and EG-N: conceived the manuscript. JR-H: made the initial version of the manuscript. All authors the signatories contributed to the analysis and interpretation of the data, made a critical review of the article with important intellectual contributions to it, and approved the final version for approval.

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BRIEF RESEARCH REPORT
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# Testing Extended Parallel Processing Model in the Korean COVID-19 Context: Effect of Moral Intuitions as Moderators

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Despite the possible social implications of the coronavirus disease 2019 (COVID-19), previous studies of the extended parallel processing model (EPPM) in the context of COVID-19 overlooked the emotional aspects when processing fear-inducing COVID-19-related messages. Drawing upon the moral foundation theory (MFT), this study aimed to (a) apply EPPM in the Korean COVID-19 context, (b) introduce MFT and explain why moral intuitions can be related to the processing of COVID-19 messages, and (c) examine the moderating role of moral intuitions in the EPPM model. Based on the theoretical backgrounds, this study tested EPPM hypotheses and also tested whether moral intuition can moderate the relationship between perceived self-efficacy, perceived threat, fear of COVID-19, and health compliance behavioral intention. This study conducted an online survey using measurements of perceived self-efficacy, perceived threat, MFQ-20, fear of COVID, and health compliance. Our study showed three main findings. First, our study found the main effects of (a) self-efficacy on health compliance behavioral intention and (b) perceived threat on health compliance behavioral intention. Second, our study found that morality moderated the main effects of self-efficacy or perceived threat and also moderated EPPM interaction on fear of COVID. Third, the moderation of morality in the relationship between self-efficacy and health compliance behavioral intention showed that health compliance intention decreased as morality increased. Our findings suggest that people can consider COVID-19 as a social and moral issue that involves protecting others.

**Keywords: COVID, morality, fear, self-efficacy, moral foundation theory, EPPM**

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## INTRODUCTION

As the coronavirus disease 2019 (COVID-19) global pandemic worsened, previous studies applied and examined the extended parallel processing model (EPPM) by Witte (1) in the COVID-19 context (2–4). Although previous studies on EPPM have found some important moderating variables, these studies overlook the role of morality in the context of EPPM and COVID-19. As Kim and Chung (5) noted, people might perceive COVID-19-related messages and behavioral intentions as a moral issue that involves their concerns about infecting and harming others. It was also suggested that people in collectivist societies, such as East Asia and South Korea, could especially perceive COVID-19 as a moral issue, rather than just a disease (5). However, previous studies on EPPM did not consider morality at all and also they did not consider it as a moderator when applying EPPM in the COVID-19 context.

One of the challenges in considering morality in the EPPM and COVID-19 context entails how to define morality and measure it for use in quantitative research. In this regard, moral foundation theory (MFT) (6) offers a useful theoretical and methodological tool that integrates morality in the COVID-19 context. Specifically, MFT suggests that human moral issues generally involve five discrete moral intuitions: care, fairness, loyalty, authority, and purity. These moral intuitions have been conceptualized and validated as quantifiable measurement tools that can be used and applied to various human moral issues (7).

Drawing upon the theory of EPPM and MFT, this study aims to (a) apply EPPM in the Korean COVID-19 context, (b) introduce MFT and explain why moral intuitions can be related to the processing of COVID-19 messages, and (c) examine the moderating role of moral intuitions in the EPPM model.

## EXTENDED PARALLEL PROCESSING MODEL

The EPPM argues that evaluating a fear-inducing message initiates either fear control or danger control processing (1, 8). It also explained that the type of processing that occurs depends on the perceived self-efficacy and perceived threat. This means that fear control processing occurs when individuals perceive the fear induced by a message as greater than self-efficacy and are consequently more likely to control the fear itself, rather than critically accept the message; therefore, they would more likely reject the message (fear control processing). Conversely, danger control processing occurs when individuals perceive self-efficacy as greater than the fear induced by the message, therefore, they would more likely accept the message (danger control processing). In short, EPPM proposes that fear control processing occurs in low efficacy/high threat conditions (LE/HT), and danger control processing occurs in high efficacy/low threat conditions (HE/LT).

Previous studies have applied EPPM in the COVID-19 context across different countries, such as East Asia (3, 4, 9), North America (10–12), and the Middle East (2, 13, 14). These studies proposed various unique variables that relate to applying EPPM to the COVID-19 context, such as age, gender, education, economic status, work experience, risk information exposure, intention to follow government recommendations, willingness to work, and self-esteem.

Although recent studies suggest that COVID-19 situations may involve morality (5, 15–17), it has not been tested as a moderator in EPPM. In the next section, we introduce MFT and argue how morality can be involved in the psychological processing of COVID-19 situations.

## MORAL FOUNDATION THEORY

In essence, morality entails judging which specific human actions are good or bad; such judgment is based on moral standards with which people can generally agree [(18), p. 119–120]. The MFT suggests that humans developed discrete categories of morality to distinguish between good and bad, which can be generally applied across cultures through human evolution (19). Specifically, such discrete morality generally involves five moral domains: care, fairness, loyalty, authority, and purity (20). Based on the idea of discrete moral domains, MFT argues that humans judge actions as good or bad using moral domains (care, fairness, loyalty, authority, purity), which are both innate and learned and vary across cultures [(6), p. 68].

Although the application of MFT heavily depends on each context, conceptualizing the five moral domains from the MFT offers some useful insights into why COVID-19 situations might involve morality issues. In COVID-19 contexts, care violation involves infecting loved ones due to not wearing masks or maintaining social distancing; fairness violation involves people who were in close contact with COVID-19-confirmed patients, but ignore the mandatory self-quarantine period; loyalty violation involves not staying at home while other community members are in lockdown situations; authority violation involves not following the COVID-19 policies of the governments and acting upon individual beliefs or false infodemic news; purity violation involves the intentional gathering of a crowd of people, even when such actions are unnecessary for survival.

Few studies have empirically tested how the five moral intuitions can be related to emotional responses or COVID-related behavioral intentions (5, 15, 21, 22). However, these studies showed mixed results. For example, Chan (15) found that care and fairness were significant predictors of COVID-19-behavioral intentions, while loyalty had a marginal effect on wearing masks and social distancing. In the context of East Asian countries, Triandis (17) explained that moral transgression in collectivist cultures, such as Korea and Japan, might depend on the communal, autonomy, and divinity codes; violating these codes may arouse contempt, anger, and disgust because of loyalty, authority, and purity domain violation [(16, 17), p. 916]. Regarding COVID-19 and moral violation in a collectivist society, Kim and Chung (5) revealed how the loyalty and authority domain in collectivist cultures is used to judge moral actions, as it shows an example of a society where mask wearing has become an autonomous communal code and not wearing a mask is considered as betraying communal expectation. This study also found that many South Koreans considered going to crowded entertainment places as an immoral act, especially during the COVID-19 pandemic. Qian and Yahara (22) conducted a cross-sectional survey using 1,856 Japanese samples; however, this study found that only care and authority were significant predictors of COVID-19 preventive behaviors. In contrast to Eastern countries, Harper et al. (21) found that all moral intuitions, except authority (i.e., care, fairness, loyalty, and purity), significantly correlated with behavioral change and fear of COVID-19.

In short, previous studies have shown how moral intuition can be related to the fear of COVID-19 and behavioral intentions. These studies suggested that the psychological processing of COVID-19-related messages can be more than the dynamics between perceived self-efficacy and threat; rather, the processing of COVID-19 messages can involve another layer, which is moral intuition. However, it is still unknown how and whether moral intuition can serve as a moderator if morality is combined with the EPPM. Therefore, this study aims to (a) apply EPPM in the Korean COVID-19 context, (b) examine whether moral intuition can moderate the effect of perceived efficacy, threat, fear, and behavioral intentions.

Hypothesis (H)1. Self-efficacy will negatively predict fear of COVID-19.
H2. Self-efficacy will positively predict health compliance behavioral intention.
H3. The threat will positively predict fear of COVID-19.
H4. The threat will negatively predict health compliance behavioral intention.
H5. Self-efficacy and threat interact with fear of COVID-19 such that participants in the HE/LT (danger control: high efficacy/low threat) conditions will show less fear than participants in the LE/HT (fear control: low efficacy/high threat) conditions.
H6. Self-efficacy and threat interact with health compliance behavioral intention so that participants in the HE/LT (danger control: high efficacy/low threat) conditions will show higher health compliance behavioral intention than participants in the LE/HT (fear control: low efficacy/high threat) conditions.
Research question 1(RQ1). Can moral intuition moderate the relationship between self-efficacy, threat, fear of COVID-19, and health compliance behavioral intention?
RQ2. What is the relationship between moral intuition, fear of COVID-19, and health compliance behavioral intention?

# METHOD

## Participants and Procedure

Samples were collected from December 16, 2020, to December 22, 2020, in South Korea, using panel sampling ($n$ = 1,500). The panel was based on age, gender, geographic region, and political orientation. A professional research company was used to conduct an online survey; 132,842 emails were sent and 2,371 people volunteered to participate. At the beginning of the online survey, participants were informed that their responses would be anonymous and informed that they are agreeing to participate by clicking and filling in responses. Volunteer participants were randomly assigned to read a mock-up personal COVID-19 story, and then all participants completed survey measurements. The final data comprised 1,500 people, with a response rate of 63.3%. All measurements and survey materials were written in Korean and approved by an institutional review board in a University in South Korea.

## Stimulus

Based on previous studies on EPPM, this study created two mock-up stories (high vs. low involvement) of a perfectly healthy person in their early 30's, who had been wearing masks but unfortunately caught up with COVID-19. The mock-up stimulus comprised about 334 words; high vs. low conditions were manipulated based on psychological and geographic distance (high—patient from South Korea, low—patient from Montenegro).

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## Measurements

### EPPM Measurements

Extended parallel processing model measurements were adopted from Witte's (23). Risk-Behavior-Diagnosis (RBD) scale and modified to fit the COVID-19 situation to measure self-efficacy and threat. Self-efficacy was measured using six items (e.g., "wearing a mask is effective for COVID-19 prevention") based on a 5-point scale (1—strongly disagree, 5—strongly agree) of the modified RBD scale (Cronbach's $\alpha = 0.90$, $M = 4.42$, Mdn $= 4.50$, SD $= 0.56$); threat was measured using six items (e.g., "COVID-19 is a serious threat") based on a 5-point scale (1 = strongly disagree, 5 = strongly agree) of the modified RBD scale ($\alpha = 0.76$, $M = 3.80$, $Mdn = 3.83$, SD $= 0.56$).

### Moral Intuition

Moral intuition was measured using the shortened version of the moral foundation questionnaire (MFQ-20). Each of the five moral intuitions was measured using four items. The MFQ-20 consisted of two parts: in part 1, the instruction was included at the top ("when you decide whether something is right or wrong, to what extent are the following considerations relevant to your thinking?), followed by statements for each moral domain (e.g., "…whether or not someone suffered emotionally"). In part 2, the instruction at the top ("please read the following sentences and indicate your agreement or disagreement") was followed by statements for each moral domain (e.g., "respect for authority is something all children need to learn"). All items were measured based on a 6-point scales (part 1: 0—not at all relevant, 5—extremely relevant; Part 2: 0—strongly disagree, 5—strongly agree) to measure the moral intuition of care ($\alpha = 0.71$, $M = 2.98$, SD $= 0.79$), fairness ($\alpha = 0.78$, $M = 3.32$, SD $= 0.81$), loyalty ($\alpha = 0.66$, $M = 2.61$, SD $= 0.83$), authority ($\alpha = 0.76$, $M = 2.49$, SD $= 0.92$), and purity ($\alpha = 0.65$, $M = 2.80$, SD $= 0.77$). Subsequently, all MFQ-20 items were averaged into a composite variable to construct the general morality ($\alpha = 0.91$, $M = 2.84$, SD $= 0.69$).

**TABLE 1** | Summary of PROCESS v.3.5.3 moderation testing (model = 1, bootstrap = 5,000, conditional effects = −1 SD, *M*, and +1 SD).

| | ***B* (S.E.)** | ***p*** | **95% *C.I.*** | **Model fit** |
|---|---|---|---|---|
| **Y: Fear of COVID** | | | | |
| Self-efficacy (X) | 0.32 (0.26) | 0.21 | −0.18, 0.83 | $R^2 = 0.17$, |
| Morality (w) | 1.05 (0.14) | 0.00*** | 0.78, 1.33 | $p < 0.001$, |
| Self-efficacy (X) × Morality (w) | −0.20 (0.09) | 0.02* | −0.38, 0.03 | $F = 99.14$ |
| **Y: Health compliance** | | | | |
| Self-efficacy (X) | 0.88 (0.21) | 0.00*** | 0.47, 1.30 | $R^2 = 0.16$, |
| Morality (w) | 0.66 (0.11) | 0.00*** | 0.43, 0.88 | $p < 0.001$, |
| Self-efficacy (X) × Morality (w) | −0.14 (0.07) | 0.045* | −0.29, −0.003 | $F = 95.77$ |
| **Y: Fear of COVID** | | | | |
| Threat (X) | −0.25 (0.24) | 0.30 | −0.73, 0.22 | $R^2 = 0.27$, |
| Morality (w) | 0.02 (0.13) | 0.91 | −0.24, 0.27 | $p < 0.001$, |
| Threat (X) × Morality (w) | 0.39 (0.08) | 0.00*** | 0.22, 0.55 | $F = 184.90$ |
| **Y: Health compliance** | | | | |
| Threat (X) | 0.59 (0.21) | 0.006** | 0.17, 1.00 | $R^2 = 0.16$, |
| Morality (w) | 0.48 (0.12) | 0.00*** | 0.25, 0.71 | $p < 0.001$, |
| Threat (X) × Morality (w) | −0.04 (0.07) | 0.60 | −0.18, 0.11 | $F = 93.47$ |
| **Y: Fear of COVID** | | | | |
| EPPM (X) (-1: fear control, +1: danger control) | 0.23 (0.19) | 0.21 | −0.13, 0.60 | $R^2 = 0.27$, |
| Morality (w) | 0.70 (0.04) | 0.00*** | 0.62, 0.78 | $p < 0.001$, |
| EPPM (X) × Morality (w) | −0.31 (0.06) | 0.00*** | −0.43, −0.19 | $F = 186.76$ |
| **Y: Health compliance** | | | | |
| EPPM (X) (-1: fear control, +1: danger control) | 0.21 (0.17) | 0.21 | −0.12, 0.54 | $R^2 = 0.11$, |
| Morality (w) | 0.49 (0.04) | 0.00*** | 0.42, 0.56 | $p < 0.001$, |
| EPPM (X) × Morality (w) | −0.07 (0.06) | 0.21 | −0.18, 0.04 | $F = 60.26$ |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

### Fear of COVID

Fear of COVID was measured using the FCV-19S from Ahorsu et al. (24). FCV-19S is a 7-point, 7-item scale that measures the fear of individuals of being infected with COVID-19. Seven items (e.g., "I am most afraid of coronavirus-19") were translated into Korean and measured on a 7-point scale (1 – strongly disagree, 7 – strongly agree) to measure fear of being infected by COVID-19 in the South Korean context ($\alpha = 0.92$, $M = 4.19$, SD = 1.26).

### Health Compliance

A health compliance scale was created to measure COVID-19-related behavioral intentions. This scale comprised eight items on a 7-point scale (1–strongly disagree, 7–strongly agree) to measure four dimensions of COVID-19-related preventive behavioral measures: handwashing, self-isolation, social distancing, and mask wearing. To avoid social desirability bias and ceiling effect (e.g., marking all items to "strongly agree" to questions, such as "do you intend to follow social distancing norms?"), each of the behavioral intentional measures was created for very specific situations. For hand washing, the items were "I will wash my hands more than 30 s every single time I use a restroom no matter how busy I am," "I will carry hand sanitizers every single time no matter how heavy my pouch is." For self-isolation, the items were "I will not go to work if I cough or feel the slightest fever," "I will not meet anybody if I cough or feel the slightest fever." For social distancing, the items were "I would rather cancel my important schedules if I can't secure a distance of at least 2-meters from other people there," "I would rather not go to socially important meetings if the meeting place is crowded." For mask wearing, the items were "I would rather put my mask back on even if I have to drink and eat in a rush," "I will not take off my mask even for 1 s, no matter how uncomfortable I feel or even when there is nobody around me when I go out." These eight items were averaged into a mean score to represent a higher score indicating more a preventive behavioral intention against COVID ($\alpha = 0.90$, $M = 5.27$, SD = 1.03).

## Analysis Plan

### EPPM Condition Construction

To create EPPM conditions (danger control condition, fear control condition) as independent variables, we adopted the median-split technique, based on the median scores ($Mdn_{efficacy} = 4.50$, $Mdn_{threat} = 3.83$). Based on the combination of high/low efficacy and threat, contrast coding was used: LE/HT (fear control) was coded as −1 ($n = 272$), either low efficacy/low threat or high efficacy/high threat was coded as 0 ($n = 895$), and HE/LT (danger control) was coded as +1 ($n = 333$).

### Hypotheses and RQ Testing

To test the hypotheses and RQs, we used Hayes (25). PROCESS Macro 3.5.3 downloaded from processmacro.org website (model = 1, bootstrap = 5,000, moderation conditioning values = −1,

**TABLE 2** | Conditional effects morality as a moderator.

| Moderator levels (w = morality) | Effect | *B* (*S.E.*) | *p* | 95% *C.I.* |
|---|---|---|---|---|
| Mean−1 S.D. | Self-efficacy → Fear of Covid | −0.11 (0.09) | 0.18 | −0.28, 0.05 |
| Mean | Self-efficacy → Fear of Covid | −0.25 (0.06) | 0.00*** | −0.37, −0.14 |
| Mean +1 S.D. | Self-efficacy → Fear of Covid | −0.39 (0.09) | 0.00*** | −0.56, −0.23 |
| Mean−1 S.D. | Self-efficacy → Health compliance | 0.57 (0.07) | 0.00*** | 0.44, 0.71 |
| Mean | Self-efficacy → Health compliance | 0.48 (0.05) | 0.00*** | 0.38, 0.57 |
| Mean+1 S.D. | Self-efficacy → Health compliance | 0.39 (0.07) | 0.00*** | 0.24, 0.51 |
| Mean−1 S.D. | Threat → Fear of COVID | 0.58 (0.08) | 0.00*** | 0.42, 0.74 |
| Mean | Threat → Fear of COVID | 0.84 (0.06) | 0.00*** | 0.73, 0.95 |
| Mean +1 S.D. | Threat → Fear of COVID | 1.10 (0.08) | 0.00*** | 0.95, 1.26 |
| Mean−1 S.D. | EPPM (-1: fear, +1: danger) → Fear of COVID | −0.43 (0.06) | 0.00*** | −0.56, −0.31 |
| Mean | EPPM (-1: fear, +1: danger) → Fear of COVID | −0.64 (0.04) | 0.00*** | −0.73, −0.56 |
| Mean +1 S.D. | EPPM (-1: fear, +1: danger) → Fear of COVID | −0.85 (0.06) | 0.00*** | −0.97, −0.74 |

***$p < 0.001$.

0, +1 SD). For hypotheses testing, each hypothesis (H1–H6) was tested with a combination of RQ1 using PROCESS MACRO v.3.5.3 model 1. The results for all analyses are shown in **Table 1**.

# RESULTS

## Descriptive Statistics

Before testing our hypotheses and RQs, we conducted descriptive statistical analyses for 1,500 samples, with gender (male−763 and female−737) age (below 20–292, 30–272, 40–329, 50–342, and above 60–265), the prevalence of any respiratory symptoms (1,337 had not experienced in the past year), median monthly income (₩4 million and ₩5 million–about $4,000–$5,000 in the U.S.), marital status (married−896), education (high school or below−297, college or below−1,056, above graduate school−147), and political orientation (conservative−270, neutral−869, liberal−361).

### Main Effects of Self-Efficacy

Hypothesis 1 predicted a negative main effect of self-efficacy on fear of COVID-19. The PROCESS MACRO analysis results did not reveal any main effect of self-efficacy condition on fear ($B = 0.32$, $SE = 0.26$, $p = 0.21$, 95% $CI = -0.18, 0.83$).

Hypothesis 2 predicted a positive main effect of self-efficacy on health compliance. The PROCESS MACRO analysis results revealed that perceived self-efficacy had a positive main effect on health compliance ($B = 0.88$, $SE = 0.21$, $p < 0.001$, 95% $CI = 0.47, 1.30$).

### The Main Effect of Threat

Hypothesis 3 predicted a positive main effect of threat on fear of COVID-19. The PROCESS MACRO analysis results did not reveal any main effect of threat condition on fear ($B = -0.25$, $SE = 0.24$, $p = 0.30$, 95% $CI = -0.73, 0.22$).

Hypothesis 4 predicted a negative main effect of threat on health compliance. The PROCESS MACRO analysis results revealed a positive main effect of threat condition on health compliance ($B = 0.59$, SE $= 0.21$, $p < 0.01$, 95% CI $= 0.17, 1.00$), which was in the opposite direction of H4.

### EPPM Effect on Fear of COVID

Hypothesis 5 tested the effect of EPPM on fear of COVID-19 so that participants in fear control processing would show greater fear compared to participants in danger control processing. The PROCESS MACRO analysis results did not reveal any interaction between self-efficacy and threat on fear ($B = 0.23$, SE $= 0.19$, $p = 0.21$, 95% CI $= -0.13, 0.60$); however, morality moderated the interaction between EPPM conditions and fear ($B = -0.31$, SE $= 0.06$, $p < 0.001$, 95% CI $= -0.43, -0.19$). These results suggest that the EPPM effect on fear of COVID was fully moderated by morality (refer to **Tables 1**, **2** and RQ1 testing below).

### EPPM Effect on Health Compliance

Hypothesis 6 tested the EPPM effect on health compliance so that participants in danger control processing would show higher health compliance than those in fear control processing. The PROCESS MACRO analysis results did not reveal any interaction between perceived self-efficacy and threat on health compliance ($B = 0.21$, SE $= 0.17$, $p = 0.21$, 95% CI $= -0.12, 0.54$).

## RQs

### RQ1: Moderating Effects of Morality

Research question 1 addressed whether morality can moderate the relationship between self-efficacy, threat, fear, and health compliance. The moderating effects of general morality were tested through H1–H6 (refer to **Tables 1**, **2**).

First, morality moderated the relationship between self-efficacy and fear of COVID-19 in medium morality ($M$) and high morality ($M$ +1 SD). Specifically, self-efficacy significantly negatively predicted fear of Covid-19 in medium morality ($B = -0.25$, $p < 0.001$, 95% CI $= -0.37, -0.14$) and high morality ($B = -0.39$, $p < 0.001$, 95% CI $= -0.56, -0.23$); the effect size of self-efficacy on fear of COVID-19 was stronger in high morality.

Next, morality moderated the relationship between self-efficacy and health compliance in all morality conditions.

Specifically, self-efficacy significantly and positively predicted health compliance in low ($B = 0.57$, $p < 0.001$, 95% CI = 0.44, 0.71), medium ($B = 0.48$, $p < 0.001$, 95% CI = 0.38, 0.57), and high ($B = 0.39$, $p < 0.001$, 95% CI = 0.24, 0.51) morality; the effect size of self-efficacy on health compliance decreased as morality increased.

Third, morality moderated the relationship between perceived threat and fear of COVID-19 in all morality conditions. Specifically, perceived threat significantly and positively predicted fear in low ($B = 0.58$, $p < 0.001$, 95% CI = 0.42, 0.74), medium ($B = 0.84$, $p < 0.001$, 95% CI = 0.73, 0.95), and high ($B = 1.10$, $p < 0.001$, 95% CI = 0.95, 1.26) morality; the effect size of perceived threat on fear of COVID increased as morality increased.

Finally, morality moderated the relationship between EPPM interaction and fear of COVID-19 in all morality conditions. Participants in the danger control processing condition were more likely to control fear, compared to participants in the fear control processing condition in low ($B = -0.43$, $p < 0.001$, 95% CI = −0.56, −0.31), medium ($B = -0.64$, $p < 0.001$, 95% CI = −0.73, −0.56), and high morality conditions ($B = -0.85$, $p <0.001$, 95% CI = −0.97, −0.74). This showed the EPPM effect on fear of COVID-19, which was in line with H5. In addition, the EPPM effect became stronger as morality increased, suggesting that the fear contrast between participants in fear control processing and participants in danger control processing was greater in the higher morality condition.

### RQ2: Morality, Fear, and Health Compliance

Correlation analyses were conducted to test RQ2, which addressed whether there are relationships between moral intuition, fear of COVID-19, and health compliance behavioral intention. It was found that moral intuition and fear of COVID were significantly related to each other, with $r$ (1,498) = 0.39, $p < 0.001$. Also, it was found that moral intuition and health compliance were significantly related to each other, with $r$ (1,498) = 0.33, $p < 0.001$.

## DISCUSSION

This study aimed to (a) apply EPPM in the COVID-19 pandemic context, and (b) investigate the role of moral intuition as a moderator to expand EPPM. The current study had several interesting findings.

First, our study showed that the EPPM hypotheses did not show significant results. Specifically, H1, H3, H5, and H6 were found to be non-significant. Although the results of our study showed non-significant results with EPPM hypotheses, this does not mean EPPM is not appropriate to be applied in the Korean COVID-19 pandemic context. This is due to two reasons: first, previous studies still suggested that EPPM can be applied in the East Asian COVID-19 context (3, 4, 9). Second, non-significant results of our study (e.g., H1, H3, H5, and H6) can be still explained in the EPPM context. That is, the current study measured self-efficacy and fear with Witte's (23). RBD scale and adopted median split technique to create EPPM condition variables; notably, the mean values of self-efficacy of 1,500 participants were 4.42 with a median value of 4.50, which was extremely high given that RBD scale is 5-point scale. In other words, this could be the case that both 272 participants in LE/HT conditions and 333 participants in HE/LT conditions were mostly going through danger control processing, instead of fear control processing. This interpretation can make sense with the unexpected finding of H4 that showed a significant positive effect of threat on health compliance, which was in opposite direction. These findings altogether suggest two things: (a) future COVID-19 EPPM studies should consider other ways to prevent the ceiling effect when measuring self-efficacy or fear, and (b) COVID-19 and EPPM can make more sense when other moderating variables, such as morality are adopted.

Moreover, statistical test results with morality as a moderator in EPPM showed that the processing of COVID-19-related messages in the self-efficacy or fear framework can be understood better with the extension of morality. Specifically, our study found that morality moderated the main effects of self-efficacy or perceived threat; morality also moderated EPPM interaction on fear of COVID. Notably, the moderation of morality in the relationship between perceived threat and fear of COVID-19 showed that the effect size of perceived threat increased as morality increased from low morality ($B = 0.58$) to medium ($B = 0.84$) and high morality ($B = 1.10$). Similarly, moderation of morality in the relationship between EPPM interaction and fear of COVID-19 revealed that participants in danger control processing showed less fear than participants in fear control processing did. The contrast of fear between fear control and danger control processing was greater, as the morality increased from low ($B = -0.43$) to medium ($B = -0.64$) and high morality ($B = -0.85$). This suggests that people might think of the threat of being infected by COVID-19 as a moral issue based on the moral intuitions of care, fairness, loyalty, authority, and purity, and such moral thinking moderates the effects on fear.

Finally, the moderation of morality in the relationship between self-efficacy and health compliance behavioral intention showed that health compliance intention decreased as morality increased. Notably, morality decreased COVID-19-related behavioral intentions; this effect could be due to moral licensing arguments [(26), p. 346]. The moral licensing argument suggests that past moral actions of individuals could cause them to take morally dubious actions in the future (e.g., "I have been acting well, so one mistake won't be too bad"). The MFQ-20 measured general moral beliefs, and it is possible that participants were primed to think about past moral deeds. In this sense, participants with higher morality might have felt less inclined to follow COVID-19-related behaviors in the future while thinking about how they had already been acting well in the COVID-19 pandemic situation. In this case, future EPPM studies should consider examining the moral licensing effect in the COVID-19 context.

Our study has several implications. First, we tested the EPPM model in the COVID-19 pandemic context in Korea. We found that EPPM could be useful in understanding how people process COVID-19-related health messages. In addition, the moderation of moral intuition in the EPPM showed that morality could serve as an important variable that can be considered in future studies on COVID-19 or other pandemics. Our findings suggest that people can consider COVID-19 as a social and moral issue that involves protecting others. Therefore, our study implies that researchers, health practitioners, and government officials should also consider social, moral aspects of COVID-19 and individual health.

## LIMITATIONS

Although our study had several useful findings for future studies, it has a few limitations as well. First, the overall mean score of participants for perceived self-efficacy was too high ($M = 4.42$); despite our efforts to suppress ceiling effects by adopting the median split technique, it could not have been completely prevented. Future studies should consider other ways to avoid ceiling effects. Second, our study included only participants from South Korea. Future studies can include other East Asian countries, such as Japan and China, to examine whether East Asian countries, in general, can perceive pandemic disease as a moral issue. Third, there was a limitation in the health compliance measures we used. Although eight items we created show high reliability of $\alpha = 0.90$, our study did not thoroughly validate these measures with other means (e.g., confirmatory factor analysis). Also, although these items were created to avoid the ceiling effect, our data showed that the mean value was still high with $M = 5.27$. Still, the results of our hypotheses testing (H2 and H4) and moderation testing show that our measure can be still useful. Future studies can include an improved measure of health compliance in the COVID-19 context.

## CONCLUSION

In conclusion, we tested the EPPM model in the COVID-19 context in South Korea and introduced moral intuition as a moderator. Our study showed that morality could serve as a new important variable in the processing of pandemic-disease messages, which can expand EPPM theory.

## 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 Hallym University Institutional Review Board. The patients/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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# Empowering Equitable Data Use Partnerships and Indigenous Data Sovereignties Amid Pandemic Genomics

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The COVID-19 pandemic has inequitably impacted Indigenous communities in the United States. In this emergency state that highlighted existing inadequacies in US government and tribal public health infrastructures, many tribal nations contracted with commercial entities and other organization types to conduct rapid diagnostic and antibody testing, often based on proprietary technologies specific to the novel pathogen. They also partnered with public-private enterprises on clinical trials to further the development of vaccines. Indigenous people contributed biological samples for assessment and, in many cases, broadly consented for indefinite use for future genomics research. A concern is that the need for crisis aid may have placed Indigenous communities in a position to forego critical review of data use agreements by tribal research governances. In effect, tribal nations were placed in the unenviable position of trading short-term public health assistance for long-term, unrestricted access to Indigenous genomes that may disempower future tribal sovereignties over community members' data. Diagnostic testing, specimen collection, and vaccine research is ongoing; thus, our aim is to outline pathways to trust that center current and future equitable relationship-building between tribal entities and public-private interests. These pathways can be utilized to increase Indigenous communities' trust of external partners and share understanding of expectations for and execution of data protections. We discuss how to navigate genomic-based data use agreements in the context of pathogen genomics. While we focus on US tribal nations, Indigenous genomic data sovereignties relate to global Indigenous nations regardless of colonial government recognition.

**Keywords: Indigenous, American Indian/Alaska Native, COVID-19, genomics, Indigenous data sovereignty, data use agreements, broad consent, vaccine research**

## INTRODUCTION

Indigenous communities continue to be disproportionately impacted by the COVID-19 (coronavirus disease 2019) pandemic. Incidence and age-adjusted mortality rates among American Indians and Alaska Natives (AI/AN) were, respectively, 3.5 times and 1.8 higher compared to non-Hispanic white persons across the United States (US) (1–3). Recent reports from August 2021 show a 600% increase in new cases among Native Hawaiians in Hawai'i, underscoring impacts of the latest surge for US Indigenous communities (4). Disparities in COVID-19 rates among Indigenous people are rooted in contemporary social and health inequities, including increased prevalence of underlying conditions, structural barriers to accessing resources for curbing viral transmission (i.e., clean water, personal protective equipment), underfunded tribal health systems, and geographic rurality (5, 6)—which are rooted in colonialism and complex histories of tribal-trust treaty relationships (7). Though apparent, the true extent of COVID-19 disparities among Indigenous people is subject to underreporting which may impede public health initiatives (8) related to biological testing and vaccination.

Amid the emergent conditions of the pandemic, concerns arise that Indigenous nations traded short-term needs for COVID-19 testing, surveillance, and vaccination with long-term, unrestricted access by non-tribal entities to Indigenous peoples' genomes which may undermine Indigenous data sovereignties. While some call for increased collection of biological data from Indigenous populations to understand the extent of COVID-19 disease burden disparities (9), we as Indigenous health researchers and non-Indigenous allies remind that extraction of any data from tribal nations without attribution to Indigenous data sovereignties can be equivalent to past research harms. Therefore, in expanding others' recognition of Indigenous sovereignties related to tribal public health responses (9–11), we outline a framework for partnering with Indigenous nations to ensure that genomic and other biological information collected from Indigenous individuals in pandemic crises–as part of diagnostic and antibody testing, clinical trial initiatives, and vaccine research–can benefit future Indigenous data sovereignties.

## INDIGENOUS GENOMIC DATA SOVEREIGNTIES

Indigenous data sovereignties are defined as the "rights and interests of Indigenous peoples relating to the collection, ownership, and application of data about their people, lifeways, and territories" (12). When referring specifically to data derived from a part or whole of Indigenous peoples' genomes, we use the term "Indigenous genomic data sovereignties" (13). Settler-colonial recognition of these sovereignties are usually limited to, in the US context, the 574 federally recognized tribes via "nation-to-nation" policies. However, we recognize that data sovereignties are intrinsic to Indigenous peoples' right to self-govern (14) and must therefore extend beyond colonially-defined arbitrations of geographic state to include urban-displaced citizens of tribal nations and Indigenous groups of special and/or unrecognized status. Further, while some approaches to collecting data from Indigenous peoples try to leverage "individual vs. group" dynamics as a means of circumventing Indigenous genomic data sovereignties (13, 15), it is up to the communities to define data access and use of biological and genomic information collected from their people. While we use community-engaged models as a basis for the suggestions on equitable data use and sharing, we argue for a more empowered approach that centers Indigenous data decision authorities (14) first and foremost.

The assertion of Indigenous governances to self-determine public health initiatives for their own people (5) brought swift changes in COVID-19 incidence rates for some tribal nations. Sometimes in stark contrast to states' responses early in the pandemic, tribal nations—in particular but not limited to Arizona (16), Montana (17), North Dakota (18), and South Dakota (19, 20)—effectively led pandemic responses by implementing local mitigation strategies, restricting travel, mandating curfews and masks, creating culturally-tailored health messaging, and instituting contact tracing within their jurisdictions. Some states achieved greater equity in vaccine distribution among AI/AN populations (3, 21). Early efforts by tribes to vaccinate their populations initially led to high, though currently stagnating (22), rates of vaccination in many tribal communities, with nearly 70% vaccination rates for eligible individuals reported for the Meskwaki Nation (Sac and Fox Tribe of the Mississippi) (23), the Navajo Nation (24), among others (25).

While these measures certainly contribute to decreasing viral transmission, many tribal nations are still ill-equipped to provide diagnostic and antibody testing to confirm, trace, and treat COVID-19 cases. Considering these pre-existing deficiencies in tribal public health infrastructures that only exacerbate the need for local testing, many tribal nations rely on federal and municipal government services, University researchers, and private companies to conduct health data and biospecimen collection for diagnostic and antibody testing, clinical trials, and vaccine research. Collected data includes tribal group identifiers, identifiable data from kin, demographic information, and specimen data from which human genomic information can potentially be derived.

The emergency urge to quickly develop and disseminate a COVID-19 vaccine also brought forth many questions related to the pace of the Operation Warp Speed Vaccine Initiative, a public-private partnership between the US government and commercial entities. The "all-in" commercial investment strategy incentivized multiple vaccine developers to scale up manufacturing and distribution prior to completion of clinical studies (26), which brought an unprecedented rapidity to clinical trialing. There were concerns among tribal public health entities that vaccine companies and researchers were rushing tribal approval procedures or recruiting tribal citizens residing outside of their tribes' jurisdictions (27). There are sustained concerns that the vaccine research overly emphasize a Western ethic of individual informed consent when recruiting

Indigenous individuals, particularly those who reside in urban city centers outside of tribal research protections, that is culturally inconsistent with Indigenous communitarian ethics and has potential to biologically re-identify Indigenous groups (15). More salient, however, is the persistent worry that Indigenous community members are broadly consenting (28) to ungoverned future use and ownership of Indigenous genomic data under the pretense of proprietary domain which may lead to co-optation and commercial exploitation (29). Compounding these concerns about the impacts of commercial interests are the ethical impacts of promoting the inclusion of Indigenous individuals in clinical trial research in ways that favor the goals of research institutions over tribal nations' sovereign rights to guarantee data governance and research benefit (30).

As a note, it is important to distinguish US Indigenous communities' relative lack of "vaccine hesitancy" for implementing a federally approved vaccine vs. the hesitation by many tribes to sign on as research trial participants prior to approval. There are distrusts related to the history of medical experimentation in Indigenous communities (31) that must be considered separately and distinctly from implementing vaccine programming after release to the general public.

## NEED FOR EQUITABLE DATA USE AGREEMENTS

Data Use Agreements (DUAs) are legally binding contracts that stipulate terms related to limited transference of restricted data from one entity to another, to include procedures of data sharing, data access, and data licensing. Although entities involved should participate in developing and enforcing DUAs, tribal nations–as owners and stewards of data collected from tribal members– should be empowered as decision-makers in agreements involving data from their communities. In university-sponsored research, it is usually the institution that reviews and ensures compliance of DUAs according to funding regulations. For federally-funded data collection, often DUAs favor deposition of data into a central repository under the ethic of open or communal research use which can incongruent with Indigenous data sovereignties (14). Since federal data repositories are outside the governance and oversight of tribes, there have been tensions in negotiating the need to protect and recognize Indigenous data sovereignties while still supporting research collaborations (32). DUAs drafted by private organizations or commercial entities may also have corporate liability protections and intellectual property terms that favor those organizations. In any case, there is usually an inequitable power dynamic in that DUAs are drafted in the perspective of those empowered to collect and store data. Until tribal nations can create their own institutions for data collection and storage, which can take many years, unfortunately tribes will likely be disempowered to represent their data concerns (33). Furthermore, tribal nations may likely not be prepared to respond as quickly as needed to represent their data concerns during times of public health crises, as underscored during the events of the current and ongoing pandemic. Therefore, the need to address these inequities will continue to persist, and it is important to push for implementation of more responsible data use practices now.

The disproportionate impact of the pandemic and the need for crisis aid place Indigenous communities in a vulnerable position to forego critical review of DUAs by tribal research governances; additionally, tribes that do not already have these data oversights are further disenfranchised. Thus, there is urgency for developing and implementing data sharing practices that best serve Indigenous communities, particularly as post-pandemic activities (such as testing, vaccination, and research) must be continued for future public health. This urgency does not preclude the need to carefully co-develop terms of a DUA, which can have sustained impacts even after the pandemic state. Developing DUAs with shared understanding of expectations and execution of current and future data protections remains a critical component of equitable partnerships.

By recognizing the legacies of research harms associated with data, potential partners are more likely to be successful in practicing ethical research methods and avoiding future legal conflicts. Part of this process also entails respecting Indigenous data sovereignties related to the collection, use, storage, and oversight of Indigenous biological samples. To think transformatively about ameliorating health disparities will entail looking beyond genomic differences, especially as COVID-19 disparities are more proximally related to structural barriers to health than between-group biological differences. Thus, public health practitioners should be looking to long-term initiatives related to economic resiliency, public health leadership, and clinical and research practices—including macro-level data practices and clinical biospecimen collection and informatics.

## FRAMEWORK GUIDELINES

### Respect and Collaboration Early in Negotiations

Creating DUAs empowers Indigenous communities as partners in the pandemic response. With sound DUAs, Indigenous communities are invited in planning conversations with potential partners to establish mutual understanding and respect that have impacts for future research. Furthermore, a DUA enables tribal nations to provide guidance on program implementation and any research products resulting from pandemic samples conducted within Indigenous landscapes. Crafting DUAs fosters discussions that could illuminate and address potential assumptions and differences in understandings before these challenges arose. If there is no clarification and resolution of issues through the DUA development, the research process can halt or another partner found to minimize any potential harms from the collection of contested data. This speaks to the importance of creating a DUA early in the process such that substantial time and resources are not devoted when a respectful and transparent partnership is unattainable.

External organizations invited to assist with pandemic response should recognize the Indigenous communities' ownership of their genomic data and show respect for local community members by involving them in the entire pandemic response, including the development, selection, analysis, presentation, and dissemination of any genomic data—whether internally, publicly, or in scientific realms. Indigenous citizen professionals working in the community engaged as part of the research can enrich the communities' understanding of the DUA processes. Community members and professionals should serve as integral members of pandemic response teams from start to finish (34).

## Specificity of Terms Is Key to Trust-Building

Tribal nations have sovereign and legal agency to self-direct their own pandemic response initiatives (35). DUAs should thus include an agreement of access for outside entities to operate in Indigenous communities. Access to what kinds of data is a key component of an access agreement (36). Access terms should specify locations, populations, records, and time frames. Though external organizations may be permitted access to certain tribal areas and populations, they should not assume they have *carte blanche* to collect any data in any form without consent. In multi-tribal partnerships, organizations should expect to establish DUAs with each Indigenous community separately with the knowledge that each community may have their own processes, priorities, foci, and expectations.

Access agreements should also detail personnel and their respective levels of data access and security (37–40). In this way, researchers can become trusted entities by which their cultural competencies, work ethics, and trustworthiness become known to tribal partners. When specific project personnel cannot be identified by name–for example, support personnel such as subcontractors or volunteers–partners should specify any credentials or qualifications (i.e. any ethical and cultural training or experience working with tribal nations) (41) of those individuals accessing Indigenous data.

Conducting emergency pandemic responses may result in unplanned access to aspects of community life and cultural practice, such as healing ceremonies, that might otherwise not be accessible to those outside of the community. External partners should by respectful and refrain from collecting any data or biological samples outside of expressed permissions. While some of these terms may be specified in research informed consent, not all public health data constitutes research. Therefore, creating access agreements between tribal nations and partners can illuminate these restrictions and increase understanding of collective goals and expectations for the rapid pandemic response and long-term collection, use, and storage of associated data.

Overall, access agreements are only one part of a macro-level data use agreements (29, 42–44). Another critical part is an agreement of for what and how the data can be used. Tribal nations should have sovereign data governance and intellectual property rights for technologies resulting from data collected on sovereign lands (44). DUAs should also indicate what will be shared, in what manner, and with whom (43). Outside entities partnering with tribal nations during pandemic times might also have specific goals regarding data-sharing, reporting measures, selling for profit, and should inform the tribal nation of any intentions to publish in journals, present at conferences, or commercialize tribal data and samples (45). A common component of DUAs is tribal right to review all dissemination products prior to publication, including press releases, manuscripts, presentations, and other reports that include data specific to their community.

## Good Data Stewardship Entails Safeguarding

Partner tribal nations should also be informed about how confidential information and samples will be protected and degrees of confidentiality from now and into the future (41). It should be the goal of the DUA to only report aggregate data, not individual data, in the report back to the tribal nation.

An important DUA safeguard is the review of jurisdiction and legal procedures early in implementation as a safety measure for both parties. External researchers and organizations should be aware that tribal nations may include clauses for the withdrawal from the contract. This is often done by tribal nations to prevent the release of sensitive information that misrepresents or stereotypes Indigenous peoples, or sensitive information that may harm the health, safety, or welfare of the communities or environment involved. It is also the case that tribal nations may stipulate that legal jurisdiction of procedures occurs in tribal court systems and that the contractual teams may be assessed fines for misconduct if harm, fraud, or unethical behavior is discovered.

It is the responsibility of both the tribal nations and the external researchers and organizations to ensure adherence to the DUA. Tribal nations are data owners and stewards, and they need to monitor who has access to the data and guide interpretations of research findings to ensure appropriate representation of tribal communities. As data users, external entities are responsible for ensuring adherence to the DUA or risk dissolution of partnerships with tribes. They should actively engage in ongoing assessment of their procedures related to data storage, use, and sharing to ensure continued adherence to the DUA regardless of staff turnover, changes in business practices and tools, and time.

## Building Sustainable Relationships

Creating DUAs will help build positive relationships between external research and organizations and the tribal nations through the process of creating equitable agreements and following an ethical framework (30, 42, 46–48). Sustained positive relationship building between these entities and respective tribal nations throughout the pandemic response is a continued step for business-to-community relationship building with tribal nations. Relationships require time to develop, strengthen, and build sustenance—even during uncertain and challenging times. The DUA process of relationship development is imperative because of historical mistrusts in Indigenous communities. Further, Indigenous culture and ways of knowing cannot be understood through brief emergency interaction during a public health crisis. Thus, tribal nations might view external entities who disengage in partnership development once access permission is granted as inauthentic, feigning to act in the best interest of Indigenous peoples, and disrespecting Indigenous sovereign public health. The most successful partnerships are those that are initiated early and actively work toward developing and strengthening the DUA-guided relationships throughout the duration of pandemic response and beyond.

## FUTURE IMPLICATIONS

Pandemic genomic investigations in tribal nations are likely to evolve as nations adopt their own tribal biorepositories, storage procedures, and template DUA language. The ability of tribal nations themselves to generate and analyze this genomic information will empower them to be creative in the development of research agendas or revisiting with entities to negotiate existing secondary pandemic related genomic data. Further, maintaining DUAs, access, and control over pandemic genomic data will be supported by emerging aspirations to realize Indigenous data sovereignty (49). Therefore, wherever possible, we hope that tribes will continue to increasingly exert their sovereignties in the space of data collection commensurate with outside entities' interest in Indigenous genomic data. It ultimately should be the tribes' responsibility to steward data decisions that concern their peoples, and it is up to partners to respect these tribal sovereignties in order to develop trust relationships. Although there are guidelines for ethical research conduct in Indigenous communities (30), there is not yet a gold standard framework that is specific to conducting this type of research and data collection in the context of pandemic genomics. Therefore, the perspectives we presented can be useful for navigating genomic-based DUAs in the pathway to creating clinical to research process that can be helpful for tribal nations, should another public health emergency emerge.

Ultimately, equitable and beneficial pandemic response in Indigenous landscapes honors Indigenous Knowledges and respects tribal sovereignties. Pandemic and post-pandemic genomic research with Indigenous communities is crucial and, when conducted respectfully, can provide guided direction for improved future societal wellness. As shared by Indigenous community leader Michael Martin, "Every action we take we have to be mindful seven generations up" (https://www.youtube.com/watch?v=YyuSc_jkG-s).

## 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

RH initiated the collaboration and wrote the first draft of the manuscript. JB, JL, JK, EH, JR, MH, and KT contributed substantial intellectual and writing contributions through multiple iterations of the manuscript. KT oversaw the writing collaboration and final drafts of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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# The Rapid Antigen Detection Test for SARS-CoV-2 Underestimates the Identification of COVID-19 Positive Cases and Compromises the Diagnosis of the SARS-CoV-2 (K417N/T, E484K, and N501Y) Variants

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Timely detection of severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) by reverse transcription quantitative polymerase chain reaction (RT-qPCR) has been the gold- strategy for identifying positive cases during the current pandemic. However, faster and less expensive methodologies are also applied for the massive diagnosis of COVID-19. In this way, the rapid antigen test (RAT) is widely used. However, it is necessary to evaluate its detection efficiency considering the current pandemic context with the circulation of new viral variants. In this study, we evaluated the sensitivity and specificity of RAT (SD BIOSENSOR, South Korea), widely used for testing and SARS-CoV-2 diagnosis in Santiago of Chile. The RAT showed a 90% (amplification range of $20 \leq Cq < 25$) and 10% (amplification range of $25 \leq Cq < 30$) of positive SARS-CoV-2 cases identified previously by RT-qPCR. Importantly, a 0% detection was obtained for samples within a Cq value>30. In SARS-CoV-2 variant detection, RAT had a 42.8% detection sensitivity in samples with RT-qPCR amplification range $20 \leq Cq < 25$ containing the single nucleotide polymorphisms (SNP) K417N/T, N501Y and E484K, associated with beta or gamma SARS-CoV-2 variants. This study alerts for the special attention that must be paid for the use of RAT at a massive diagnosis level, especially in the current scenario of appearance of several new SARS-CoV-2 variants which could generate false negatives and the compromise of possible viral outbreaks.

**Keywords: rapid antigen test, SARS-CoV-2 detection, COVID-19 diagnosis, COVID-19 false negative rapid test for COVID-19 diagnosis, pandemic control strategies**



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# INTRODUCTION

The 2019 coronavirus disease (COVID-19) is a current pandemic respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). In Chile, more than 1.6 million infections and 37 thousand deaths have been reported from this disease (2). Currently, the most effective way to prevent and control its spread is the timely detection and isolation of infected people. The reverse transcription quantitative PCR (RT-qPCR) is the recommended and widely used technique for diagnosis due to its high sensitivity and precision (3). However, new and faster methodologies for detecting and diagnosing have recently been implemented, including the rapid antigen test (RAT) for SARS-CoV-2. The technique's principle consists of a rapid chromatographic immunoassay for the qualitative detection of specific SARS-CoV-2 antigens from nasopharyngeal swab samples (NPSs) (4). This strategy has begun to be used in several countries, and its effectiveness compared to the standard RT-qPCR method has been the target of study and analysis (5). In Chile, it was implemented in Health centers by the Ministry of Health in March 2021 as an alternative to RT-qPCR. More than 20 million RT-qPCR tests and more than 750 thousand RATs have been carried out in Chile. Although its effectiveness has been verified in various studies showing differences between manufacturers, currently, there are no studies on the effectiveness of the antigenic tests used in Chile, nor on their performance for detecting the outbreak of new SARS-CoV-2 variants. In this study, we compare the efficacy of the results of 55 NPSs obtained by the rapid antigen test for SARS-CoV-2 (SD Biosensor, South Korea), a chromatographic assay using a monoclonal antibody against the nucleocapsid (N) protein of the SARS-CoV-2 virus, and the standard RT-qPCR detection method. We observed differences in the detection of positive COVID-19 cases for the different ranges of amplification assessed. Interestingly, we determined that this antigen test loses sensitivity for detecting SARS-CoV-2 variants carrying the K417N/T, E484K and N501Y single nucleotide polymorphisms (SNPs).

# MATERIALS AND METHODS

## Samples

Nasopharyngeal swab samples (NPSs) of clinical patients included in this study were collected by the Primary Care Centers and the Hospitals that belong to the Central Metropolitan Health Service (Santiago of Chile) (SSMC, acronym in Spanish). The swab samples were taken, preserved, and transported using the CITOSWAB® transport kit (Cat. No. 2118-0015; Citotest Labware Manufacturing Co., Ltd, Jiangsu, China). All the samples arrived at the laboratory before the first 24 h after the sampling collection. These samples were processed in the laboratory of Virology (University of Santiago of Chile, USACH). Total RNA was extracted using the AccuPrep® Universal RNA Extraction Kit (Bionner, Daejeon, South Korea. Code product: K-3140) following the manufacturer's instructions. The extracted RNA was used immediately for RT-qPCR assays.

## SARS-CoV-2 Identification by Rapid Antigen Test (RAT), RT-qPCR, and Detection of Variants

The SARS-CoV-2 identification by rapid antigen test (SD BIOSENSOR, South Korea; Cat no: 99COV30D-ML02; Lot: QCO391081I) was made following the manufacturer's instructions. The viral SARS-CoV-2 genome sequence was carried out using the ORF1ab probe (TaqMan™ 2019nCoV Assay Kit v1; Thermo Fisher Scientific, Cat. No. A47532) following a one-step strategy. Positive internal control probes for ORF1ab and RNase P (TaqMan™ 2019-nCoV Control Kit v1; Thermo Fisher Scientific, Cat. No. A47533) were included and assessed individually in the 96-well PCR plate. The polymerase from TaqMan™ Fast Virus 1-Step Master Mix (Applied Biosystems™, Cat. No. 44-444-36) was included in each reaction. Each reaction contained 5 µl of TaqMan™ Fast Virus 1-Step Master Mix 4X, 1 µl of ORF1ab assay 20X (FAM detector channel), 1 µl of RNase P assay 20X (HEX detector channel), 11 µl of nuclease-free water, and 2 µl of extracted RNA sample. The thermal amplification conditions include the reverse transcription at 50 °C for 5 min, predenaturation at 95 °C for 20 s, followed by 40 cycles at 95 °C for 3 seconds and 60 °C for 30 seconds. All the RT-qPCR reactions were performed on the Agilent AriaMx Real-Time PCR System (Agilent Technologies, Part. No. G8830A). Data and graphics were extracted using the Agilent AriaMx software. The detection of different variants was made by the AccuPower® SARS-CoV-2 Variants ID Real-Time RT-PCR kit (Bioneer Cat. No. SMVR-2112) according to manufacturer instructions. The Exicycler 96 V4 Real-Time thermal cycler (Bioneer) was used for detecting fluorescence on the TET, TexasRed, FAM, TAMRA, and Cyanine5 channels. The data obtained were exported in an Excel spreadsheet, and the Cq value and relative fluorescence intensity were analyzed for the internal positive control, IPC (TAMRA), and each of the assessed variants.

## Ethics Statement

The experimental procedures included in this study were authorized by the Ethical Committee of the University of Santiago of Chile (No. 226/2021) and the Scientific Ethical Committee of the Central Metropolitan Health Service, Ministry of Health, Government of Chile (No. 370/2021), and following the Chilean law in force. Verbal consent for using of the sample for SARS-CoV-2 diagnostic purposes was given to the healthcare professional at CESFAM. Results were communicated to the patient in the Family Health Center they attended (CESFAM, acronym in Spanish; Central Metropolitan Health Service, Ministry of Health, Government of Chile).

# RESULTS

To determine the detection sensitivity of the rapid antigen test (RAT), we evaluated 55 samples in different ranges of the cycle of quantification (Cq) for ORF1ab, in a similar way to studies previously reported (6, 7). The sensitivity of RAT was performed

| RT-qPCR | | | | | | Rapid Antigen Test (RAT) | |
|---|---|---|---|---|---|---|---|
| **Cq Range** | **Cq** | **RFU** | **Viral copies** | **Result** | **% Sensitivity** | **Result** | **% Sensitivity** |
| **20≤Cq<25** | 22.34 | 5852.34 | 6.57x10$^{5}$ | Positive | **100%** | Positive | **90%** |
| | 22.86 | 2946.17 | 4.45x10$^{5}$ | Positive | | Positive | |
| | 21.14 | 3503.32 | 1.62x10$^{6}$ | Positive | | Positive | |
| | 20.90 | 3990.20 | 1.93x10$^{6}$ | Positive | | Positive | |
| | 24.12 | 4701.14 | 1.73x10$^{5}$ | Positive | | Positive | |
| | 24.68 | 3572.17 | 1.14x10$^{5}$ | Positive | | Positive | |
| | 20.40 | 6044.88 | 2.82x10$^{6}$ | Positive | | Positive | |
| | 21.30 | 5059.46 | 1.43x10$^{6}$ | Positive | | Positive | |
| | 23.16 | 2908.19 | 3.55x10$^{5}$ | Positive | | Positive | |
| | 22.34 | 5852.34 | 6.57x10$^{5}$ | Positive | | Negative | |
| **25≤Cq<30** | 26.99 | 4727.29 | 2.01x10$^{4}$ | Positive | **100%** | Positive | **10%** |
| | 25.21 | 4911.24 | 7.63x10$^{4}$ | Positive | | Negative | |
| | 28.84 | 4048.84 | 5.02x10$^{3}$ | Positive | | Negative | |
| | 29.72 | 3909.44 | 2.59x10$^{3}$ | Positive | | Negative | |
| | 25.65 | 4162.97 | 5.49x10$^{4}$ | Positive | | Negative | |
| | 27.91 | 3225.55 | 1.01x10$^{4}$ | Positive | | Negative | |
| | 28.25 | 4298.27 | 7.81x10$^{3}$ | Positive | | Negative | |
| | 26.71 | 4032.16 | 2.48x10$^{4}$ | Positive | | Negative | |
| | 27.78 | 3291.31 | 1.11x10$^{4}$ | Positive | | Negative | |
| | 27.95 | 4694.29 | 9.78x10$^{3}$ | Positive | | Negative | |
| **30≤Cq<35** | 32.08 | 2913.82 | 4.42x10$^{2}$ | Positive | **100%** | Negative | **0%** |
| | 32.90 | 2232.87 | 2.39x10$^{2}$ | Positive | | Negative | |
| | 31.50 | 3881.33 | 6.82x10$^{2}$ | Positive | | Negative | |
| | 33.25 | 2803.85 | 1.84x10$^{2}$ | Positive | | Negative | |
| | 30.33 | 4826.31 | 1.64x10$^{3}$ | Positive | | Negative | |
| | 30.48 | 3189.43 | 1.47x10$^{3}$ | Positive | | Negative | |
| | 31.97 | 2431.61 | 4.79x10$^{2}$ | Positive | | Negative | |
| | 33.53 | 1872.56 | 1.49x10$^{2}$ | Positive | | Negative | |
| | 34.18 | 1977.75 | 9.14x10$^{1}$ | Positive | | Negative | |
| | 34.85 | 2196.28 | 5.53x10$^{1}$ | Positive | | Negative | |
| **Cq≥35** | 35.21 | 1598.79 | 4.22x10$^{1}$ | Positive | **100%** | Negative | **0%** |
| | 35.69 | 782.77 | 2.94x10$^{1}$ | Positive | | Negative | |
| | 35.74 | 1814.18 | 2.84x10$^{1}$ | Positive | | Negative | |
| | 35.77 | 1997.38 | 2.77x10$^{1}$ | Positive | | Negative | |
| | 36.16 | 1750.37 | 2.07x10$^{1}$ | Positive | | Negative | |
| | 36.27 | 1609.83 | 1.91x10$^{1}$ | Positive | | Negative | |
| | 35.11 | 2958.09 | 4.55x10$^{1}$ | Positive | | Negative | |
| | 35.23 | 1355.05 | 4.16x10$^{1}$ | Positive | | Negative | |
| | 35.52 | 2734.07 | 3.35x10$^{1}$ | Positive | | Negative | |
| | 35.61 | 648.90 | 3.13x10$^{1}$ | Positive | | Negative | |

**FIGURE 1 |** Sensitivity evaluation of the rapid antigen test (RAT; SD BIOSENSOR, South Korea) at different ranges of Cq values for ancestral strain of SARS-CoV-2 positive samples diagnosed by RT-qPCR. SARS-CoV-2 detection by RAT from RT-qPCR positive samples with Cq value between 20≤Cq<25, 25≤Cq<30, 30≤Cq<35, and Cq≥35, respectively. All samples were positive by RT-qPCR. Table shows: the RFU (relative fluorescence units) and Cq value for the viral ORF1ab probe ($n$ = 10 samples per Cq range).

only for those samples containing the ancestral strain SARS-CoV-2 from Wuhan. Using NPSs, we determined that the detection sensitivity of RAT for the RT-qPCR Cq range 20≤Cq<25 was 90% (**Figure 1**), while a 10% sensitivity was observed for samples comprised within the range of 25≤Cq<30 (**Figure 1**). On the other hand, at higher Cq values, which include lower viral loads, the detection sensitivity was 0% for both Cq value ranges, 30≤Cq<35 and Cq≥35 (**Figure 1**). We made semi-quantitative analysis of the RAT band intensity, where the SARS-CoV-2 positive samples for the Cq range 20≤Cq<25 and 25≤Cq<30 showed a high band intensity (**Table 1**). Negative NPSs samples were also determined. Altogether, data showed a significantly lower sensitivity of RAT for the detection of SARS-CoV-2 in comparison to RT-qPCR technique.

On the other hand, we determined the ability of RAT to detect variants of the SARS-CoV-2 virus. We select NPSs from patients diagnosed as SARS-CoV-2 positive by RT-qPCR, containing variants according to the RT-qPCR SNP detection. When we evaluated these NPSs containing SARS-CoV-2 variants, we observed that the sensitivity of RAT decreased in the variants that carry K417N/T and E484K amino acid substitutions, even in samples with the lowest ranges of Cq (20≤Cq<25). As a result, detection sensitivity decreases to 42% detection, obtaining 58% false-negative samples when the virus presents these mutations (**Figure 2**). Interestingly, from the three SARS-CoV-2 (K417N/T, E484K, and N501Y) positive samples for RAT, two of them presented a band of low intensity (**Table 2**) compared to SARS-CoV-2 samples with no mutations identified, which present a high-intensity band in the range 20≥Cq<25 (**Table 1**). Furthermore, for Cq over 25 no SARS-CoV-2 variant (K417N/T, E484K, and N501Y) sample was detected by RAT. A flow chart of the results obtained are described on **Figure 3.**

Taking together, these data suggest that RAT loses its full ability to detect SARS-CoV-2 against these variants.

## DISCUSSION

RT-qPCR test is the gold standard technique for COVID-19 diagnosis (3). However, despite its high sensitivity, the extent of analysis and the associated costs have encouraged the use of faster and low-cost SARS-CoV-2 detection assays for better control of the pandemic (8). Previous studies have documented the efficiency of different brands of rapid antigen tests for SARS-CoV-2 detection as a diagnostic alternative compared to standard RT-qPCR. For example, Chaimayo et al. compared the sensitivity and specificity of the Standard Q COVID-19 Ag rapid test (SD Biosensor) against Allplex ™ 2019-nCoV Assay RT-qPCR assay (Seegene) in the diagnosis of COVID-19 in a Thailand population (9). They showed a 98% of comparable sensitivity with the real-time RT-PCR assay. Other rapid detection kits have shown, for example, a sensitivity of 85% (Shenzhen Bioeasy Biotech-2019-nCoV Ag) (10) or 72% (Abbott-Panbio COVID-19 Ag) (11), while the minimum sensitivity accepted in the rapid test by the World Health Organization is 80% for its diagnostic use (12). Dinnes et al. (5), after an analysis of 58 rapid tests, concluded that sensitivity of antigen assays significantly decrease in asymptomatic patients or after the second week of infection and, indicated that the sensitivity of these tests increases with the Cq≤25. For example, Linares et al. (13) reported that patients with less than seven days of symptoms showed a high viral load and a sensitivity of 86.5%, while the sensitivity dropped to 53.8% in asymptomatic patients or lower viral loads using the Panbio COVID-19 Ag Rapid Test Device (Abbot). The same effect was observed using the SD Biosensor-STANDARD Q COVID-19 test, where a sensitivity of 65.3% was observed in symptomatic patients and 44% in asymptomatic patients (14). Krüttgen et al. (6) using the rapid SARS-CoV-2 antigen test from the Roche manufacturer, indicated that the sensitivity of the assay in 75 NPSs is 100% (Cq≤25), 95% (Cq≤30), 44.8% (Cq≤35), and 22.2% (Cq>35) compared to RT-qPCR. Such sensitivity is directly related to the patient's viral load. In the same line, Schildgen et al. (15) reported a sensitivity of 100% in symptomatic patients and 84.6% in asymptomatic patients using the rapid test from Roche.

In this study, we observed that the rapid antigen test (SD Biosensor) has a detection efficiency depending on the Cq values, being 90, 10, 0, and 0% within the ranges of 20≤Cq<25; 25≤Cq<30; 30≤Cq<35, and Cq≥35, respectively. In this regard, the manufacturer and distributor indicate that 95.5% of effectiveness at Cq<30. Although our study shows lower sensitivity as previously described, it is also important to mention that we used a smaller number of samples in each Cq range compared to previous evidence (16). Furthermore, we observed that RAT sensitivity for detecting ancestral strain of SARS-CoV-2 decreased from 90 to 42.8% with the SARS-CoV-2 variants that carry K417N/T, E484K and N501Y amino acid substitutions, even in the lower Cq range of 20≤Cq<25. The low intensity of bands showed for two of the three SARS-CoV-2 variants identified by RAT suggests a decreased specificity for samples with the K417N/T, E484K, and N501Y mutations. By contrast, the virus with no mutations showed a high intensity band of detection by RAT in the 90% of the samples evaluated. Because the amino acid substitutions E484K and N501Y are present in the beta (B.1.351) and gamma (P.1) variants, and the substitution K417N is found in the beta variant and K417T in the gamma variant (17), we hypothesized that RAT might not detect both or at least one of these two virus variants. In this line, Frediani et al. (7) reported that the Abbott BinaxNOW COVID-19 Ag Card rapid test detects the P.1 variant, even between the Cq ranges of 20-22. However, this data corresponds only to one sample analyzed (7). Other variant studies using rapid antigen tests, including analysis

**TABLE 1 |** Qualitative analysis of SARS-CoV-2 samples tested by Rapid Antigen Test (RAT).

| | Band intensity in RAT | | |
|---|---|---|---|
| **Cq ranges** | **None** | **Low** | **High** |
| 20≤Cq<25 | 1 | 0 | 9 |
| 25≤Cq<30 | 9 | 0 | 1 |
| 30≤Cq<35 | 10 | 0 | 0 |
| Cq≥35 | 10 | 0 | 0 |

| RT-qPCR | | | | | | | Rapid Antigen Test (RAT) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cq Range** | **Cq** | **RFU** | **Viral copies** | **SARS-CoV-2 mutation** | **Result** | **% Sensitivity** | **SARS-CoV-2 mutation** | **Result** | **% Sensitivity** |
| 20≤Cq<25 | 21.30 | 5695.52 | $1.43 \times 10^{6}$ | K417N/T. E484K. N501Y. | Positive | **100%** | K417N/T. E484K. N501Y. | Positive | **42.8%** |
| | 20.21 | 4853.36 | $3.25 \times 10^{6}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Positive | |
| | 22.29 | 5899.33 | $6.82 \times 10^{5}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Positive | |
| | 22.6 | 3509.51 | $5.41 \times 10^{5}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| | 22.62 | 3006.71 | $5.33 \times 10^{5}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| | 24.25 | 2629.85 | $1.57 \times 10^{5}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| | 20.42 | 4704.13 | $2.77 \times 10^{6}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| 25≤Cq<30 | 25.04 | 4349.95 | $8.67 \times 10^{4}$ | K417N/T. E484K. N501Y. | Positive | **100%** | K417N/T. E484K. N501Y. | Negative | **0%** |
| | 25.71 | 4536.41 | $5.25 \times 10^{4}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| | 25.94 | 3878.15 | $4.42 \times 10^{4}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| | 27.55 | 4868.30 | $1.32 \times 10^{4}$ | K417N/T. E484K. | Positive | | K417N/T. E484K. | Negative | |
| | 28.99 | 4738.70 | $4.48 \times 10^{3}$ | K417N/T. E484K. N501Y. | Positive | | K417N/T. E484K. N501Y. | Negative | |
| 30≤Cq<35 | 4267.17 | 30.54 | $1.40 \times 10^{3}$ | K417N/T. E484K. N501Y. | Positive | **100%** | K417N/T. E484K. N501Y. | Negative | **0%** |
| | 3345.16 | 32.85 | $2.48 \times 10^{2}$ | K417N/T. E484K. | Positive | | K417N/T. E484K. | Negative | |
| | 3163.99 | 33.32 | $1.74 \times 10^{2}$ | K417N/T. E484K. | Positive | | K417N/T. E484K. | Negative | |

**FIGURE 2 |** SARS-CoV-2 Variant detection by RAT. RAT detection of SARS-CoV-2 variants which contain K417N/T, E484K, and N501Y mutations, from RT-qPCR positive samples with Cq value between 20≥Cq<25, 25≥Cq<30, 30≥Cq<35. All samples were positive by RT-qPCR. Table shows: the RFU (relative fluorescence units) and Cq value for the viral ORF1ab probe (*n* = 16).

**TABLE 2 |** Qualitative analysis of SARS-CoV-2 variant (K417N/T/, E484K, and N501Y) samples tested by Rapid Antigen Test (RAT).

| | Band intensity in RAT | | |
|---|---|---|---|
| **Cq Ranges** | **None** | **Low** | **High** |
| 20≤Cq<25 | 4 | 2 | 1 |
| 25≤Cq<30 | 5 | 0 | 0 |
| 30≤Cq<35 | 3 | 0 | 0 |

of the alpha (B.1.1.7) and beta (B.1.351) variants (18), showed no detection at Cq values between 29–35 (7) like this study.

The rapid antigen test analyzed in this study detects the nucleocapsid (N) of the original SARS-CoV-2 virus using a monoclonal antibody. This kind of detection can explain the low capacity of RAT to detect the variants, which has the substitutions P80R and R203K in the N protein. These data further suggest that this rapid antigen test could also fail to detect other variants, such as delta (B.1.617.2), because, in addition of Spike protein mutations (19), the delta variant also has mutations in the N protein (different to R203K). This data suggests a lack of specificity of RAT to detect specific variants, which agrees with the fact that RAT initially manufactured to detect the ancestral strain of SARS-CoV-2. In addition, this takes on real relevance

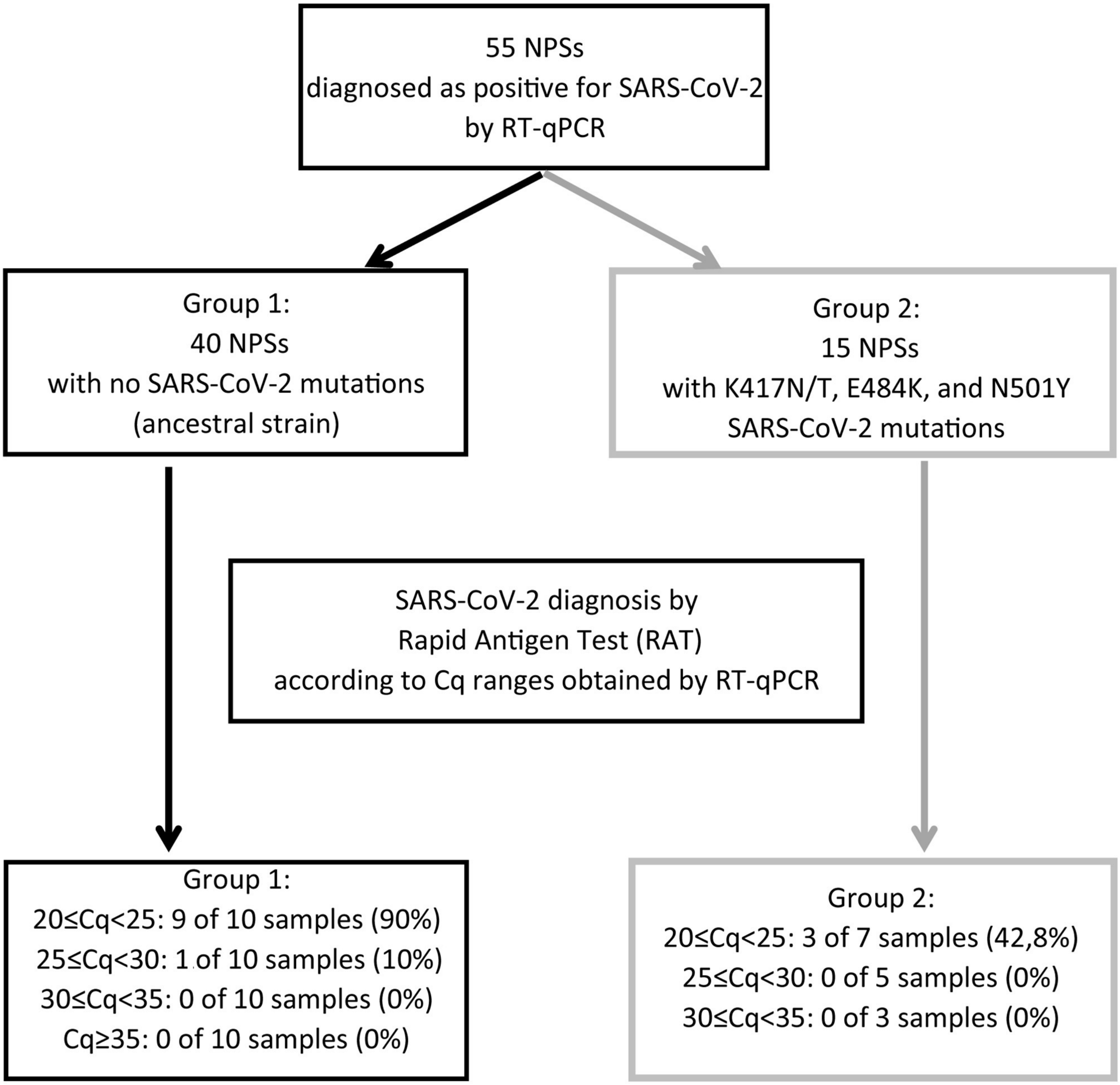


**FIGURE 3 |** Summary of the results obtained for the analysis of the 55 nasopharyngeal swab samples (NPSs) evaluated by Rapid Antigen Test (RAT). The 55 NPSs were diagnosed as positive for SARS-CoV-2 using the ORF1ab probe following a one-step strategy. From them, 40 NPSs showed no mutations for SARS-CoV-2 (black arrow) (Group 1). By contrast, in the other 15 positive samples we identified the SARS-CoV-2 variants K417N/T, E484K, and N501Y (gray arrows) (Group 2). Each one of these groups were used to evaluate the sensitivity of the Rapid Antigen Test (RAT) according to the Cq ranges previously obtained by RT-qPCR. The group 1 showed a 90% of positive diagnosis using the RAT. However, the group 2 showed only a 42.8% of positive diagnosis. Importantly, all of them were grouped in the $20 \leq Cq < 25$ interval.

when the RAT is used as an active search or mass testing in public places in infected patients with a high Cq (low viral load). According to the results shown in our work, the diagnosis by RAT will be negative, and the patient will be able to infect their contacts and, consequently, may generate important local outbreaks. Therefore, detecting positive patients with low viral load, who will probably be asymptomatic, should be done only by the RT-qPCR assay, one of the safest ways to be massively tested in the population to control the pandemic. Further studies are needed for evaluating by RAT a higher number of samples and SARS-CoV-2 variants. Although we found significant differences in each condition (ancestral strain of SARS-CoV-2; SARS-CoV-2 variants), it is still necessary to increase the number of samples to obtain more accurate detection percentages of SARS-CoV-2 in each range of Cq analyzed. We suggest restricting the use of RAT only to confirm COVID-19 symptomatic positive cases but not as a massive strategy for traceability and identification of cases in the population.

## CONCLUSIONS

The sensitivity of the rapid antigen test (SD Biosensor, South Korea) is determined by the viral load of the sample. While high viral loads ($20 \leq Cq < 25$) present 90% sensitivity, $25 \leq Cq < 30$ and $>30$ present 10 and 0% respectively. On the other hand, the rapid test reduces its detection sensitivity compared to samples positive for SARS-CoV-2, but that present the mutations K417N/T, E484K, and N501Y observing a detection capacity of 42% in ranges of $20 \leq Cq < 25$.

## 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 Ethical Committee of the University of Santiago of Chile (No. 226/2021), and Scientific Ethical Committee of the Central Metropolitan Health Service, Ministry of Health, Government of Chile (No. 370/2021). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

CB-A, RL, MI, CA-C, FER-L, and AMS: conceptualization. CB-A, RL, and FER-L: data curation. CB-A, RL, FER-L, and AMS: formal analysis. MI, CA-C, FER-L, and AMS: funding acquisition. CB-A, AM-T, FH, MF, and CR: investigation. CB-A, EV-V, FER-L, and AMS: methodology. DV, FER-L, and AMS: supervision. DV, MI, CA-C, FER-L, and AMS: validation. CB-A, RL, CA-C, and FER-L: writing—original draft. CB-A, RL, EV-V, CA-C, MI, FER-L, and AMS: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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# Estimating the Effects of Public Health Measures by SEIR(MH) Model of COVID-19 Epidemic in Local Geographic Areas

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The COVID-19 pandemic of 2020–21 has been a major challenge to public health systems worldwide. Mathematical models of epidemic are useful tools for assessment of the situation and for providing decision-making support for relevant authorities. We developed and implemented SEIR(MH) model that extends the conventional SEIR model with parameters that define public lockdown (the level and start of lockdown) and the medical system capacity to contain patients. Comparative modeling of four regions in Europe that have similar population sizes and age structures, but different public health systems, was performed: Baden-Württemberg, Lombardy, Belgium, and Switzerland. Modeling suggests that the most effective measure for controlling epidemic is early lockdown (exponential effect), followed by the number of available hospital beds (linear effect if the capacity is insufficient, with diminishing returns when the capacity is sufficient). Dynamic management of lockdown levels is likely to produce better outcomes than strict lockdown.

**Keywords: mathematical model, public health policies, lockdown, hospital capacity, COVID-19**

## INTRODUCTION

Mathematical models of epidemic help predict the spread of infection and identify the likely outcomes of an epidemic (1, 2). These models provide information about the likely effects of public health interventions enacted to control the epidemic. Epidemiological models provide support for decision making related to early intervention or ending the measures. Imposing effective and timely measures is essential for the disruption of the rapid spread stage of epidemics (3). Compartmental epidemiological models assign population to compartments labeled by their health status. For example, the SEIR model assigns population to **S**usceptible, **E**xposed, **I**nfectious, and **R**ecovered subpopulation compartments (4, 5). These models are used to predict epidemiological parameters, such as disease spread, the total number of infections, and the shape of epidemiological curves (6–8). SEIR models have been used for modeling epidemics caused by influenza virus (9), Ebola virus (10), Middle East respiratory syndrome-related coronavirus (MERS-CoV) (11), and human immunodeficiency virus (HIV) (12).

In the past, actual epidemiological data were available only with a delay. Earlier models could only assess the dynamics of the outbreak and the effects of control measures after the outbreak (1, 13). The post-epidemic models focused on modeling the natural spread of infection and usually did not include the intervention measures as part of the model. Rather, the interventions were considered as the means to change the basic epidemic parameters directly. Advances in information and communication technologies have enabled an unprecedented speed of data exchange, and the updates of basic epidemiological parameters are now available daily (5). Timely updates enable building of modified SEIR models that incorporate public health measures as internal model parameters. This, in turn, enables the adjustment of basic SEIR models, as observed during the COVID-19 pandemic (6, 8, 14). The modifications include the addition of relevant parameters, such as migration index (15), speed of the infection during latent period (16), asymptomatic carriers' populations and personal intervention strategy (17, 18), simulation of the final phase of the outbreak (19), or seasonality (20). These adjustable models were developed using early data from specific limited locations and are based on assumptions that were not yet confirmed at the time of modeling. The common theme with these models is that they are reasonable approximations of actual epidemic spread. Most of these models represent extensions of the basic model, for example, the SIDARTHE model (14) defines eight population compartments that provide additional insight about populations at risk. Our extension of the basic SEIR model considers key public health variables and their combined effect on the control of epidemic.

We developed a modified SEIR model, SEIR(MH), that includes additional modeling parameters as compared to the base model. These additional parameters include the capacity of the public health system to support control measures, such as the conditions of public lockdown (level of lockdown F, and the start date of lockdown $T_L$), and the available capacity of the medical system to contain patients (the population with access to healthcare M, and the number of dedicated hospital beds H). The SEIR(MH) model was applied to the COVID-19 data from four regions in Europe that are comparable by population sizes and socio-economic status: Baden-Württemberg (Germany), Lombardy (Italy), Belgium, and Switzerland. These four regions represent a variety of lockdown conditions and different initial capacities of the medical system to contain the spread of infection. The results of simulations by the SEIR(MH) model agreed well with the observed curves of daily epidemic reports. Using these data and the SEIR(MH) model, we estimated the actual COVID-19 epidemic progression in these four regions during the first wave. We used the resulting models to analyze what-if scenarios to study the effects of different lockdown policies and the numbers of COVID-19 available beds, using the real reports data. Finally, we performed simulations of COVID-19 epidemic situations in three virtual cities with different age structures to demonstrate the potential utility of the SEIR(MH) modeling for designing optimized public health measures.

# MATERIALS AND METHODS

## Data Sources and Assumptions

The daily statistics of new infections, current infections, and fatalities in four studied regions (Baden-Württemberg, Belgium, Lombardy, and Switzerland) were obtained from the COVID-19 projections of IHME (21). In this resource, the migration index before and after the lockdown was also collected, as well as the COVID-19 available beds (**Supplementary Table 1**) (21). These data have been updated daily through concerted effort of many individuals and organizations and rapidly shared with the community.

We added two state variables including $M$ and $H$ to extend the traditional SEIR model (5, 15). Variables $S$, $E$, $I$, $R$, and $M$ represent the total number of people in each corresponding state. $S$, $E$, $I$, and $R$ represent the number of susceptible, exposed (infected without symptoms), infected with symptoms, and removed individuals, respectively. $M$ represents the number of people with medical care and $H$ represents COVID-19 available beds in hospitals (22). Current number of infections is defined as $I + M$ and the total number of infected individuals as $I + M + R$. For modeling, we made the following assumptions:

- People in state $S$ will transit to state $E$ after infection and cannot transit to state $I$ directly.
- All people in state $E$ will eventually transit to state $I$ after the incubation period.
- People in state $I$ will transit to state $M$ when beds are sufficient, or transit to state $R$ when self-recovered or died, without medical care.
- People in state $M$ will transit to state $R$ when recovered or died. We did not consider the possibility of re-infection in the current model.
- People in states $E$ and $I$ are infectious with the infection coefficients of $\alpha$ and $\beta$, people in state $M$ are not infectious. $\alpha$ and $\beta$ are mobility-related parameters.
- The number of individuals in state $M$ should be less than or equal to the total number of $H$ at each time point.
- The incubation period follows Poisson distribution with the mean time between 4 and 7 days (23).
- The COVID-19 available beds indicate the capacity of hospitals to take in COVID-19 patients.
- The probability of people to transit from $I$ to $M$ is a function of the current number of beds and waiting time for hospitalization. The more available beds and the longer the waiting time, the higher the probability. The conversion probability for each day follows the sigmoid function with the mean waiting time between 4 and 8 days (24).
- The hospitalization time follows Poisson distribution with the median time between 7 and 14 days (24).

## Model Specification

The SEIR(MH) model is a state recursive model, where the estimated values of key model parameters were calculated using recursive formulas based on daily simulation of epidemic. Model inputs were the reported data from previous days. For SEIR(MH) modeling, the epidemic is divided into evenly spaced time steps measured in days. The size of SEIR(MH) population in each time step is described by the corresponding states: *Susceptible* (S), *Exposed without symptoms* (E), *Infected with symptoms* (I), *Removed from the system* (R), *with medical care* (M), and *the maximum number of beds in hospitals* (H).

We use symbols $X$ and $Y$ for state transitions. The uppercase $T$ is used for the absolute date and lowercase $t$ is used for the offset in days (e.g., $t = 3$ or $-3$ mean "3 days later" or "3 days

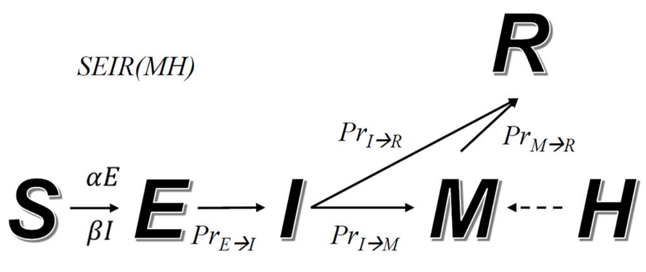


**FIGURE 1 |** Transition diagram of the SEIR(MH) model. S, E, I, M, and R represent individuals in states: susceptible, exposed without symptoms, infected with symptoms, with medical care, and removed from the system. The number M cannot be larger than the current number of beds in hospitals, defined as H. The arrow indicates the direction of state transmission. The infection coefficients determine transition numbers S to E ($\alpha$) and S to I ($\beta$). $Pr_{E \to I}$, $Pr_{I \to R}$, $Pr_{I \to M}$ and $Pr_{M \to R}$ represent transmission probability between indicated states.

earlier"). For any day $T$ and state $X$, $X(T)$ stands for the size of population in state $X$ on day $T$. For instance, $I(T)$ is the number of symptomatic infections on day $T$. The epidemic states on each day $T$ are represented by $\{X(T) \mid X \in \{S, E, I, R, M, H\}\}$.

During an epidemic, we assume that a fraction of the population will transit from one state to another. For instance, a fraction of the population infected with symptoms (state $I$) starts to receive medical care (changing to state $M$). The relations among these states are defined by a transition diagram, shown in **Figure 1**. Among the variables, $S$, $E$, $I$, $R$, and $M$ make direct transitions, while the value of $H$ is the upper bound of $M$, meaning that hospitals cannot receive more patients than their capacity.

Our model simulates the progression of an epidemic. The transition rules (i.e., how many people will transit from one state to another at any time step) are defined by a set of formulas and adjustable parameters. Given two different states $X$ and $Y$, $Pr_{X \to Y}(t)$ represents the probability for a person in state $X$ to transit to state $Y$ after $t$ days. According to the state transition diagram, we have the following functions: $Pr_{E \to I}(t)$, $Pr_{I \to R}(t)$, and $Pr_{M \to R}(t)$. An exception is $Pr_{I \to M}(t|T-t)$ which depends on both $T$ and $T-t$. This is related to the fact that $M(T)$ (number of people in hospital) has upper bound $H(T)$ (hospital capacity), which changes over time (due to addition of hospital beds). Other parameters include infection coefficients $\alpha$ and $\beta$ that control how fast individuals in states $E$ and $I$ infect unexposed individuals. $\alpha$ and $\beta$ are constant when interventions remain unchanged or no intervention is taken.

$\Delta X(T) = X(T) - X(T-1)$ is the difference between population sizes in state $X$ on days $T$ and $T-1$. Positive $\Delta X(T)$ indicates the growth of population $X$ between $T-1$ and $T$, zero indicates stable situation, while negative number indicates decline. In our simulation, the values of $\Delta E(T)$, $\Delta I(T)$, $\Delta M(T)$, $\Delta H(T)$, and $\Delta R(T)$ are calculated for each day $T$. By definition $X(T) = X(0) + \Delta X(1) + \ldots + \Delta X(T)$ for any state $X$, where $X(0)$ as the initial input. Thus, we can simulate the status for any day $T$ and $X$ by calculating $X(T)$. The patient zero (index case) $E(0)$ and the day of patient zero $T_0$ are not the actual cases because the initial infection is usually a cluster of cases imported from outside. The $E(0)$ and $T_0$ are an idealized case where there is a virtual patient on a particular day that would produce the same infection dynamics as the imported cluster of cases.

We defined $\Delta^+ X(T)$ as transit population from the preceding state to state $X$, which must be non-negative. For instance, when the exposed with symptoms ($E$) are 0, no people will transit to the infected state ($I$) and $\Delta^+ X(T) = 0$. $\Delta^+ X(T-t)\, Pr_{X \to Y}(t)$ represents the number of people who enter the state $X$ on day $T-t$ and then change to state $Y$ on day t (after $t$ days). For instance, $\Delta^+ E(T-1)\, Pr_{E \to I}(1)$ is the number of individuals who became infected with symptoms (enter state $E$) on day $T-1$ and start to show symptoms on the next day (enter state $I$). If $\Delta E(T-1) < 0$, $\Delta^+ E(T-1)\, Pr_{E \to I}(1) = 0$.

## Transition Rules

The definition of the symbols $\Delta X(T)$ for $X \in \{S, E, I, R, M, H\}$ as well as transition probability $Pr_{X \to Y}(t)$ are defined as:

$\mathbf{\Delta E(T)}$ consists of two components corresponding to two scenarios: (1) susceptible population (in $S$) become infected (enter state $E$), (2) infected population (in $E$) start to show symptoms (enter state $I$). For $S$ to $E$ transition, $\min\{1, E(T-1)\alpha + I(T-1)\beta\}$ was defined for the overall infection probability due to contact with populations $E$ and $I$. We added the min operator to ensure the probability cannot exceed 1. Multiplying this probability by $S(T)$ leads to the increase of the population in state-$E$. For $E$ to $I$ transition, $\Delta^+ E(T-t)\, Pr_{E \to I}(t)$ equals to the number of people who become infected on $T-t$ and start showing symptoms $t$ days later. For simulations we define a time span of $k$ days. Thus, a total number of $\sum_{t=1}^{k} \Delta^+ E(T-t)\, Pr_{E \to I}(t)$ that transit from $E$ to $I$ are:

$$\Delta E(T) = S(T)\,(E(T-1)\alpha + I(T-1)\beta) - \sum_{t=1}^{k} E(T-t)\, Pr_{E \to I}(t) \qquad (1)$$

$\boldsymbol{\Delta I(T)}$ has three components: (1) infected people (in $E$) start showing symptoms (enter state $I$), (2) people with symptoms (in $I$) start to receive treatment in hospital (enter state $M$), and (3) people with symptoms (in $I$) die or recover (enter state $R$). The first component maps to the last term in equation (1). The last two components are defined as:

$$\Delta I(T) = \sum_{t=1}^{k} \Delta^+ E(T-t) Pr_{E \to I}(t) - \sum_{t=1}^{k} \Delta^+ I(T-t) Pr_{I \to M}(t|T-t) - \sum_{t=1}^{k} \Delta^+ I(T-t) Pr_{I \to R}(t) \qquad (2)$$

$\boldsymbol{\Delta M(T)}$ captures the following scenarios: (1) patients under medical treatment (in state $M$) can recover or die (enter state $R$), (2) population of infected individuals (in status $I$) can be admitted to hospital (in state $M$), and (3) the number of new admissions to hospitals must not exceed the hospital capacity.

The $\Delta M(T)$ captures three scenarios:

$$\Delta M(T) = min[\sum_{t=1}^{k} \Delta^{+} I(T-t) Pr_{I\rightarrow M}(t|T-t) - \sum_{t=1}^{k} \Delta^{+} M(T-t) Pr_{M\rightarrow R}(t), H(T-1) - M(T-1)] \quad (3)$$

$\Delta$***R(T)*** captures the population that entered state $R$ from either state $I$ or $M$, which are both non-positive:

$$\Delta R(T) = \sum_{t=1}^{k} [\Delta^{+} I(T-t) Pr_{I\rightarrow R}(t) + \Delta^{+} M(T-t) Pr_{M\rightarrow R}(t)] \quad (4)$$

$\boldsymbol{Pr_{E\rightarrow I}}$. We assume $Pr_{E\rightarrow I}(t)$ follows Poisson distribution where $\lambda_{E\rightarrow I}$ is the average number of days for infected individuals to start showing symptoms:

$$Pr_{E\rightarrow I}(t) = Poission\ (t;\ \lambda_{E\rightarrow I}) \quad (5)$$

$\boldsymbol{Pr_{I\rightarrow M}}$. $Pr_{I\rightarrow M}(t|T-t)$ is the probability of being admitted to a hospital after $t$ days since day $T$. We assume $Pr_{I\rightarrow M}(t|T-t)$ follows geometric distribution where $P_{T-t}$ is the probability that an infected individual is admitted to hospital precisely on the day $T-t$. During the time of an epidemic, people who need hospitalization may not be admitted if the hospital capacity is full, so placement in another hospital will be requested. The larger the number of the patients already in hospital, the more difficult it is for newly diagnosed patients to find a place in the hospital. This situation is well-represented by geometric distribution:

$$Pr_{I\rightarrow M}(t|T-t) = P_T \cdot \prod_{t=1}^{T} (1 - P_{T-t}) \quad (6)$$

$P_T$ is a variant of logistic function:

$$P_T = \begin{cases} \frac{1}{1+\exp(-k(H(T)-M(T)-x_0))}, & H(T) - M(T) > 0 \\ 0, & otherwise \end{cases} \quad (7)$$

where $k$ and $x_0$ are model parameters to be fitted according to the waiting time for people to receive medical care. $P_T > 0$ when the hospital capacity for COVID-19 is not reached, $H(T) - M(T) > 0$.

$\boldsymbol{Pr_{I\rightarrow R}}$. We assume that infected population either recovers or dies (enter $R$) if they are not admitted to hospital after $t_x$ days. $t_x$ is a model parameter to be fitted and $Pr_{I\rightarrow R}(t)$ is defined as:

$$Pr_{I\rightarrow R}(t) = \begin{cases} > t_x, & 1 \\ 0, & otherwise \end{cases} \quad (8)$$

$Pr_{M\rightarrow R}$. We assume that $Pr_{M\rightarrow R}(T)$ follows Poisson distribution where $\lambda_{M\rightarrow R}$ is the average number of days for transition from $M$ to $R$, e.g., average days to recovery or before death under medical care:

$$Pr_{M\rightarrow R}(T) = Poisson\,(T;\lambda_{M\rightarrow R}) \quad (9)$$

## Model Parameters Fitting

The fitting objective was to minimize the mean absolute error between the predicted number of increased infections ($I$) and the observed number of increased infections. Since SEIR(MH) is a state recursive model, the estimated number of increased infections ($I$) at time $T$ and the estimated number of increased exposed population ($\Delta$E) at time $T$ do not have a closed-form solution for given sets of parameters. The estimated values of ($\Delta$I) and ($\Delta$E) could not be obtained by parameter estimation but were assessed by exploration of the search space. Thus, model optimization is a non-trivial task. To ensure that the solution space is fully explored, we resorted to brute-force search over the pre-specified ranges of parameters. To reduce computation overhead, the range of each parameter was discretized into evenly spaced values. In addition, we performed search of the optimized parameters in two steps: (1) narrowed down the searching space in the first round and (2) refined to a greater precision in the second round.

The infection coefficients before the lockdown are $\alpha_{pre}$ and $\beta_{pre}$ and after the lockdown are $\alpha$ and $\beta$. The infection coefficients $\alpha$ and $\beta$ were estimated for each region by model fitting to the reported data. Lockdowns cause changes of the mobility factor (parameter F). In our model F ranges from 1 (no reduction of mobility) to 6 (extremely high reduction of mobility). The corresponding infection coefficients before the lockdown were calculated by $\alpha_{pre} = \alpha \times F$ and $\beta_{pre} = \beta \times F$.

## Simulation of Virtual Cities

The overall goal of virtual city epidemic simulations was to help identify the optimal level of public health measures given three variables: the lockdown date, lockdown level, and the number of beds. The lockdown date $T_{SDn}$ is time in days from the estimated patient zero day ($T_{SD0}$). The earliest lockdown date in simulation was $T_{SD24}$, 24 days from $T_{SD0}$. The latest lockdown date in simulation was $T_{SD72}$, 72 days from $T_{SD0}$. In the first stage, we fixed the number of COVID-19 beds (four per thousands) and performed the simulation analysis of TNI and TND for three virtual cities. Two parameters were varied in this simulation: days between the first patient to lockdown date ($T_{SDn}$) and the lockdown factor. The second stage of simulation involved the same procedure as in stage 1, but for eight additional available COVID-19 bed values (0.5 to 4, increment 0.5). The third stage involved systematic changes of all three variables to identify optimal lockdown level for each lockdown start date (24 to 72, increment 2) and three levels of the number of beds (1, 2, and 4).

The total number of infected people (TNI) on any day during the epidemic was defined as the total number of people in status $I$, status $M$, and status $R$. The COVID-19 infection rate ($CIR$) at each day equals the ratio $TNI/TPO$ where $TPO$ is the total population of the region. Using the SEIR(MH) modeling, the CIR on each day of the three virtual cities was calculated. The overall death rate in a population ($PDR$) was calculated as $PDR = CIR \times CDR$, and the total number of COVID-19 deaths was calculated as $TND = CIR \times CDR \times TPO$. Using the simulation, we could estimate the effects of public health strategies (lockdown time, lockdown level, and available beds for COVID-19) for regions with different age structures

**TABLE 1 |** Parameters used in SEIR(MH) modeling.

| Variable | Variable meaning | BW[b] | Bel[c] | Lom[d] | Swi[e] | Estimation |
|---|---|---|---|---|---|---|
| α[a] | Infection coefficient by people at state E | $1.1 \times 10^{-8}$ | $1.1 \times 10^{-8}$ | $1.2 \times 10^{-8}$ | $1.3 \times 10^{-8}$ | Data fitting |
| β[a] | Infection coefficient by people at state I | $1.8 \times 10^{-9}$ | $1.1 \times 10^{-9}$ | $1.4 \times 10^{-9}$ | $1.3 \times 10^{-9}$ | Data fitting |
| T(E->I) | Average days for people converting from E to I | 6 | 6 | 6 | 6 | PMID[f]: 31995857[1] |
| T(I->M) | Average days for people converting from I to M | 7 | 7 | 7 | 7 | PMID[f]: 32031570[7] |
| T(I->R) | Average days for people converting from I to R | 14 | 14 | 14 | 14 | Data fitting[g] |
| T(M->R) | Average days for people converting from M to R | 10 | 10 | 10 | 10 | PMID[f]: 32031570[7] |
| F | Mobility change due to lockdown | 3.00 | 3.47 | 3.85 | 2.55 | Data fitting |
| O(T) | Days between first patient to lockdown | 39 | 31 | 31 | 59 | Data fitting |
| ΔT[h] | Shift curve to earlier date | 0 | 0 | −7 | 0 | Adjustment |

*[a]α and β are the infection coefficients after the lockdown. The corresponding infection coefficients before the lockdown are calculated as $\alpha_{pre} = \alpha \times F$ and $\beta_{pre} = \beta \times F$. The infection coefficient before lockdown is associated with the mobility. The infection coefficients were estimated for each region by data fitting, considering changes of the factor of mobility after the lockdown (parameter F). In our model it ranges from 1 (no reduction of mobility) to 6 (extremely high reduction of mobility). [b]Baden-Württemberg in Germany (BW), [c]Belgium (Bel), [d]Lombardy in Italy (Lom), [e]Switzerland (Swi). [f]Pubmed ID. [g]Considering it is a disease-related intrinsic parameter, we assume the T(I->R) in each region is equal. [h]Early outbreaks are associated with delayed reporting of cases, lack of testing kits, and difficulties in identification true cases.*

using the overall number of deaths in each region (*TND*) as the minimization target. The simulation variables for cities are available in **Supplementary Table 2**. The first stage had a total of 2,100 simulations, the second stage involved an additional 4,200 simulations, and the third stage involved 4,725 simulations. All simulations used a quasi-exhaustive search (25) to find the best level of lockdown for possible situations arising from combinations of the lockdown date, number of beds, and the age structure.

# RESULTS

## Estimation of Parameters of the SEIR(MH) Model

In our model, we divided the epidemic progress into discrete periods, measured in days. The model has four population variables and two health system capacity variables. The population variables provide the size of epidemiology categories (or compartments): *Susceptible* (S), *Exposed without symptoms* (E), *Infected with symptoms* (I), and *Removed from the system* (R). The health system capacity variables include the *population with medical care* (M) and the *maximum number of beds in hospitals* (H). All of these variables are time dependent. Among them, the values of $S$, $E$, $I$, $R$, and $M$ at each date are simulated, and the values of $H$ are pre-specified.

The SEIR(MH) model contains eight epidemiological parameters including infection coefficients $\alpha$ and $\beta$; transition times $T(E \rightarrow I)$, $T(I \rightarrow M)$, $T(I \rightarrow R)$, $T(M \rightarrow R)$; the mobility change factor $F$; the region-specific constant $O(T)$; and region-specific time shift variable ΔT. In this study, the SEIR(MH) model was generated using data from four European regions including Baden-Württemberg, Lombardy, Belgium, and Switzerland. These regions have comparable population sizes, ranging from 8.57 to 11.48 million, and a similar age distribution of population (**Supplementary Table 3**). The values of model parameters in these four regions, their descriptions, and how they are determined are shown in **Table 1**. Among them, the values of $\alpha$, $\beta$, $T(I \rightarrow R)$, $F$, and $O(T)$ were fitted to the model

**TABLE 2 |** Estimated model parameters and observed values in four studied regions.

| Region | Baden-württemberg | Belgium | Lombardy | Switzerland |
|---|---|---|---|---|
| Period[a] | February 15–July 4, 2020 | | | |
| r[b] | 0.83 | 0.84 | 0.88 | 0.93 |
| Days | 140 | | | |
| OPT[c] | March 28 | March 28 (true)/April 15 (outlier) | March 21 | March 23 |
| OPI[d] | 1,603 | 1,850/2,454 | 3,268 | 1,321 |
| EPT[e] | March 27 | March 27 | March 20 | March 25 |
| EPI[f] | 2,093 | 2,259 | 3,815 | 1,739 |
| S[g] | 11.07 | 11.48 | 9.95 | 8.57 |
| oTNI[h] | 36,275 | 61,837 | 94,318 | 32,198 |
| eTNI[h] | 54,494 | 67,239 | 127,899 | 42,848 |
| eTNI[i] | 54,646 | 67,691 | 128,584 | 42,892 |

*[a]Calendar periods of SEIR(MH) modeling for each region. [b]Correlation coefficient between observed and estimated infections (r). [c]Observed peak time (OPT). [d]Observed peak infections (OPI). [e]Estimated peak time (EPT). [f]Estimated peak infections (EPI). [g]Total population (millions) in each of the four regions (source: data.worldbank.org), [h]Total number of observed (oTNI) and estimated (eTNI) infections till July 4, 2020. [i]Total number of estimated (eTNI) infections till estimated end point.*

using data from daily reports of the new infections in studied regions. The values of $T(E \rightarrow I)$, $T(I \rightarrow M)$, and $T(M \rightarrow R)$ were pre-specified using data from published research and available reports. A detailed description of parameter fitting is described in the ***Materials and Methods*** section.

## Agreement of Fitted Models With the Reported Data From the Studied Regions

The SEIR(MH) model was evaluated using observed data from the four European regions (**Table 2**). These regions differed in their public health policies and utilization of medical resources during the first onset of the COVID-19

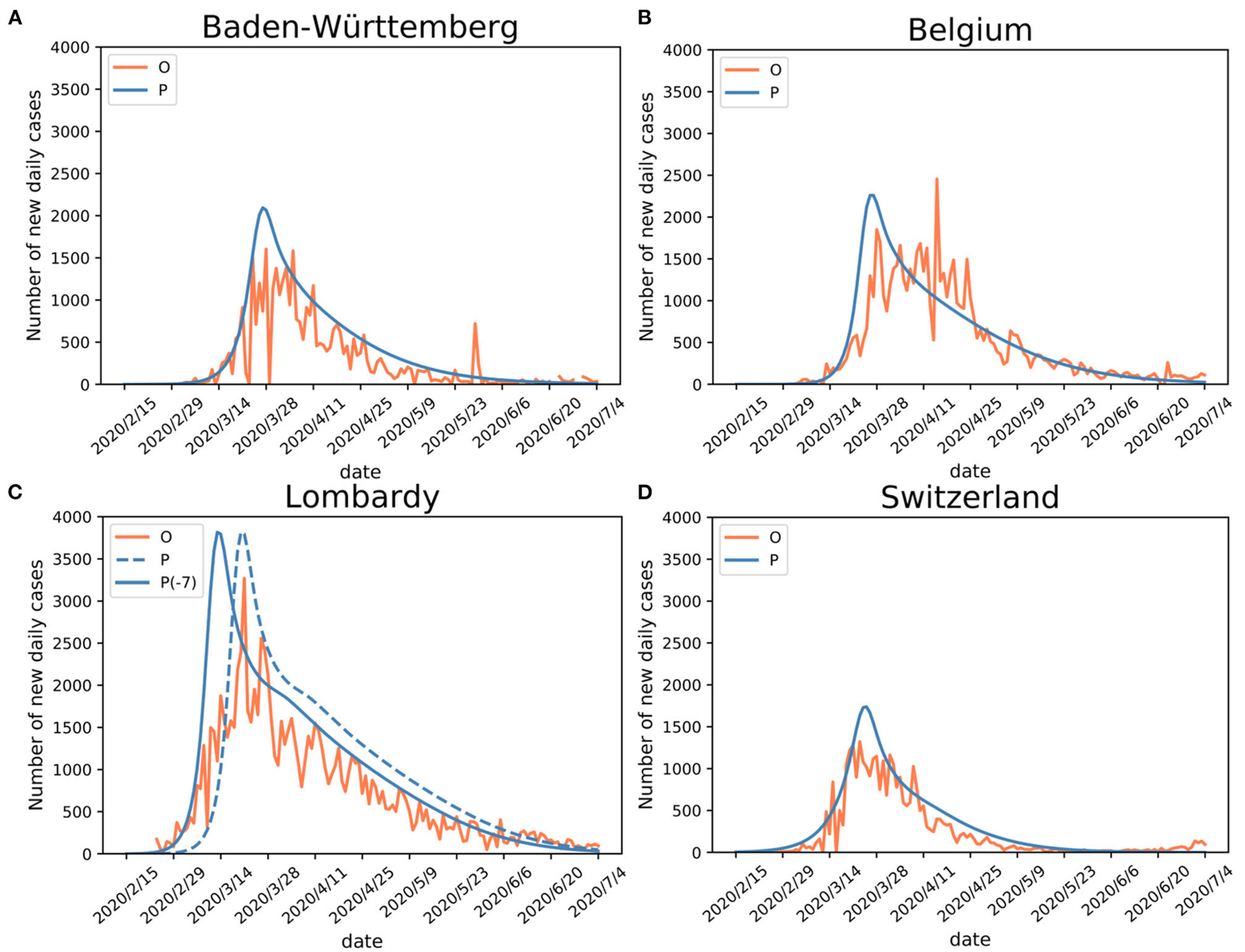


**FIGURE 2 |** Validation of SEIR(MH) model. Comparisons of the Infected with symptoms (I) population (observed "O" and estimated "P") curves in **(A)** Baden-Württemberg, **(B)** Belgium, **(C)** Lombardy ( "P-7" stands for adjusted curve), and **(D)** Switzerland. Shifting the curve to the earlier days ($\Delta T = -7$) shows better matching with the observed data during the early epidemic period in Lombardy. The justification for Lombardy model adjustment is given in the main text.

pandemic. For each region, the number of active infections was used as the indicator for model evaluation. Using the mobility data derived from COVID-19 projections of the Institute for Health Metrics and Evaluation (IHME) (21), we defined two distinct stages of the early period of the epidemic: initial stage (without movement restrictions) and public measure stage (with movement restrictions—the lockdown). The performance of the SEIR(MH) model in comparison to the actual reported observations is shown in **Figure 2**.

For Baden-Württemberg, the correlation coefficient between the observed and estimated daily active infections (population $I$) was $r = 0.83$ from February 15 to July 4. The observed peak of daily new infections happened between March 24 and April 5. There were three days with the values of $I$ number larger than 1,500 (March 24, March 28, and April 5). The infection peak estimated by the model occurred on March 27, with 2,093 people estimated to be in status $I$ (**Figure 2A**; **Table 2**).

For Belgium, the correlation coefficient between observed and estimated daily active infections was $r = 0.84$. The first observed peak appeared on March 28, with 1,850 infections, in agreement with the estimated peak on March 27, with 2,259 estimated infections in status $I$ for both days (**Figure 2B**). Belgium had a second peak observed on April 15, with 2,454 infections. This peak appears to be a reporting artifact (only ∼500 infections were reported on the previous day).

The comparison of observed and estimated populations $I$ for Lombardy-Italy ($r = 0.88$) and Switzerland ($r = 0.93$) showed good agreements between the observed and estimated numbers of active infections (**Figures 2C,D**). The detailed information is shown in **Table 2**. The number of newly reported infections can substantially differ from the actual number of new cases due to reporting and testing delays (26). After considering these delays, our model shows consistency between the estimated infection curves (theoretical expectations) and the observed reported cases. Our modeling results show similar patterns of infection curves in the four regions. The main difference between the overall estimated infection curves is the flatness of the infection curves. The infection rates in Belgium and Switzerland showed slower decline of the infection curve than those in Baden-Württemberg and Lombardy during the middle of the epidemic period. The comparison of estimated infection curves to the actual data indicated that the SEIR(MH) of the COVID-19 epidemic is consistent with the actual epidemiological situation observed in these four regions during the epidemic.

The infection curve for Lombardy shows a poor match between observed and estimated (by model) infections during the earliest stage of the infection spread. The analysis of Lombardy data suggested that the reporting of the actual number of infections was delayed by up to 7 days. The evidence for delayed reporting includes (1) the first reporting on February 23 was a cluster of cases rather than the individual index case (https://www.ecdc.europa.eu/en). (2) On February 14 a 38-year-old Italian in Lombardy felt unwell and visited a doctor. The patient was prescribed treatments for influenza but was later confirmed as a COVID-19 case (as reported in Italian and Swiss newspapers). Thus, the adjusted curve for Lombardy was moved to 7 days earlier to accommodate the initial delay (shown in **Figure 2C**).

## Dynamic Modeling of the Epidemic in Four European Regions

Using fitted parameters, the epidemic dynamic in four studied European regions was estimated using the SEIR(MH) modeling. For each region, the epidemic was divided into two periods. The time from the first patient to the date which the mobility reduced to the minimum level is considered as the period before lockdown. The other period covers time after the lockdown.

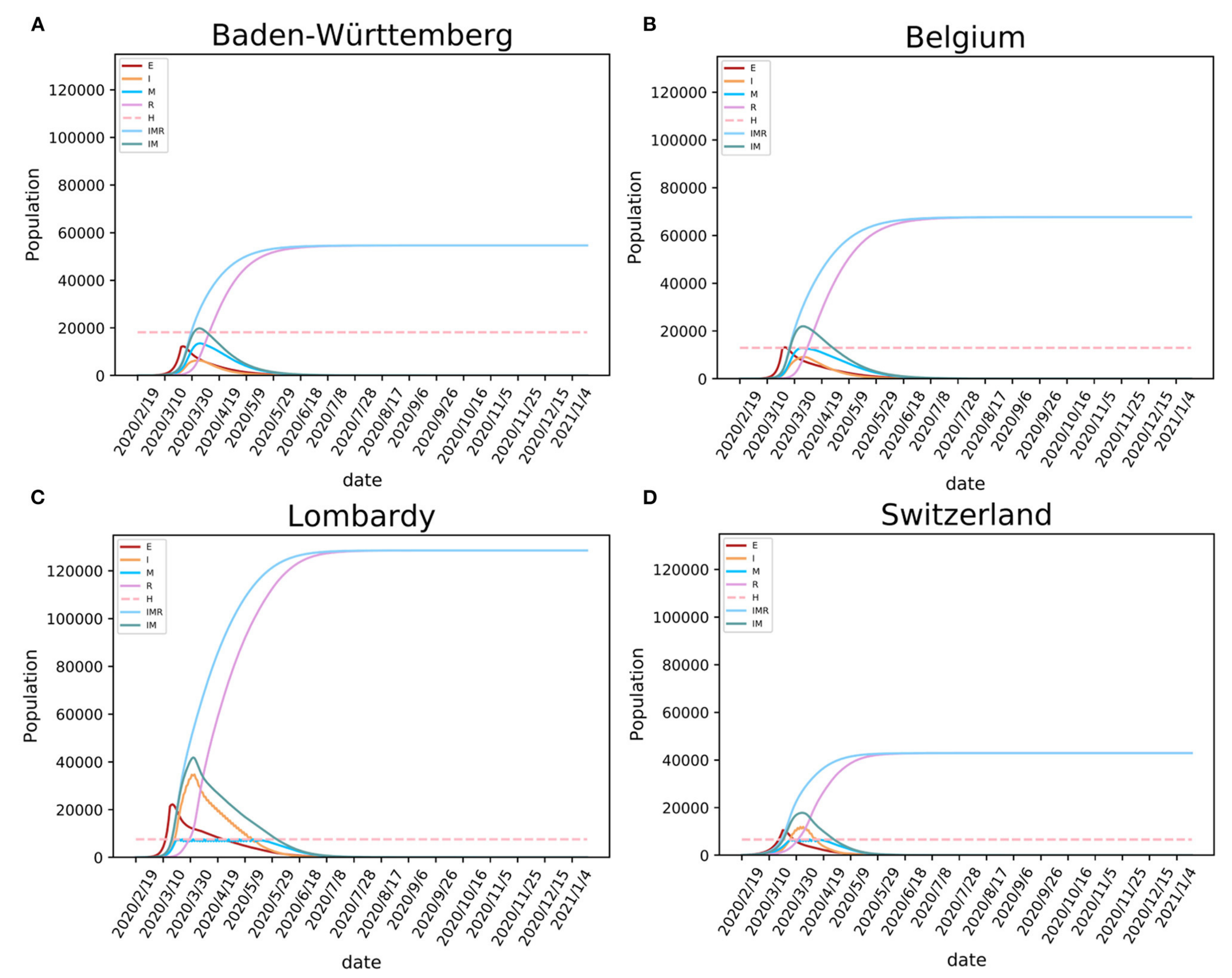


**FIGURE 3 |** Modeling the SARS-CoV-2 epidemic in four European regions. The epidemic models of SARS-CoV-2 are shown for **(A)** Baden-Württemberg (Germany), **(B)** Belgium, **(C)** Lombardy (Italy), and **(D)** Switzerland. E, I, and R stand for exposed, infected, and recovered population, M for population having medical care in hospitals (occupancy of beds), IMR stands for I+M+R, and IM stands for I+M (active cases).

**TABLE 3 |** The lockdown levels and available beds of four regions.

| Region | Highest mobility[a] | Lowest mobility[b] | Lockdown level[c] | Beds available[d] |
|---|---|---|---|---|
| Baden-württemberg | 14.10 | −55.54 | 69.65 | 18,114 |
| Belgium | 3.44 | −77.61 | 81.05 | 12,955 |
| Lombardy | 4.45 | −83.44 | 87.89 | 7,535 |
| Switzerland | 0.77 | −45.11 | 45.88 | 6,596 |

*The [a]highest and [b]lowest mobility values in each region during the observed period, from the COVID-19 projections of IHME[20]. [c]The lockdown level was evaluated by the difference between the highest mobility and the lowest mobility estimated from the mobile phone mobility data. [d]The number of available beds was obtained from COVID-19 projections of IHME[20]; the number of beds in Baden-Württemberg was calculated from the total number of beds available in Germany multiplied by the number representing the proportion of Baden-Württemberg within the total population of Germany.*

The populations with the daily status of *S*, *E*, *I*, *R*, and *M* at each specific date were estimated by the model. The values of *H* are public health statistics data that were obtained from the COVID-19 projections at IHME (21). For Baden-Württemberg, the first period was from February 12 to March 22, 2020. During that period weaker public health interventions were applied, and the number of infections increased rapidly (**Figure 3A**). After the lockdown, the mobility of people decreased sharply. We estimated that the population sizes representing states *E*, *I*, and *M* on March 22, 2020, were 11,977, 1,709, and 2,530, respectively. The model showed 4,239 infected individuals with symptoms (people in states *I* and *M*), similar to the reported number of 3,768 on the same date. However, our model estimated 11,977 individuals that were exposed but without symptoms who could also be infectious. After the lockdown, the daily infections quickly reached the peak and then started dropping rapidly (**Figure 3A**). The shapes of the curves indicate the benefit from the decrease of mobility following the lockdown. The epidemic estimations for Belgium, Lombardy, and Switzerland (**Figures 3B–D**) show similar shapes of infection curves to Baden-Württemberg: rapid increase before the lockdown followed by sharp decrease after the peak.

Our model showed that the need for hospital beds (curve *M*) is always lower than the available beds for COVID-19 (curve *H*) in Baden-Württemberg and Belgium (**Figure 3**). These numbers indicate that there was sufficient hospital capacity for COVID-19 patients. In Lombardy and Switzerland, bed numbers were lower than needed during the early period of the epidemic. In Switzerland, this period lasted for 18 days, from March 26 to April 12. During this period, over 14,518 infections were observed, 806 infections per day on average. This created a significant requirement for new beds designated for COVID-19, given the initially available number of 6,596 (21). In Lombardy, this period lasted for 58 days, from March 20 to May 16. In addition to beds designated for COVID-19, the four regions had additional medical resources that could provide a total number of 3.2–8 beds per thousand population (https://data.worldbank.org/indicator/SH.MED.BEDS.ZS) The COVID-19 pressure on limited medical resources precipitated government intervention of strict lockdown, such as one enforced in Lombardy.

Modeling results suggest that, if the regions kept strict lockdown policies, the first wave of the epidemic in Baden-Württemberg would end by August 31 with 54,646 total infections. Under conditions of prolonged lockdown, our model suggests that the end of the first wave would happen by September 24, 2020, in Belgium with 67,691 total infections, by September 17 in Lombardy with 128,584 total infections, and by July 24 in Switzerland with 42,892 total infections (**Table 2**). These results must be considered with caution because ideal situations are difficult to implement in a real-world situation. Due to socioeconomic issues and other cost of lockdowns, it may be difficult to maintain the lockdown for a long time. The release of lockdown and the influx of imported cases may lead to subsequent waves of the epidemic. The end of the epidemic would come earliest as the result of the lockdown, while the total number of infections would also be relatively low given that sufficiently large numbers of hospital beds were available, but the population will not develop useful levels of herd immunity. In reality, the epidemic in these regions did enter the second wave that has shown different dynamics (larger number of infections and lower mortality rate) than the first wave. Considering that studied regions implemented different policies of lockdown and had different initial resource availability, this case study provides means to study the consequences of the date of lockdown, the level of lockdown, and the number of available hospital beds for control of COVID-19 spread (**Table 3**).

## Effects of Public Health Intervention Measures

### Impact of Mobility (Lockdown) on the Epidemic

The policy of city lockdown involved two elements: the time of introduction of the lockdown, and the level of mobility restriction. In this study, we explored scenarios of making the lockdown date earlier or delaying it, as well as varying the level of mobility restriction after the lockdown. Our estimates do not use the dates that governments announced lockdowns, but from the actual mobility data traced through mobile phone networks.

We performed a simulation for the actual lockdown ("day L") and then explored possible effects of early or delayed lockdowns. We performed 14 simulations for days −7 to −1 and days +1 to +7 relative to day L (**Figures 4A–D**). Modeling results suggest that early lockdown would shorten the epidemic, while the delay would prolong it. The results indicate that, maintaining the strictest level of lockdown, the 7 days earlier lockdown date of March 15 in Baden-Württemberg would have resulted in epidemic duration of 160 days (end around July 20) with 9,206 total infections, 42 days earlier than the estimated real end point

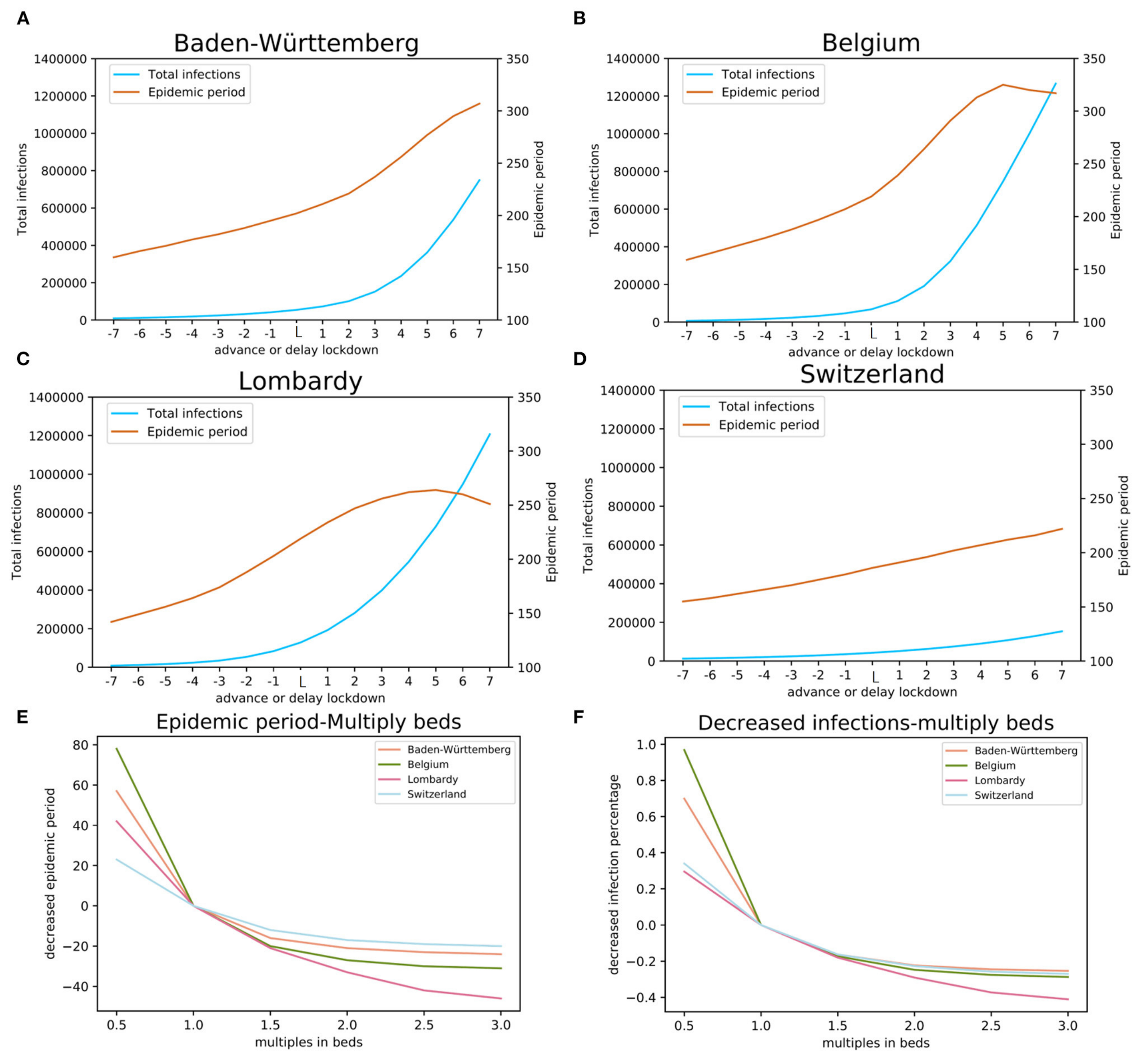


**FIGURE 4 |** The impact of lockdown date and COVID-19 available beds. The estimates of the total number of infections and the length of epidemic period with earlier (days−7 through−1) and delayed (+1, through +7 days) lockdown relative to the actual lockdown day (day L): **(A)** Baden-Württemberg, Germany, **(B)** Belgium, **(C)** Lombardy, Italy, and **(D)** Switzerland. Estimates of the effects of multiples of available beds on the total number of infections are shown in panel **(E)** and estimates of the length of the epidemic period are shown in panel **(F)**.

of the first wave (**Figure 4A**). Even a one-day advance would have reduced the number of total infections by 24% (41,514 total infections) compared with the day L estimation (54,646). The simulation results suggest that one-day delay in lockdown would have resulted in 34% more infections (73,028 total infections), while the 7 days delay scenario would have a total of 749,315 infections (**Figure 4A**). The simulation for the four studied regions illustrated that moving the lockdown to an earlier date would significantly reduce the total number of infections and markedly shorten the time to the end point of the first wave (**Figure 4**). On the other hand, the delay of lockdown date would have exponentially increased the total number of infections.

The level of mobility restriction also impacts the dynamics of epidemic. The infection coefficients α and β (**Table 1**) are model parameters affected by the mobility: high mobility is represented by high infection coefficients, while low mobility is represented by low infection coefficients. The mobility change factor F (the "lockdown level," **Table 1**) reflects the effect of mobility change to infection coefficients after the lockdown, as compared with their values before the lockdown. For the four studied regions, factor

F was calculated by model fitting and has respective values of 2.55, 3.00, 3.47, and 3.85 for Switzerland, Baden-Württemberg, Belgium, and Lombardy. The spread of these values agrees well with the actual difference of mobility in the four regions (**Table 3**).

## Impact of Medical Resources (Available Beds for COVID-19) on the Epidemic

We modeled the effect of local hospital capacity available for COVID-19 patients; the number of hospital beds was chosen as a proxy for such capacity (**Figures 4E,F**). We simulated the effects of reduced or increased number of beds for COVID-19. In our simulation, this factor had values from 0.5 to 3 with a step of 0.5. Hospital beds capacity is classified into three categories (levels): (1) sufficient, with the maximum occupancy lower than 80%, (2) heavily loaded, the maximum occupancy is higher than 80% but below the capacity, and (3) insufficient, where the occupancy demand is higher than the available beds (>100%).

The simulation results indicate that reduced available bed capacity increases the total number of infections and the

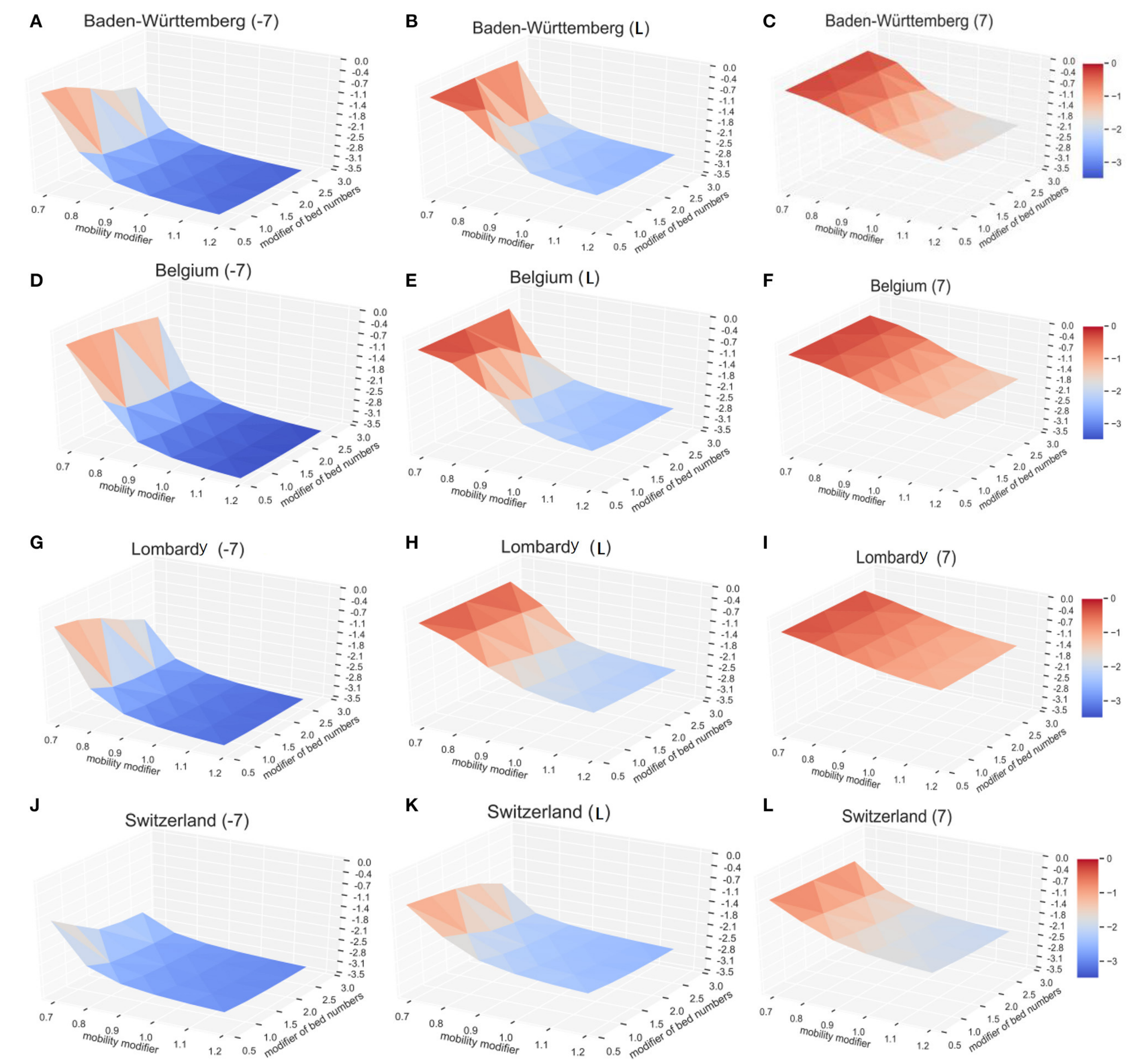


**FIGURE 5 |** The impact of lockdown time, lockdown level, and the available beds on the number of COVID-19. The vertical axis shows relative infection rates: the normalized infection percentage after 200 days in Baden-Württemberg for **(A)** 7 days early lockdown, **(B)** actual lockdown, and **(C)** late lockdown. The corresponding results are shown for Belgium **(D–F)**, Lombardy **(G–I)**, and Switzerland **(J–L)**. For better illustration, the infection level (vertical axis) here is defined as the $\log_{10}$CDR.

increased number of beds decreases the total number of infections (**Figure 4E**). For Baden-Württemberg, the number of beds available for COVID-19 was sufficient, even during the most severe period. The total infections were estimated as 45,747, 42,423, 41,248, and 40,781 (bed multiple factors of 1.5, 2.0, 2.5, and 3.0, respectively). Compared with the actual situation of 54,646 total infections, increasing the number of beds would reduce the total infections by 16.3, 22.4, 24.5, and 25.4%. On the other hand, the modeling results indicate that halving the number of beds (multiplication factor of 0.5) would result in 70.0% more infections (92,841 in total). In Lombardy, where the number of available beds for COVID-19 was insufficient, increasing the bed capacity would significantly reduce the total number of infections from the actual 128,584 to 105,396, 91,199, 80,627, and 75,751 (bed multiple factors of 1.5, 2.0, 2.5, and 3.0, respectively). Our model estimated that reduction in total infections would be 18.0, 29.1, 37.3, and 41.1%, respectively. The modeling results indicate that changing the number of COVID-19 dedicated beds would change the total number of infections. An important finding from our model is, when the number of beds has already been sufficient, increasing the number of beds would result in rapidly diminishing gain and is, likely, economically not viable.

To model the effects of COVID-19 available beds we set the comparison baseline as half of the beds that were available in the health system. For each region, this number would be insufficient. The effects of the total number of COVID-19 available beds on the total number of infections and the length of epidemic period were estimated using our model with the actual number of beds, and up to three times the actual number of beds (**Figures 4E,F**). The results of modeling indicate that the number of COVID-19 available beds was optimized in Switzerland, Belgium, and Baden-Württemberg for managing the number of infections while for this purpose the number of beds initially available was insufficient in Lombardy (**Figure 4E**). On the other hand, modeling shows that the initial number of COVID-19 available beds was also optimized for the shortest duration of epidemic in Baden-Württemberg, Switzerland, and Belgium, while it was less effective in Lombardy (**Figure 4F**).

## Combined Impact of the Lockdown and the Available Beds

To explore possible effects, we modeled three potential time points of lockdown, 7 days early (−7), the actual situation (day L), and the lockdown with 7 days delay (+7). By varying the multiplication factor of lockdown level (mobility modifier in **Figure 5**) from 0.7 to 1.2 (0.7 times to 1.2 times of current situation in different regions) and the COVID-19 available beds (modifier of bed numbers in **Figure 5**) from 0.5 to 2.5 times of current situation in different regions, we calculated the expected COVID-19 infection rates (CIR) on day 200 after the first patient (Patient 0) was identified (vertical axis—$\log_{10}$CIR in **Figure 5**). Modeling results indicate that the lockdown date is the primary influencing factor. For each region, the total infection rates are much lower for 7 days earlier lockdown scenario (**Figure 5A**) than the current situation (**Figure 5B**). With 7 days delay of lockdown (**Figure 5C**), irrespective of the bed numbers and the lockdown level, modeled infection rates are higher than the current scenario (**Figure 5**). Also, lockdown level significantly affects the resulting infection rate. For example, in Baden-Württemberg, the highest lockdown level (multiplication factor of 1.2) with the existing bed number (multiplication factor of 1) would reduce the infection rate at 200 days (since the start of epidemic) from 0.49 to 0.32% (**Figure 5B**). This would result in a 35.0% drop in the number of infections, as compared to the actual situation. The simulation results suggested that the number of infections at 200 days would drop, relative to the actual situation, by 16.3, 22.3, and 24.5% if the number beds increased by 1.5, 2.0, and 2.5 times, respectively (**Figure 5B**). If the lockdown level was increased to 1.2 times relative to the actual situation, even with 50% of available beds, the total infection rate at day 200 will be only 83.7% of the actual. The increase of the number of COVID-19 beds by multiplication factor of 2.5 would practically result in the control the infection at 200 days (the infection rate would drop from 0.49 to 0.27%). The lockdown date in actual situation with the lockdown factor 0.7 and beds factor of 0.5 would result in infection rate of 55.4% (**Figure 5B**) and increase to 56.7% (**Figure 5C**) with the lockdown of 7 days delay. The actual lockdown level and COVID-available beds results in infection rate at day 200 of 0.49% (**Figure 5B**) and 6.69% (**Figure 5C**) with the actual lockdown date and 7 days of delay, respectively.

Similar results were observed with the infection models in Belgium, Lombardy, and Switzerland. The solution surface for seven days earlier lockdown models in Belgium (**Figure 5D**), Lombardy (**Figure 5G**), and Switzerland (**Figure 5J**) show reductions of infections relative to the numbers representing actual situation (**Figures 5E,H,K**). The earlier lockdown models have much more pronounced improvements relative to the late lockdown (**Figures 5F,I,L**). Our model, as expected, shows that the early lockdown date and increased lockdown level would significantly reduce the progress of epidemic. Modeling results also suggest that sufficient medical resources—the COVID-19 available beds—help reduce the number of total infections, but their impact is lower than the impact of the lockdown level. Increasing the COVID-19 available beds by 2.5-fold (multiply by 2.5) in Baden-Württemberg would reduce the total number of infections on day 200 by 24.5%, as compared to increasing the lockdown factor by 20% (multiply by 1.2) that will reduce the number of total infections on day 200 by 35.1%.

Our observations were supported by the outcomes of epidemic in several other regions. Strict and early lockdown resulted in a rapid control of COVID-19 infection in places such as Wuhan-China (27), Denmark (28), and Norway (29). The opposite case was in Sweden that had no lockdown, and both the relative numbers of infections and deaths were larger than in the neighboring countries that have similar resources but enforced the lockdown (Denmark and Norway) (28, 29). The combination of lockdown and the rapid increase of available beds in Wuhan, China, helped achieve the effective control of the epidemic in Wuhan within 76 days (from the lockdown on January 23 to the lockdown release on April 8). Delayed increase in the number of beds in Switzerland did not markedly improve the epidemic outcomes (**Figures 5J–L**). While these results are intuitive, the advantage of modeling is that it provides quantitative results

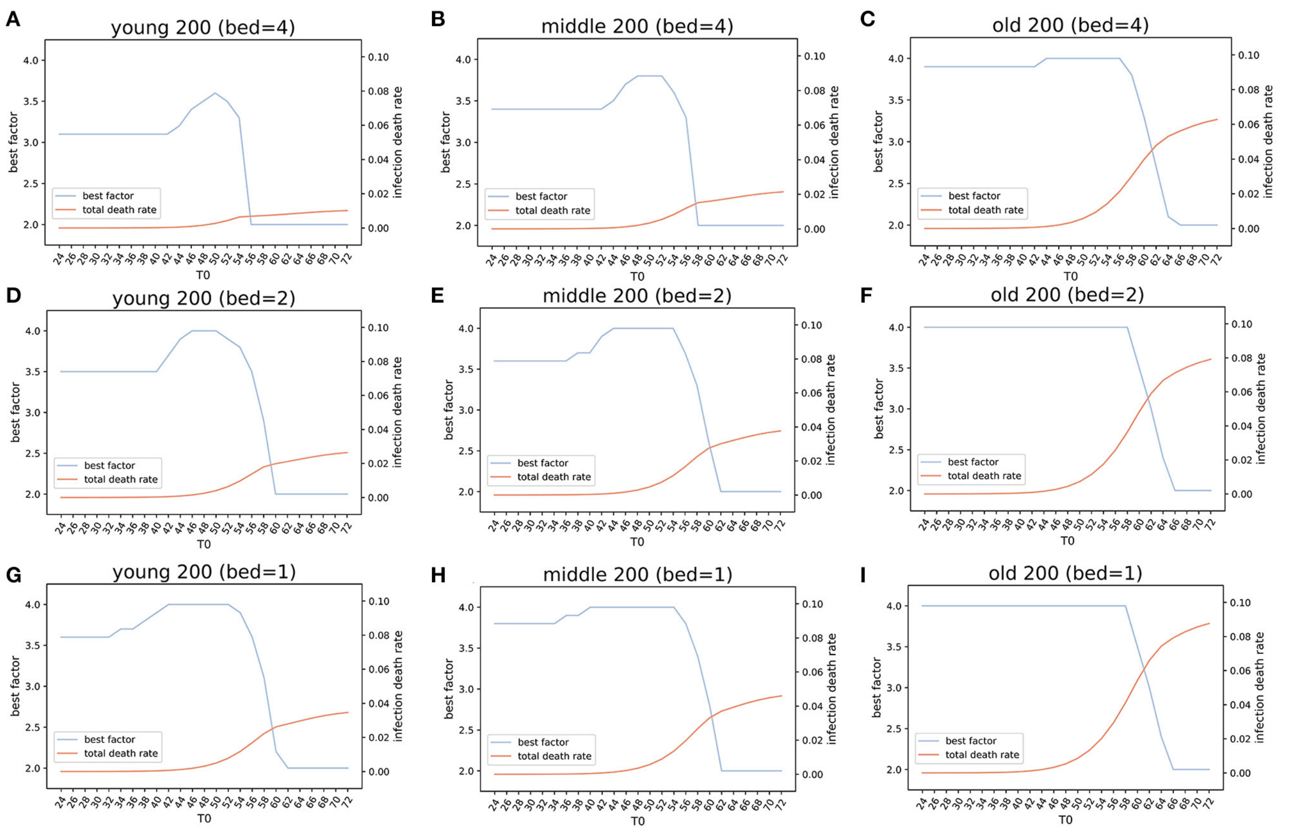


**FIGURE 6 |** Estimation of the optimized policies in three virtual cities. Optimized lockdown factor and the corresponding death rate with different lockdown dates and four COVID-19 available beds per thousand people in three virtual cities younger, middle, and older populations). Four beds: **(A)** *Ytown*, **(B)** *Mtown*, **(C)** *Otown*. Two beds: **(D)** *Ytown*, **(E)** *Mtown*, **(F)** *Otown*. One bed: **(G)** *Ytown*, **(H)** *Mtown*, **(I)** *Otown*. The "best factor" is optimized lockdown level (factor F) that minimizes total deaths for various scenarios of lockdown date and the number of beds. The infection death rate in our model is the death rate within population that got infected at any time (total infections). The simulations indicate that the optimal policies vary between different communities.

about expected outcomes that can be used for optimal timing of the public health measures.

## The Impact of Lockdown Level, Bed Numbers, and the Population Age Structure on the COVID-19 Death Rate

According to our modeling results, the early lockdown, strict lockdown level, and sufficient bed numbers are essential for effective control of the epidemic. However, by investigating the current COVID-19 death rate (CDR) in 36 European countries (**Supplementary Table 4**), we found that the countries with high CDR (including France, Italy, and Belgium) did implement strict lockdown policies that resulted in mobility score derived from IHME (21) decreases of 92.7, 83.7, and 81.0 (absolute numbers), respectively. The population aged above 65 years in these countries are 20.4, 23.0, and 19.0%, respectively. The average mobility score in 10 countries with the highest CDR was 71.7, while the average proportion of populations aged 65 years or more was 19.45%. The corresponding data for 10 countries with the lowest CDR showed the average decrease of mobility score of 64.1, and 17.2% of their populations were older than 65 years of age.

We defined a function of COVID-19 death rate, which included the parameters of lockdown level (F), available COVID-19 beds (H), population percentage of people younger than 15 (P15), population percentage of people aged from 15 to 65 (P15–65), and the population percentage of people older than 65 (P65). By utilizing a regression model, we calculated the coefficient of each parameter: $F = 0.003$, $H = -0.008$, P15 = −0.062, P15–65 = −0.137, and p65 = 0.264. The results suggest that the population with larger proportion of P15–65 population will have fewer COVID-19 deaths, while larger P65 population will have more deaths.

# Assessment by Simulation of the Optimized Public Health Strategies

We simulated three virtual cities, named *Ytown*, *Mtown*, and *Otown*, with different age structures of their population. The three virtual cities were modeled to match the younger age structure of Niger (*Ytown*), average which based on the overall age structure of China (*Mtown*), and older based on the age structure of Italy (*Otown*), respectively (**Supplementary Figure 1**). The total population of each virtual city was set to 10 million, and the initial infection coefficients $\alpha$ and $\beta$ were set as the average of the four simulated European regions.

The results of simulations suggest that early lockdown is the most effective policy in reducing the total number of COVID-19 infections (TNI) and total number of COVID-19 deaths (TND), regardless of the lockdown level and the number of available beds for control of COVID-19 (**Supplementary Figures 2–4**). The number of available beds for control of COVID-19 shows reverse-proportional effects: a larger number of beds linearly decreases the death rate (**Supplementary Figure 5**). The death rates are similar in the regions with younger and average age populations. The simulated death rates in these regions are approximately half of the death rates in regions with older population when other conditions are similar.

If all three virtual cities had exactly four beds per thousand people available for COVID-19 control, the lockdown policies enacted on the simulated day 24 ($T_{SD24}$) from the day of the first patient ($T_{SD0}$), modeling results suggest that epidemic control would be effective irrespective of the number of beds (within the range 1–4) or the level of lockdown (within the range 2–4). Early lockdown would reduce both TNI (**Supplementary Figure 6**) and TND (**Supplementary Figures 2–4**) by at least an order of magnitude (10-fold). The level of lockdown is an important consideration: in the simulation, the lockdown level 2 resulted in reduction of both TND and TNI by an order of magnitude, but both numbers kept increasing up to day 200 ($T_{SD200}$) (**Supplementary Figure 6A**). The lockdown of level 3 rapidly stabilized both the TNI and TND; early lockdown ($T_{SD24}$) resulted in TNI $\sim$1,000 (**Supplementary Figure 6B**) and TND <100 for all simulated age structures (**Supplementary Figures 2D–F**, **3D–F**, **4D–F**). For every 8 days of the lockdown delay, the TNI and TND increased approximately 10-fold (**Supplementary Figures 2–4**, **6**).

Simulations of three cities where the lockdown factor varied from 2.0 to 4.0, increment 0.1, showed that the total number of infections was 10–100 times higher under lockdown level 2 condition than under higher (3–4) lockdown level (**Supplementary Figures 2–4**). The CDR (death rate of infected population) was lower for lower levels of lockdown, and conversely was higher for higher level of lockdown (**Supplementary Figure 5**). Four beds per 1,000 population reduced death rate in all population structures approximately by half as compared to one bed per 1,000. The simulated CDR in middle-age population (*Mtown*) showed 20–100% increase (depending on variables) as compared to the younger (*Ytown*) population. The CDR in older population (*Otown*) was approximately two to six times larger than the CDR in the young population (**Supplementary Figure 5**). Collectively, these results indicate complex relationships between variables (lockdown date, lockdown level, and number of beds).

Simulation results showed that under an early lockdown ($T_0$ = 24) with the optimal lockdown level (*Ytown* = 3.1, *Mtown* = 3.4, and *Otown* = 3.9), the overall death rate in populations (PDR) for all three virtual cities were <0.001% ($PDR_{Ytown}$ = 0.00039%, $PDR_{Mtown}$ = 0.00053%, and $PDR_{Otown}$ = 0.00096%). The corresponding TND values after 200 days ($TND_{SD200}$) were 39 for *Ytown*, 53 for *Mtown*, and 96 for *Otown* (**Figures 6A–C**). Considering that on day 24, the number of observed infections was only 105, it is unlikely that, at this point, the local authorities would notice the epidemic if it was the first epidemic outbreak (like COVID-19 outbreaks in Wuhan, China, or Lombardy, Italy). However, if local authorities were on alert, due to knowledge of the ongoing epidemics in other regions, like in Australia, early responses appear to be viable options. Our simulations suggested that if the lockdown is delayed for 8, 16, and 24 days, the $TND_{SD200}$ number in *Ytown* will quickly increase from 39 ($T_{SD24}$) to 264 ($T_{SD32}$), 1773 ($T_{SD40}$), and 15,962 ($T_{SD48}$).

For *Ytown*, if COVID-19 available beds were four per 1,000, and the city lockdown happened between day $T_{SD24}$ and $T_{SD42}$, the total death rate would range from 0.00039 to 0.029%. The TND would be between 39 and 2,873 for the optimized lockdown of 3.1 (**Figure 6A**). If the local authority started lockdown $T_{SD44}$ and $T_{SD54}$, the TND would increase sharply, and the optimized lockdown factor would change from 3.2 to 3.6. These results reflect the need for dynamic management of public health policies in response to different situations. During the lockdown starting between $T_{SD44}$ and $T_{SD54}$, the TND would range from 4,950 to 63,629. However, if the local authority provided no lockdown policies before day 56, the later lockdown policies will have little effect. This scenario indicates that more than 50% of the population will be infected, and the overall deaths will be close to 1% of the total population (**Figure 6A**). The early lockdown response has proven to be effective in control of the second wave of COVID-19 in Victoria, Australia (lockdown from August 2 to September 6, which was gradually easing until October 26). Similar successes in the control of COVID-19 epidemics with early lockdowns were reported in Greece (30) and South Africa (31).

The results of simulations in *Mtown* were similar to the *Ytown* results. When T0 ranged from 24 to 42, the optimal lockdown factor was 3.4, with total death rate slowly increasing. The overall simulated death number was between 53 (day 24) and 3,908 (day 42). The second stage was for T0 between 44 and 56, with the optimal factor changed from 3.5 to 3.8 and the overall deaths from 6,586 to 119,513. After 58 days, the optimized policy is pursuing herd immunity, which will result in 1.5–2.0% deaths within the whole population (**Figure 6B**). Interestingly, the optimized lockdown factor is different for three virtual cities. For *Otown* (city with >23% of the aged population), the best policy is strict lockdown of the city with the lockdown factor of $F = 3.9$, close to the upper limit in our simulation (**Figure 6C**). However, for *Ytown* and *Mtown*, the best policy may not be the total lockdown of the city. Our estimation showed that the lockdown factors between $F = 3.1$ and $F = 3.4$ will result in the lowest total death rate. This indicates that different public health strategies are appropriate for cities with different age structures. To reduce the CDR for aged people, an early strict lockdown policy is needed. In fact, in *Otown*, the lockdown level of 4 will be the optimal policy when the lockdown is not announced early (**Figure 6C**). If herd immunity policy is pursued (no lockdown) in *Otown*, without any reduction in mobility, the overall death will increase to 627,867 and the death rate will exceed 6% even if the beds are sufficient (four per thousand).

The number of available beds is a modifier of best lockdown level in simulated scenarios. If the number of available beds for COVID-19 is halved (2 per thousand), the optimized factor of lockdown would be increased from $F = 3.1$ to $F = 3.5$ for *Ytown* (**Figure 6D**), from $F = 3.4$ to $F = 3.6$ for *Mtown* (**Figure 6E**), and from $F = 3.9$ to $F = 4.0$ for *Otown* (**Figure 6F**), respectively. When the number of beds is reduced to one quarter (one per thousand), the optimized lockdown factor would increase to $F = 3.6$ for *Ytown* (**Figure 6G**), $F = 3.8$ for *Mtown* (**Figure 6H**), and $F = 4.0$ for *Otown* (**Figure 6I**). Moreover, reducing the number of beds will result in more deaths for any lockdown date irrespective of the adjustment of the lockdown factor.

Overall, our results suggest that (1) reducing the social distance (lockdown) at the early stage is the most effective policy to reduce total infections, and (2) the optimized level of lockdown differs for cities with different age structures. For an aged society, strict lockdown appears to be more effective in reducing the CDR. For younger societies, relatively loose lockdown level (around $F = 3$ to $F = 3.4$) may minimize the total death rate. (3) The increase of the number of COVID-19 available beds strongly impacts both the infection rate and the total death rate when numbers are insufficient; when beds are sufficient, the improvements in infection rate and CDR are modest (diminishing returns). The proposed SEIR(MH) model can quantify the combined impact of multiple public health interventions in populations that have different characteristics and simulations have shown excellent concordance with the actual situations in studied regions. This model has a potential to assist in designing optimized public health interventions in regions that have different sociodemographic properties.

## DISCUSSION

The global pandemic of COVID-19 is a huge public health issue for human society. During the epidemic period, adequate nowcasting (estimating the current status) and forecasting (predicting future status) are crucial for public health planning and epidemic control (5, 28). We constructed a real-time status dynamic SEIR(MH) model to estimate the epidemic in local geographic areas. By adding the parameters of status M and H to a traditional SEIR model, we accurately modeled COVID-19 epidemics for four European regions. Our model allows quantification of the lockdown measures using mobility as proxy. Also, we could quantify the effects of available bed capacity. The quantification allows forecasting of the effects of public health measures and optimizing their impact under different constraints. The SEIR(MH) model could simulate the effects of public health policies in isolation or in combination, such as assessing the effects of (1) the date of lockdown measure, (2) the level of lockdown, (3) the number of dedicated beds, and (4) the effect of population age structure. The SEIR(MH) model can help rapidly assess the possible effects of complex combinations of public health measures for the epidemic control.

The timing of mobility restriction (lockdown) is the most important public health measure for the control of an epidemic that has characteristics of COVID-19. The lockdown at early stage will help quickly end the epidemic with significantly reduced total infections and death numbers. The analysis of data from 184 countries indicated that, on average, better control of COVID-19 epidemic correlated with earlier lockdowns (32). We defined four levels of lockdown: basic ($F = 1$), low ($F = 2$), moderate ($F = 3$), and strict ($F = 4$). Our simulation results suggest that the lockdown that starts only one week earlier than the lockdown dates observed for COVID-19 would end the epidemic 42 days earlier than the current situation and reduce the number of total infections in a region with over 10 million populations such as Baden-Württemberg, Germany, by more than 80%. On the other hand, 7 days delay would lead to 16-fold increase in total infections than the observed situation. Based on our estimates, Belgium responded most quickly in 31 days after the potential patient 0, followed by Italy (38 days considering the 7 days modification) and Germany (39 days). Switzerland did not announce the lockdown policy in early stages and delayed the lockdown after almost two months of the estimated patient 0. The decision of lockdown in a region with 10 million populations is not an easy decision, since the lockdown will significantly affect the daily activities of the citizens, affect economic development, and create other health problems due to reduced access to regular health care, among others. It is not feasible to lock down a city or a region when only a few cases are discovered. However, the epidemic like COVID-19 transmits rapidly at the early stage; therefore, it is easy to miss the best window of opportunity for epidemic prevention and control. Potential utility of such models is high because regional health authorities can easily get informed from the regions that experienced early outbreaks, such as Wuhan in China and Lombardy in Italy.

The lockdowns also increase the pressure on local medical resources. By using the COVID-19 available beds as proxy, our model illustrated the effect of increasing medical resources. In bed-sufficient regions such as Baden-Württemberg, Germany, the increase of the number of COVID-19 available beds will slightly decrease the total infections. Our estimation for Baden-Württemberg, Germany, suggested that doubling COVID-19 available beds would decrease 22.4% of infections, while tripling the number of COVID-19 available beds would result in 25.4% decrease of total infections. In bed-insufficient regions, such as Lombardy, Italy, doubling or tripling the current available beds would result in the decrease of total infections by 29.1 and 41.1%, respectively.

The lockdown level for epidemic control is important but, interestingly, our modeling indicates that strict lockdown is not always the best solution for controlling epidemics. Our model has suggested that strict lockdown ($F = 3.8$ to $F = 4.0$) is effective only in regions with older population. For populations that have middle or younger age structure, moderate lockdown measures ($F = 3.0$ to $F = 3.4$) may produce better epidemiological outcomes. Obviously, more strict restrictions will lead to larger social distance and reduce the number of total infections. However, the total lockdown may increase pressure on local medical infrastructure including rapidly growing demands for hospitalization and shortage of medical staff and medical supplies, which may lead to increased death rate from other causes. In the first wave of COVID-19, regions with higher death rate such as France, Italy, and Belgium imposed high-level lockdown with a very high mobility decrease (21). The age structure of population is important; populations with older age structure have shown a higher COVID-19 death rate (24, 33). According to our simulation of three virtual cities, stricter lockdown policies, around 3.8 to 4.0, are required to decrease the total COVID-19 death rate in societies with older age structure. On the other hand, looser lockdown policies, around 3.2–3.4, may be preferred for populations with lower or middle age structures. The analysis of data from 184 countries (32) suggested that partial lockdowns may be as effective in controlling the epidemic as strict lockdowns. The advantage of the SEIR(MH) model is that it offers not only qualitative assessment but it also produces quantitative projections that can be used for comparative analysis of the effects of combined public health interventions.

Most of the European regions released the lockdown and now are experiencing the second wave of the epidemic (21). The second COVID-19 wave has different characteristics, with larger number of infections, lower death rates, different demographics of epidemics, and the availability of vaccines. We considered only the first wave of COVID-19 for our modeling.

Our modeling indicates that the relationships between public health measures and the epidemic outcomes (including the length of epidemic period and total number of infections) are complex and depend on the population behavior that can be captured in mobility and other geo-social data (34). A note of caution is that these results should be used only for better understanding of the effects of specific public health measures (level, start time, and the duration of lockdown, as well as the management of the number of available beds) on the dynamics and the direct outcomes of COVID-19 epidemics. The lockdowns and rearranging the bed capacity for the control of an epidemic will have a broader range of socio-economic and medical consequences that need to be considered in parallel with analyses that focus purely on the epidemic.

While studied regions are adjacent and have similar population and relative level of economic development, their key underlying public health parameters are very different. This is best observed in the differences in infection parameters, mobility factor F (**Table 1**), and mobility levels before and after the lockdown (**Table 3**). The mobility factor F and the level of mobility decrease are related. For example, the mobility factor of 3.0 means the pre-lockdown infection coefficients $\alpha_{pre}$ and $\beta_{pre}$ are three times larger than the post-lockdown infection coefficients α and β. Higher mobility factor F means stricter lockdown level. On the other hand, the mobility level was calculated from the observed mobility data in IHME. The difference between the highest mobility before lockdown and the lowest mobility after lockdown were used to calculate the level of mobility decrease. The mobility factors were estimated by parameter fitting, while the lockdown levels were calculated from the observed data. In the four studied regions, the real lockdown levels were Lombardy (87.89) > Belgium (81.05) > Baden-Württemberg (69.65) > Switzerland (45.88). These data were consistent with the estimated values of F: Lombardy (3.85) > Belgium (3.47) > Baden-Württemberg (3.00) > Switzerland (2.55). Methods of reporting COVID-19 cases and approaches to protecting elderly are also different between the regions (35). Therefore, the absolute numbers of reported cases are not directly comparable, but the shapes of the infection curves indicate the actual dynamics of epidemics in studied regions. Our model has demonstrated robustness since it produced infection curves that closely resemble the actual reported numbers, where all modeled infection curves show good agreement with the actual data. The COVID-19 infection curves are non-linear and asymmetric, showing a rapid exponential growth that reaches the peak followed by a delayed reduction in new cases, with a long right tail spreading throughout the summer, never reaching zero.

### Limitations

The issues that affect the relevancy and accuracy, or limitations, of the model are data issues and model issues. The data issues include the complexity and hierarchical nature of real-world processes that generate data, fuzziness of data, biases and potential misconceptions in data, and the noise and errors in data (36). Mathematical models are simplifications of real-life systems and are based on assumptions that approximate real-life situations (21). Considering the extremely complex nature of epidemics/pandemics, any epidemic model will be a simplification of the real situation that may vary from one region to another. Mathematical modeling requires compromises; the results of modeling must be reasonably accurate, but modeling must also be computationally viable. To make our model realistic, data were smoothed, and the model parameters were fitted to data. Necessary corrections were made to the model, when discrepancies between the model output and the actual data were observed. We considered model adjustments and collected additional evidence to justify these changes. The simplifying assumptions of the regional SEIR(MH) model include considering the epidemic in geographic areas that are isolated and our model assumes that the infections rate in each geographic area is divided into two stages, before the lockdown and after the lockdown, with constant infection rate throughout the first stage of epidemic, and reduced infection rate, another constant, throughout the second stage of epidemic. While these limitations are a modeling concern, the conclusions derived from the results of simulations are consistent with the observed data across different countries (21, 22). Irrespective of the conditions specific for different countries, the SEIR(MH) model has demonstrated it is robust and it enables the analysis of outcomes of public health measures. This strategy needs to be combined with vaccination because early lockdown slows down the development of herd immunity.

## CONCLUSIONS

In general, as the simplification of real-life systems, the mathematical models could approximate real-life situations based on reasonable assumptions. In this study, we extended the conventional SEIR model by adding the parameters that define public lockdown and the the number of dedicated hospital beds to simulate the real-life situations such as lockdown policies or construction of temporary hospitals in measured regions. Further, by performing simulations on virtual cities with different age structure, our model could provide optimized policy combinations by setting the total infections and COVID-19 related death rate as goal. The robustness of the SEIR(MH) model illustrated the utility of this model to analysis the outcomes of different public health measures.

## 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

TQ and VB collected the data, designed the study, performed simulations, interpreted the results, and co-supervise the whole project. HX designed and implemented the model and performed parameter fitting. 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.2021.728525/full#supplementary-material

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# Covid Adult Mortality in Brazil: An Analysis of Multiple Causes of Death

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**Objective:** This study aimed to analyze the chain of events and contributing causes associated with COVID-19 adult mortality (30–69 years old), based on qualified data on CoD from three Brazilian capitals cities, Belo Horizonte, Salvador, and Natal, in 2020.

**Methods:** Data of all deaths among residents in the three capitals in 2020 were provided by these municipalities' routine Mortality Information System (SIM). Mentions B34.2 with the markers U07.1 and U07.2 in the death certificate identified COVID-19 deaths. We used a multiple-cause-of-death approach better to understand the complexity of the morbid process of COVID-19. Conditions that appeared more frequently in the same line or above the COVID-19 mentions in the death certificate were considered a chain-of-event. Conditions that occurred more often after the codes for COVID-19 were considered as contributing.

**Results:** In 2020, 7,029 records from COVID-19 as the underlying cause of death were registered in SIM in the three capitals. Among these, 2,921 (41.6%) were deceased between 30 and 69 years old, representing 17.0% of deaths in this age group. As chain-of-events, the most frequent conditions mentioned were sepsis (33.4%), SARS (32.0%), acute respiratory failure (31.9%), unspecified lower respiratory infections (unspecified pneumonia) (20.1%), and other specified respiratory disorders (14.1%). Hypertension (33.3%), diabetes unspecified type (21.7%), renal failure (12.7%), obesity (9.8%), other chronic kidney diseases (4.9%), and diabetes mellitus type 2 (4.7%) were the most frequent contributing conditions. On average, 3.04 conditions were mentioned in the death certificate besides COVID-19. This average varied according to age, place of death, and capital.

**Conclusion:** The multiple-cause analysis is a powerful tool to better understand the morbid process due to COVID-19 and highlight the importance of chronic non-communicable diseases as contributing conditions.

**Keywords: COVID-19, multiple cause of death, non-communicable diseases, Brazil, mortality**



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# INTRODUCTION

The importance of vital statistics to support the planning, evaluation, and monitoring of health programs and policies is widely recognized (1, 2). In the current scenario of the COVID-19 pandemic, the availability of vital statistics data is essential to follow the evolution and characteristics of cases and deaths (3). This information must be timely and with a satisfactory level of quality for its use. In Brazil, the Mortality Information System (SIM) from the Ministry of Health (MS) provides data on mortality for the whole country since 1976. SIM is a decentralized system in which each municipality (5,570 in total) is responsible for collecting and inputting data from the death certificate that the physician must sign (4). Although recent studies have shown that SIM has a high completeness level, there are still problems with the quality of information on causes of death (CoD) (5).

Several initiatives to improve the quality of information have been adopted, including physician training to improve the certification of the cause of death. The investigation of deaths with underlying cause classified as garbage code (CG) was carried out in 2017 in 60 municipalities in the five regions of the country, an initiative coordinated by the MS, in partnership with the Federal University of Minas Gerais (UFMG) and with support from Vital Strategies, through the Bloomberg Foundation. The investigation resulted in the reclassification for specific causes of 58% of deaths with GC (6).

In 2019, to promote the sustainability of the previous improvements achieved in selected municipalities in Brazil, a new initiative proposed to work more deeply with only three cities, Belo Horizonte with 2.5 million inhabitants, Salvador, 2.9, and Natal, 0.9 (7). The first municipality is in the Southeast region and the two others in the Northeast. Due to the emergence of the new Coronavirus (COVID-19), the initiative in these three cities changed its former aim and focused on an investigation to correctly identify deaths from COVID-19.

COVID-19 epidemic has led to an overload on the health system in Brazil, with a negative impact on all health programs (8). It has significantly compromised the achievement of Goal 3 of the Sustainable Development Objectives (SDG), more specifically, the target 3.4 of SDG that pointed, by 2030, a reduction of one-third premature mortality (adults under 70 years old) from non-communicable diseases (NCD) (9).

Non-communicable diseases are the leading causes of death (CoD) for adults and the elderly (10). They are also the main comorbidities that contribute to the severity of COVID-19 (11). As death is not a single event, the multiple-cause-of-death approach can contribute to understanding the complexity of the morbid process of COVID-19 since the traditional focus on underlying CoD statistics is insufficient in facing the challenges posed by this epidemic (12).

To better describe and understand the morbid process of COVID-19 mortality and its association with NCD, the present study aims to analyze the chain of events and contributing causes associated with COVID-19 adult mortality (30–69 years old), based on qualified data on CoD from the three capitals cities in 2020. Although these three capitals do not represent the entire country, they can provide essential information about the morbid process caused by COVID-19 and its contributing causes.

# MATERIALS AND METHODS

## Data

We used data of all deaths among residents in the three capitals (Belo Horizonte, Salvador, and Natal) that occurred in 2020, provided by these municipalities' routine Mortality Information System (SIM). The available database contains information on the characteristics of the deceased, the circumstance of death, causes of death (underlying cause and associated causes), and the investigation process. For this study we selected deaths from 30 to 69 years old that correspond to premature mortality, according to the WHO Global Action Plan for the prevention and control of non-communicable diseases (13, 14).

## Cause of Death Statistics

Even though to statistical purpose, for each death, only one CoD is tabulated, certifier physicians must fill the death certificate with all conditions considered to have caused or contributed to the death. The order that all causes are mentioned in the death certificate can show the sequence of events that caused the death. In that sequence, the underlying cause of death (UCoD) will be (a) the disease or injury that initiated the train of events leading directly to death, or (b) the circumstances of the accident or violence that produced the fatal injury.

This sequence results from a complex pathological process. Thus, the UCoD approach underestimates mortality from diseases not selected as the underlying cause but contributing to death, as with chronic conditions. Using the multiple-cause-of-death approach, all causes present in the morbid process and informed by the certifying physician can be analyzed.

## Medical Certification and ICD Mortality Coding of COVID-19

The first step in this work was to understand the medical certification and ICD mortality coding of COVID-19 in Brazil. For the codification of the COVID-19 death, Ministry of Health guidelines (15) established the use of ICD-10 code B34.2 with markers U07.1 (COVID-19, virus identified) and U07.2 (COVID-19, virus not identified). The markers would help the investigation of the cause of death process, specifying if the diagnosis of COVID-19 was confirmed or not. At the beginning of the pandemic, coders used the U04.9 code that refers to severe acute respiratory syndrome (SARS) to identify deaths from COVID-19 in the country. In July 2020, the MH issued a note informing that the codification of deaths with a mention of COVID-19 should be revised (16). The U04.9 code would only remain in the SIM if the SARS was part of the events chain that led to death.

Then, to identify the deaths due to COVID-19, we considered the mentions B34.2 with the markers U07.1 and U07.2 in the death certificate.

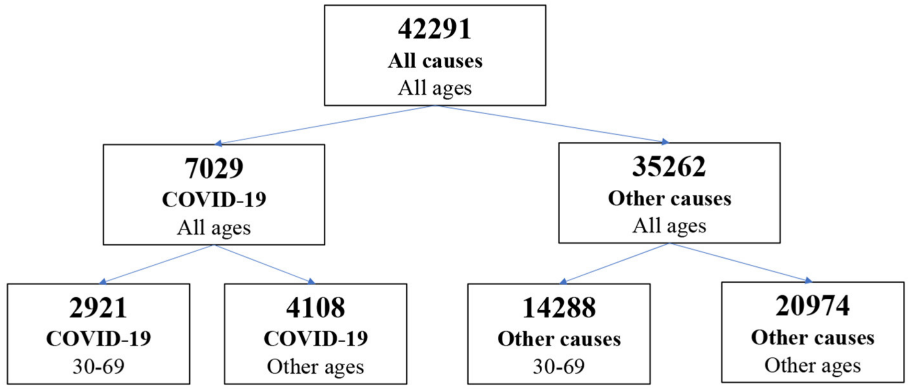


**FIGURE 1 |** Number of death certificates according to age and cause of death, in three Brazilian capitals, 2020.

## Multiple Cause of Death Analysis

To proceed with the analysis of causes associated with COVID-19 mortality, we used a multiple-cause-of-death approach, including all conditions, diseases, and injuries mentioned on the death certificate. Considering the significant number of possible conditions informed in the DC for this analysis, we decided to group the ICD-10 codes into groups with similar diagnoses. The initial classification was based on the Global Burden of Diseases study (GBD 2017) (17) and adapted to the Brazilian epidemiological profile. The **Supplementary Table A** presents the Group of conditions analyzed and respective ICD-10 codes.

We classified the conditions into two categories: chain-of-event or contributing. In Part I of the death certificate, we considered conditions that appeared more frequently (60% or more) in the same line or above the mentions B34.2, U0.7.1, U07.2, as a chain-of-event of COVID-19 mortality. Conditions that appeared more frequently (60% or more) after the codes for COVID-19 in Part I or, mainly, in Part II, were considered a contributing condition. Conditions that did not meet the requirements above or mentioned in <0.5% of the analyzed death certificates were not classified.

## Statistical Analysis

Other than the cause of death, we consider age, gender, and race/color as characteristics of the deceased and local of death.

All data were analyzed using R-Studio with libraries readxl, foreign, tidyverse, and writexl.

## Ethics

The analyzed data were in the public domain, preserving anonymity. Therefore, the project was approved by the Research Ethics Committee of the Federal University of Minas Gerais (COEP/UFMG) under number 4749326.

# RESULTS

In 2020, 7,029 records from COVID-19 as the underlying cause of death (UCoD) were registered by the routine SIM in the three Brazilian capitals cities (Belo Horizonte, Salvador, and Natal) (**Figure 1**). Of these, 62.5% were investigated to confirm the COVID-19 diagnosis and complete information about causes of death. The three capitals presented different investigation rates for COVID-19 mortality: 93.4% in Belo Horizonte ($n = 2{,}018$), 48.2% in Salvador ($n = 1{,}812$), and 51.9% in Natal ($n = 571$).

Among the deaths from COVID-19 as UCoD, 2,921 (41.6%) were from deceased between 30 and 69 years old, representing 17.0% of deaths in this group of ages. The virus SARS-COV2 was identified in 85.8% of deaths (U07.1), and for 14%, the COVID-19 diagnosis was clinical or epidemiological (U07.2).

**Table 1** shows the distribution of COVID-19 deaths according to some characteristics and the proportion in relation to the total number of deaths in each category. Firstly, the number of deaths is concentrated in older ages: 50.2% of deaths are in the 60–69 age group. Likewise, the proportion of COVID-19 deaths increases with age: from 11% (IC 95% 9.5–12.4%) in the 30–39 age group to 19.2% (IC 95% 18.3–20.1%) in the 60–69 age group.

Although the number of deaths from COVID-19 is higher among men (58.7%), the proportion of deaths from COVID-19 in the total number of deaths is very similar between men and women, between 30 and 69 years (17.1 among women and 16.9 among men).

Regarding race/color categories, 68.2% of death from COVID-19 are of blacks or browns in these three capitals. We can also observe that the proportion of COVID-19 deaths among whites (15.6–IC 95% 14.3–16.7%) is lower than among blacks (18.4–IC 95% 17.1–19.8%). Among the "others" category of race/color, the proportion of deaths by COVID-19 is much higher (25.5–IC 95% 24.7–31.3%).

Concerning the place of occurrence of the death, we found that 95.9% of deaths occurred in hospitals or health centers. Thus, the proportion of COVID-19 deaths in total hospital deaths is much higher than that among deaths occurring outside hospital units (21.5 vs. 2.9%).

Considering the distribution of deaths among the three capitals, we observed that Salvador concentrated 57.7% of COVID-19 deaths in 2020. The proportion of COVID-19 deaths in the total number of deaths in Salvador is much higher than in the other two capitals [21.3% (20.4–22.2%) in Salvador vs.

**TABLE 1 |** Number of death certificates due to COVID-19 and all causes of death according to characteristics of the deceased and local of death, at ages 30–69 years, in three Brazilian capitals, 2020.

| Characteristics | Number of death certificates | | | Ratio | | |
|---|---|---|---|---|---|---|
| | All causes | COVID-19 | | (COVID-19/All causes) | | |
| | | *n* | % | % | IC 95% | |
| Total | 17,209 | 2,921 | 100.0 | 17.0 | 16.4 | 17.5 |
| **Age** | | | | | | |
| 30–39 | 1,716 | 188 | 6.4 | 11.0 | 9.5 | 12.4 |
| 40–49 | 2,815 | 408 | 14.0 | 14.5 | 13.2 | 15.8 |
| 50–59 | 5,045 | 860 | 29.4 | 17.0 | 16.0 | 18.1 |
| 60–69 | 7,633 | 1,465 | 50.2 | 19.2 | 18.3 | 20.1 |
| **Gender** | | | | | | |
| Female | 7,035 | 1,205 | 41.3 | 17.1 | 16.2 | 18.0 |
| Male | 10,174 | 1,716 | 58.7 | 16.9 | 16.1 | 17.6 |
| **Race/color** | | | | | | |
| White | 4,675 | 731 | 25.0 | 15.6 | 14.6 | 16.7 |
| Black | 3,173 | 585 | 20.0 | 18.4 | 17.1 | 19.8 |
| Brown | 8,654 | 1,407 | 48.2 | 16.3 | 15.5 | 17.0 |
| Others | 707 | 198 | 6.8 | 28.0 | 24.7 | 31.3 |
| **Place of death** | | | | | | |
| Outside a hospital or health center | 4,173 | 121 | 4.1 | 2.9 | 2.4 | 3.4 |
| Inside a hospital or health center | 13,036 | 2,800 | 95.9 | 21.5 | 20.8 | 22.2 |
| **Capital** | | | | | | |
| Belo Horizonte | 6,810 | 790 | 27.0 | 11.6 | 10.8 | 12.4 |
| Salvador | 7,916 | 1,686 | 57.7 | 21.3 | 20.4 | 22.2 |
| Natal | 2,483 | 445 | 15.2 | 17.9 | 16.4 | 19.4 |

*Source: Ministry of Health, Mortality System Information.*

17.9% (16.4–19.4%) and 11.6% (10.8–12.4%) in Natal and Belo Horizonte, respectively].

**Table 2** shows the conditions mentioned in at least 0.5% of the death certificates where COVID-19 was the UCoD, and their classification as chain-of-events, contributing condition or not classified. **Supplementary Table B** presents all conditions mentioned classified as chain-of-events and contributing conditions. In 98.4% of DC with COVID-19 as UCoD ($n = 2,843$), there was at least one condition mention besides the COVID-19 diagnosis.

As chain-of-events, the most frequent conditions mentioned on the death certificate were sepsis (33.4%), SARS (32.0%), acute respiratory failure (31.9%), unspecified lower respiratory infections (unspecified pneumonia) (20.1%), and other specified respiratory disorders (14.1%). These five conditions corresponded to 42.4% of all conditions mentioned in DC analyzed.

Among the other conditions in the chain of events, we highlight the external cause–other factors condition mentioned in 1.1% of DC. A more detailed analysis showed that the most frequent code in this group (77%) corresponds to Y95, nosocomial condition.

As contributing conditions, hypertension (33.3%), diabetes unspecified type (21.7%), renal failure (12.7%), obesity (9.8%), other chronic kidney diseases (4.9%), and diabetes mellitus type 2 (4.7%) were the most frequent conditions mentioned in DC. These six conditions corresponded to 28.1% of all conditions mentioned in DC analyzed.

Among the other contributing conditions, we have mentions related to cardiovascular diseases, as left heart failure (3.7%), ischemic heart disease (3.5%), and unspecified stroke (1.5%), related to kidney diseases, as hemodialysis (2.9%) and chronic kidney disease due to glomerulonephritis (2.8%), related to respiratory diseases, as chronic obstructive pulmonary disease (2.8%) and asthma (1.4%), related to mental disorders, as alcohol use disorders (1.5%) and other mental disorders (2.3%). Related to neoplasms, the condition most frequent was tracheal, bronchus, and lung cancer (1.2%).

Still, we have external causes as the adverse effects of medical treatment in 1.5% of DC as contributing conditions.

Conditions not classified as chain-of-events or contributing were the group of injuries (0.8%), gastrointestinal bleeding (0.8%), flutter and fibrillation (0.7%), and hepatic failure (0.7%), among others less frequently mentioned.

**Table 3** shows the distribution of death certificates according to the type of conditions associated with COVID-19. In general, 64.1% of DC present the two kinds of conditions: chain-of-events and contributing. This proportion varies according to (1) the age, from 51.6% in the 30–39 age group to 66.1% in the 60–69; (2) the gender, 67.8% among women and 61.5% among men; (3) the

**TABLE 2 |** Most frequent conditions listed in death certificates by position in relation to COVID-19 diagnosis, at ages 30–69 years, in three Brazilian capitals, 2020.

| Conditions (group of IC-10 codes) | Number of mentions | | Position in relation to COVID-19 diagnosis | | % of COVID-19 deaths certificates ($n$ = 2,843) |
|---|---|---|---|---|---|
| | ***n*** | **%** | **Above** | **Below** | |
| **Chain-of-events** | | | | | |
| Sepsis | 950 | 10.8 | 96.1 | 3.9 | 33.4 |
| SARS | 909 | 10.3 | 99.4 | 0.6 | 32.0 |
| Acute respiratory failure | 907 | 10.3 | 96.1 | 3.9 | 31.9 |
| Unspecified lower respiratory infectious (Unspecified Pneumonia) | 571 | 6.5 | 94.2 | 5.8 | 20.1 |
| Other specified respiratory disorders (SARS*) | 400 | 4.5 | 96.5 | 3.5 | 14.1 |
| Cardiac arrest and shock | 257 | 2.9 | 97.7 | 2.3 | 9.0 |
| Other lower respiratory infections (Pneumonia) | 141 | 1.6 | 95.0 | 5.0 | 5.0 |
| Other respiratory diseases | 105 | 1.2 | 94.3 | 5.7 | 3.7 |
| Symptoms and signs not classified elsewhere | 98 | 1.0 | 96.7 | 3.3 | 3.4 |
| Asphyxia and hypoxemia | 89 | 1.0 | 94.4 | 5.6 | 3.1 |
| Pulmonary embolism | 61 | 0.7 | 77.0 | 23.0 | 2.1 |
| External causes–other factors | 30 | 0.3 | 86.7 | 13.3 | 1.1 |
| **Contributing conditions** | | | | | |
| Hypertension | 947 | 10.8 | 0.4 | 99.6 | 33.3 |
| Diabetes unspecified type | 617 | 7.0 | 0.5 | 99.5 | 21.7 |
| Renal failure | 360 | 4.1 | 30.3 | 69.7 | 12.7 |
| Obesity | 280 | 3.2 | 0.0 | 100.0 | 9.8 |
| Other chronic kidney diseases | 140 | 1.6 | 13.6 | 86.4 | 4.9 |
| Diabetes mellitus type 2 | 133 | 1.5 | 0.8 | 99.2 | 4.7 |
| Left heart failure | 104 | 1.2 | 26.0 | 74.0 | 3.7 |
| Ischemic heart disease | 100 | 1.1 | 38.0 | 62.0 | 3.5 |
| Hemodialysis | 83 | 0.9 | 21.7 | 78.3 | 2.9 |
| Chronic obstructive pulmonary disease | 79 | 0.9 | 5.1 | 94.9 | 2.8 |
| Chronic kidney disease due to glomerulonephritis | 79 | 0.9 | 7.6 | 92.4 | 2.8 |
| Other mental disorders | 65 | 0.7 | 1.5 | 98.5 | 2.3 |
| Unspecified stroke | 62 | 0.7 | 17.7 | 82.3 | 2.2 |
| Alcohol use disorders | 42 | 0.5 | 0.0 | 100.0 | 1.5 |
| Adverse effects of medical treatment | 42 | 0.5 | 38.1 | 61.9 | 1.5 |
| Asthma | 41 | 0.5 | 4.9 | 95.1 | 1.4 |
| Cirrhosis and other chronic liver diseases | 35 | 0.4 | 8.6 | 91.4 | 1.2 |
| Tracheal, bronchus, and lung cancer | 33 | 0.4 | 3.0 | 97.0 | 1.2 |

*Source: Ministry of Health, Mortality System Information.*

place of death, 64.4% for deaths occurred inside a hospital or health center, and 56.2% for deaths occurred elsewhere; (4) the capitals, 64.1 and 66.2% in Belo Horizonte and Salvador, against 56.2% in Natal.

We can note that deaths that occurred outside a hospital or health center are more likely to have no other condition mentioned in DC besides COVID-19 (7.4%) or contributing only (16.5%). We observe the same for deaths registered in the city of Natal. We also note that deaths in the 30–39 age group are more likely to present only chain-of-events conditions (36.7%) than other groups of ages. We observe the same for men (27.0%) in comparison to women (22.7%).

For all death certificates analyzed, we have 3.04 (IC 95%: 2.99–3.10) conditions mentioned on average in **Table 4**. Nevertheless, this average varied according to age, place of death, and capital. For the first characteristic, we observe that the mean number of conditions increases with age. From 2.48 mentions (IC 95%: 2.30–2.66) on average for the age group 30–39 to 3.16 mentions (IC 95%: 3.08–3.24) for 60–69. Deaths that occurred inside a hospital or health center present a higher number of conditions mentioned on average than deaths that occurred elsewhere (3.07 vs. 2.53). Belo Horizonte presents a higher number of conditions mentioned on average than the other two capitals. In Belo Horizonte, the mean number of conditions mentioned was 3.39

**TABLE 3 |** Distribution of conditions associated with COVID-19 by category according to characteristics of the deceased and local of death, at ages 30–69 years, in three Brazilian capitals, 2020.

| Characteristics | Number of death certificates | Category of condition associated with COVID-19 (%) | | | | |
|---|---|---|---|---|---|---|
| | | None | Chain of events only | Contributing only | Chain of events and contributing | Not classified |
| Total | 2,921 | 2.7 | 25.2 | 7.6 | 64.1 | 0.4 |
| **Age** | | | | | | |
| 30–39 | 188 | 2.7 | 36.7 | 8.0 | 51.6 | 1.1 |
| 40–49 | 408 | 2.0 | 28.2 | 7.1 | 62.3 | 0.5 |
| 50–59 | 860 | 2.7 | 24.9 | 8.0 | 64.2 | 0.2 |
| 60–69 | 1,465 | 2.9 | 23.1 | 7.4 | 66.1 | 0.4 |
| **Gender** | | | | | | |
| Female | 1,205 | 1.7 | 22.7 | 7.1 | 67.8 | 0.7 |
| Male | 1,716 | 3.3 | 27.0 | 7.9 | 61.5 | 0.2 |
| **Race/color** | | | | | | |
| White | 731 | 2.3 | 26.3 | 8.1 | 62.9 | 0.4 |
| Black | 585 | 3.1 | 25.3 | 8.9 | 62.2 | 0.5 |
| Brown | 1,407 | 2.6 | 24.6 | 7.2 | 65.2 | 0.4 |
| Others | 198 | 3.0 | 25.8 | 5.1 | 66.2 | 0.0 |
| **Place of death** | | | | | | |
| Outside a hospital or health center | 121 | 7.4 | 19.8 | 16.5 | 56.2 | 0.0 |
| Inside a hospital or health center | 2,800 | 2.5 | 25.5 | 7.2 | 64.4 | 0.4 |
| **Capital** | | | | | | |
| Belo Horizonte | 790 | 1.3 | 26.6 | 7.5 | 64.1 | 0.6 |
| Salvador | 1,686 | 2.8 | 25.0 | 5.7 | 66.2 | 0.4 |
| Natal | 445 | 4.7 | 23.8 | 15.1 | 56.2 | 0.2 |

*Source: Ministry of Health, Mortality System Information.*

(IC 95%: 3.28–3.50) against 2.94 (IC 95%: 2.87–3.01) and 2.81 (IC 95%: 2.68–2.94) for Salvador and Natal, respectively.

## DISCUSSION

This study provided important information on the chain of events and contributing causes of COVID-19 adult mortality (30–69 years old) from the three Brazilian capitals cities in 2020. Three aspects were highlighted from this analysis: first, the quality of medical certification of the COVID-19 mortality; second, the importance of the process of codification of all mentions declared in the death certificate and the role of the process of investigation of the cause of death in detailing the chain of events; third, the large concentration of mentions in just a few different causes or groups of causes highlights problems in-hospital care in patients with severe COVID-19 infection, on the one hand, and the relevance of non-communicable chronic diseases as contributing conditions to the worsening of COVID-19 infection.

Regarding the first aspect, we observed that 64% of 2,921 deaths certificated with COVID-19 have the documented chain-of-event and contributing conditions. Causes mentioned as chain-of-event or contributing are in accordance with other studies (18, 19), revealing the quality of death certificates filled out by physicians in these municipalities.

The number of causes mentioned on the death certificate also indicates the quality of filling in the medical certification, reporting possible multi-morbidity, and revealing the probable access to diagnostic procedures (20, 21). On average, there were 3.04 additional conditions in death certificates with COVID-19 as UCoD. However, data showed differences among the capitals. Belo Horizonte presented a significative higher mean number of mentions than the other two capitals. These differences may be associated with the different conditions of medical care given to COVID-19 patients, the different working conditions of physicians during the pandemic, and the different cultures of medical certification of the cause of death (21). In this sense and to clarify the reasons for these differences, it is essential to carry out more in-depth research that raises the factors mentioned above and describes the process of medical certification of the cause of death by COVID-19, compared to non- COVID-19 deaths. As a background for these differences, one must consider the social and economic inequalities that distinguish the three capitals, with Belo Horizonte located in an economically more favored region than Salvador and Natal (22).

Concerning the second aspect, we must remember that the quality of cause of death statistics also depends on the coding and investigation of the cause of death process carried out by the

**TABLE 4 |** Mean number of conditions mentioned in death certificate according to characteristics of the deceased and local of death, at ages 30–69 years, in three Brazilian capitals, 2020.

| Characteristics | Mean of conditions (besides COVID-19) | | |
|---|---|---|---|
| | Mean | IC 95% | |
| Total | 3.04 | 2.99 | 3.10 |
| **Age** | | | |
| 30–39 | 2.48 | 2.30 | 2.66 |
| 40–49 | 2.85 | 2.72 | 2.98 |
| 50–59 | 3.07 | 2.98 | 3.16 |
| 60–69 | 3.16 | 3.08 | 3.24 |
| **Gender** | | | |
| Female | 3.11 | 3.03 | 3.19 |
| Male | 3.00 | 2.93 | 3.07 |
| **Race/color** | | | |
| White | 3.09 | 2.98 | 3.20 |
| Black | 2.98 | 2.86 | 3.10 |
| Brown | 3.06 | 2.98 | 3.14 |
| Others | 2.94 | 2.75 | 3.13 |
| **Place of death** | | | |
| Outside a hospital or health center | 2.53 | 2.27 | 2.79 |
| Inside a hospital or health center | 3.07 | 3.02 | 3.12 |
| **Capital** | | | |
| Belo Horizonte | 3.39 | 3.28 | 3.50 |
| Salvador | 2.94 | 2.87 | 3.01 |
| Natal | 2.81 | 2.68 | 2.94 |

*Source: Ministry of Health, Mortality System Information.*

municipality's health departments and how the guidelines from the Ministry of Health were proposed and implemented locally. In Brazil, the automatic Underlying Cause Selection System (SCB–"Seletor de Causa Básica," in Portuguese) used in the SIM, initially code U04.9 as a marker of the COVID-19 pandemic. Subsequently and following the WHO recommendation, all death records in which the code U04.9 appeared as a pandemic marker of COVID-19 should go through the SIM update process to include the new recommended COVID-19 codes (B34.2 with the markers U07.1 or U07.2) (15, 16).

A problem with the SARS (severe acute respiratory syndrome) diagnosis mentioned in the death certificate emerged with the updated coding guidelines. Following the guidelines, the SIM would retain U04.9 (ICD-10 code for SARS) only if SARS was mentioned in the death certificate. Nevertheless, preceding these guidelines, the Ministry of Health recommended code J98.8 (other specified respiratory disorders in ICD-10) when SARS was mentioned as a single cause or accompanied by an ill-defined condition in Part I, and with no additional condition in Part II of the death certificate.

How the local coders interpreted these recommendations and guidelines and carried out a review of the codes used to identify deaths from COVID-19 is a factor that impacts the number of mentions of causes reported to the System. Thus, in the analysis of the multiple causes of death approach, it is essential to consider that, in situations such as the SARS in COVID-19 deaths, the number of codes may be higher than the mentions of diagnoses informed by the physician. In some cases, excluding diagnostic duplicity is necessary when there is more than one diagnosis meaning the same cause or more than one code for the same diagnosis.

In this study, we chose to separately present the two codes used for SARS diagnosis (U04.9 and J98.8) and emphasize the influence of coding rules and recommendations in the count of the number of diagnoses mentioned in the death certificates. A more detailed analysis to verify the co-occurrence of the two codes in the death certificates should be carried out to, eventually, correct the number of different diagnoses of causes reported by the physician.

About the investigation process, it is important to consider that the three municipalities' health departments carried out an epidemiological investigation for most of the death certificates with COVID-19 as UCoD (62.5%). However, the quality of the investigation and the information collected during this procedure also will determine the quality of cause of death statistics. Advancing this analysis to other causes would bring crucial contributions to the elucidation of the differences of number of conditions mentioned in the death certificates among the three capitals and understand the role of the codification and investigation process in improving the quality of mortality statistics.

Concerning the third aspect, more than 70% of all causes mentioned in the medical certificate in the three capitals concentrated on five conditions classified as the chain of events and six as contributing causes. As conditions that describe the chain of events that led to death by COVID-19, different respiratory complications were often mentioned as SARS, unspecified pneumonia, and acute respiratory failure. Nevertheless, the high proportion of sepsis concerns and the mention of nosocomial conditions (Y95) may be associated with the quality of the health attention in-hospital during the pandemic. An analysis of this question goes beyond the objectives of this study. This finding suggests further new studies on sepsis, such as the trend (23) and association with other causes of death through more specific multiple cause of death analysis.

As contributing conditions, there is sufficient evidence that patients with non-communicable diseases (NCD) are at higher risk of worse consequences if they contract COVID-19 (12, 24, 25). Our study also observed that the most frequent contributing conditions are hypertension, diabetes, obesity, and complications related to kidney diseases. Our results were consistent with other studies about COVID-19 associated outcomes (18). Nevertheless, it is important to note that deaths from COVID-19 are closely related to the presence of chronic conditions for the old ages (26–28). In contrast, in adults under 50, this situation is less common (19).

Considering that the situation is worse in low- and middle-income countries due to the interaction between socioecological and biological factors (29, 30), the high prevalence of NCD, the accelerated demographic transition process and the great social inequality (31) contribute to a challenging scenario in the Brazilian context of the COVID-19 pandemic.

The information obtained through this study provides essential insight on how these three capitals and other Brazilian cities need support to respond quickly and effectively to COVID-19. Also, it will be vital to ensure primary health assistance for NCD after the pandemic (24, 25, 32, 33).

However, some significant limitations of the study must be addressed. The first refers to the classification of conditions associated with COVID-19 into a chain of events and contributing. Our classification observed only the position in which the cause appeared on the death certificate. Thus, our classification depends on the accuracy with which physicians report all conditions of the morbid process and how they fill out death certificates. A second limitation is the codification process of the causes associated with COVID-19, which changed throughout 2020.

Nevertheless, the multiple-cause-of-death approach provides a starting point for the identification of other conditions that might contribute to adult mortality, considering lesser-known conditions that are not yet understood to be associated with or contribute to death from COVID-19.

## DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://datasus.saude.gov.br/transferencia-de-arquivos/.

## ETHICS STATEMENT

The analyzed data were in the public domain, preserving anonymity. Therefore, the project was approved by the Research Ethics Committee of the Federal University of Minas Gerais (COEP/UFMG) under number 4749326.

## AUTHOR CONTRIBUTIONS

AN performed data analysis and interpretation. LI, DA, and EF proposed the grouping of causes. All authors made substantial contributions to the content, writing of this paper, conceived the study, made substantial intellectual contributions to several drafts, and approved the final 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/fpubh.2021.788932/full#supplementary-material

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# The COVID-19 Pandemic and Cancer Patients in Germany: Impact on Treatment, Follow-Up Care and Psychological Burden

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In response to the ongoing coronavirus disease 2019 (COVID-19) pandemic, governments imposed various measures to decrease the rate of disease spread, and health care policy makers prioritized resource allocation to accommodate COVID-19 patients. We conducted a cross-sectional online survey in Germany (July 2020–June 2021) to assess the frequency of changes to cancer care among cancer patients and to explore the psychological impact of the pandemic writ large. Cancer patients who contacted the Cancer Information Service (Krebsinformationsdienst, KID) of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) via email were invited to complete an online questionnaire, capturing demographics, cancer specifics (e.g., type, disease phase, primary place of treatment, etc.), and any changes to their medical, follow-up, psycho-oncological or nursing care. General level of psychological distress was measured using the Hospital Anxiety and Depression Scale (HADS) along with face-validated items regarding worries and social isolation specific to the pandemic. In total, 13% of 621 patients reported a change to their treatment or care plan. Of those patients with changes, the majority of changes were made to follow-up care after treatment (56%), to monitoring during treatment (29%) and to psychological counseling (20%). Of the overall sample, more than half of patients (55%) reported symptoms of anxiety and 39% reported symptoms of depression. Patients with a change in cancer care were more likely to report symptoms of depression than those with no change (AOR: 2.18; 95% CI: 1.26–3.76). Concern about the pandemic affecting the quality of health care was a predictor of both anxiety (AOR: 2.76; 95% CI: 1.75–4.35) and depression (AOR: 2.15; 95% CI: 1.43–3.23). Results showed that the majority of cancer patients in our study did not experience a change in their cancer care. However, the level of anxiety and psycho-social burden of cancer patients during the pandemic was high throughout the study period. Our findings underscore the need for health care services and policy makers to assess and to attend cancer patients' medical needs, with added emphasis on patients' psychological and social well-being. This applies particularly in situations where the healthcare system is strained and prioritization is necessary.

**Keywords: COVID-19, cancer care, changes in treatment, anxiety, depression, health care management**

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a global impact on health care. The pandemic reached Germany in January 2020 and within 100 days, the number of confirmed cases exceeded 150,000, with over 6,200 deaths (1). The rise in incidence occurred despite unprecedented measures that were taken by both national and regional governments in Germany to control the pandemic. By late March, 2020, business closures were mandated, school classes were relegated to being conducted online, and gatherings of people were greatly restricted. Some of these restrictions were eased by late April; however, a second wave (i.e., a substantial increase in COVID-19 infections) in the fall of 2020 and a third wave in the spring of 2021 kept varying restrictions in place on businesses, schools and social gatherings. By September 23, 2021, over four million cases and more than 93,000 deaths had been confirmed in the country (2).

Within the domain of health care, an attempt to mitigate the potential overload on the healthcare system, particularly in hospitals and intensive care units (ICUs), additional staff were recruited, elective procedures (operations and other medical interventions) were postponed and hospital and ICU capacity was kept available for patients severely sickened with COVID-19 (3). The prioritization of medical resources for COVID-19 patients means potential shortcomings in the care of other vulnerable patient groups, such as cancer patients. Discussion is ongoing over the ethics of resource allocation (4–7). Evidence has shown that delays in cancer treatment can have detrimental health effects. For instance, Hanna et al. found that even a 4 week delay in surgical, systemic or radiation treatment is associated with greater risk of death for seven cancer types (8). Yet, cancer patients may be at greater risk of a COVID-19 infection or related death (9, 10), thus there is a trade-off between patients receiving care and being protected from the risk of infection.

Beyond cancer care, social distancing, regardless of it being government- or self-imposed, potentially has negative mental health consequences (11, 12). Cancer patients are particularly vulnerable irrespective of the COVID-19 pandemic in terms of depression and anxiety (13–15) and also social isolation (16). The added strain of the pandemic, whether it be restricted access to care, fear of being infected with COVID-19, missing contact with other people, among other factors (e.g., financial distress) may compound these already existing issues.

During a pandemic, in the domain of public health and health services research, it is important to gather real-life data from vulnerable groups, such as cancer patients, who might be affected. The present study assessed the frequency of changes to treatment and follow-up care among cancer patients and explored the psychological impact of such changes as well as the psychological impact of the pandemic in general. In addition, we sought to identify possible vulnerable subpopulations to help healthcare professionals and policy makers assess needs and prioritize services to allocate equitable care.

## MATERIALS AND METHODS

### Design and Study Population

Data was gathered using an anonymized online questionnaire. To obtain estimates with high precision, a sample size of 600 evaluable cases was estimated to be appropriate based on the Clopper–Pearson interval method. Study participants were cancer patients recruited consecutively after they sent an email inquiry regarding their illness to the Cancer Information Service (Krebsinformationsdienst, KID) of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). In their email response to these inquiries, staff members of the KID included an invitation to the study with a link to the questionnaire. Inclusion criteria were a confirmed cancer diagnosis, permanent residence in Germany, and age 18 or older. Patients were excluded (i.e., were not asked to participate in the study) if they were undergoing initial diagnostic procedures for suspected cancer, if the study recruiter had doubts about a cancer diagnosis or the potential responder's German language proficiency. Participation in the study was voluntary and could be terminated at any time while taking the questionnaire. All email inquiries were deleted after they had been addressed; therefore, no personal information (names or email addresses) was retained. Furthermore, the link to the questionnaire provided in the invitation email was not personalized, rendering it impossible to know which email recipients participated in the study. Data was collected from July 10, 2020 to June 30, 2021. The principles of the Helsinki Declaration were followed. The ethics committee of the University of Heidelberg approved the study (S-350/2020). In addition, prior to the study being launched, the DKFZ data protection officer reviewed the participant information, consent, and online questionnaire to ensure participant anonymity.

### Online Questionnaire

The questionnaire was programed using the open-sourced web survey application, LimeSurvey, and consisted of five sections: (1) demographics; (2) cancer status (3) experiences with health care during the pandemic (i.e., changes in treatment); (4) psycho-social distress and quality of life; and (5) the financial effects of cancer during the pandemic.

Cancer status items included cancer diagnosis, specific information regarding the cancer (e.g., type, phase, metastasis) and the type of treatment (e.g., which treatment regimen was ongoing or next planned, place of primary treatment). Health care during the pandemic consisted of items about whether the respondent had been infected with COVID-19 or if a family member or friend was infected; whether there had been a change in the treatment or follow-up plan during the pandemic, and, if applicable, what type of change or changes had occurred, as well as specific information about these changes. Types of possible changes to care included: operation, systemic therapy, radiotherapy, progress monitoring during treatment, follow-up after treatment, psycho-social or psycho-oncological counseling, and nursing care. Multiple changes to planned treatment were possible. Questions on the cancer disease (e.g., tumor type, phase of treatment) were informed by evaluations of the routine KID inquiry documentation (17).

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) (18). The German version of the HADS has been validated (19, 20). This measure uses 14-items (seven questions each for the two subscales) with a 4-point Likert scale. Items are scored from 0 to 3 with higher scores indicating higher symptom burden. Scores of 11 or higher per subscale are considered exceeding criteria (i.e., caseness) and scores between eight and ten as being borderline. Authorization to use the HADS scale was obtained. Finally, questions regarding subjective worry as well as social isolation specific to the pandemic were designed *ad hoc* for this study. These questions were face-validated and cognitively pre-tested for comprehensibility prior to the study's launch. The subjective worry items use a 5-point Likert scale (strongly agree to strongly disagree) and items include "As a consequence of the pandemic, I am worried about the possible effects on the quality of my medical care," "...I am worried that I could be sickened or die from a COVID-19 infection," and "...I am worried that family or friends could be sickened or die from a COVID-19 infection." Finally, social isolation items include "Due to restrictions, to what extent do you miss personal contact with relatives, friends, work colleagues, and neighbors?", "...with other patients and support groups?", "...with physicians and nurses?", "...with caregivers, therapists and other helpers?", "...with personal contacts in the public (e.g., going to a pub, park, concert, theater, shopping?" with a 5-point Likert scale (miss it extremely to do not miss it at all).

## Data Analysis

Statistical analyses were conducted using the statistical program IBM SPSS Statistics (version 27). Descriptive statistics displaying sample sizes and percentages were performed to summarize the responses to demographic and clinical features. Chi-square or Fisher's exact test were used for categorical variables to test associations. Results of these analyses are provided in the **Supplementary Material**. Correction for confounders was made by multivariate logistic regression analysis. Chi-square significance evaluated at the 0.1 alpha level was included in the regression models to reduce the likelihood of missing potentially associated variables (21). A two-tailed $p$-value $<$ 0.05 was considered statistically significant for the regression analysis. Unadjusted (univariate) and adjusted (multivariate) results are presented.

To examine participants subjective worries during the pandemic, we dichotomized the following responses (agree and strongly agree vs. neutral to strongly disagree) for the questions, "I am worried that I could be sickened or die from the coronavirus infection," "I am worried that family or friends could be sickened or die from the coronavirus infection," and "I am worried that the effects of the pandemic could affect the quality of medical treatment." To consider how COVID-19 restrictions affected patients, we dichotomized the responses (miss it extremely and miss it quite a bit vs. neutral, do not miss it a lot, do not miss it at all) for the question, "How do you feel about the limitations of personal encounters due to the Coronavirus pandemic? Personal contacts with relatives, friends, work colleagues, neighbors..." For the HADS we used the cut-off that included borderline scores (subscale sum scores $\geq$8) to better capture vulnerable sub-populations, which is consistent with most other publications measuring depression and anxiety during the COVID-19 pandemic (22). Cronbach's alpha was used to demonstrate internal consistency of the HADS.

Analyses presented here focus on whether there was a change in cancer care, on identifying any subgroups vulnerable to changes in care, on the psychological impact of changes to care (patients with changes compared to those without) and on the psychological impact of the pandemic to all patients regardless if there was a change in care, and which

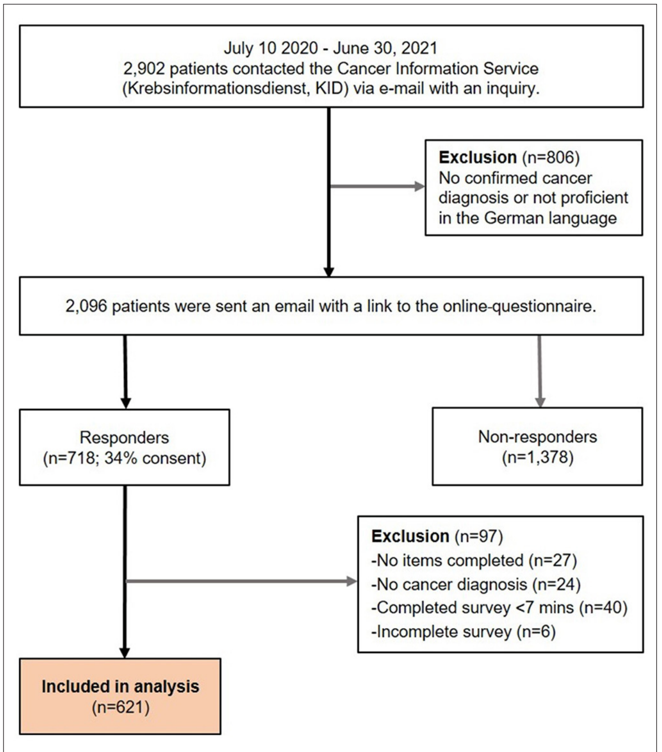


**FIGURE 1 |** Flow diagram of inclusion of study participants.

sub-groups may be associated with higher rates of psychosocial distress.

## RESULTS

### Patients' Sociodemographic Characteristics and Clinical Features

In total, 718 patients took the survey, rendering a consent rate of 34%. After data cleaning, 621 patients were included in the analyses. **Figure 1** displays a flowchart of participant inclusion.

The demographic characteristics and clinical features of respondents are provided in **Table 1**. The mean age was 60 years with a standard deviation of 11.8. As this is a convenience sample of cancer patients actively seeking information, the characteristics are neither representative of the German population nor of the cancer patients in Germany with regard to distribution of sex (76% female), age (63% were 41–65 years vs. 36% based on the population in 2019) (23), education (64% university entrance qualification vs. 35% of the population older than 20 years of age) (23) and cancer site (50% breast cancer vs. 20% based on 5-year-prevalence 2017) (24). Regarding health insurance, 17.6% had private health insurance vs. 11% based on the population (25).

One or multiple cancer treatments or examinations were ongoing or planned for participants. Treatments included surgery to remove primary tumor or metastases (100, 16%); systemic therapy before planned surgery (52, 8.4%), after planned surgery (207, 33.3%), and for advanced disease (112, 18.0%); and radiotherapy to tumor region or to metastases (102, 16.4%). Examinations included monitoring during therapy (138, 22.2%), follow-up in aftercare (247, 39.8%), or patients might be in a phase of "wait and see" (50, 8.1%). Uncertainty of next planned treatment was reported by 18 patients (2.9%). Regarding the setting for primary treatment, 30.3% of participants were treated in hospital outpatient clinics, 25.9% in an oncology practice, and 5% as hospital inpatient. The plurality of participants reported "other" as setting (38.7%). Upon examination of what this comprised—information was provided in free-text on the online questionnaire—other settings consisted of specialized clinics corresponding to cancer type (e.g., breast cancer patients being treated in gynecology clinics, prostate cancer patients in urology).

### Changes to Cancer Care

Overall, 79 respondents (12.9%) reported a change (i.e., a postponement, cancellation, or another type of treatment/mode of communication, such as videoconferencing) to a scheduled treatment, examination or care plan. The changes were as follows: 10 patients reported a change to a planned operation (1.6% of sample; 12.7% of those reporting a change); 14 reported a change to systemic therapy (2.3%; 17.7%); one person reported a change to radiotherapy (0.2%; 1.3%); 23 had a change to progress monitoring during treatment (3.7%; 29.1%) and 44 to a follow-up after treatment (7.1%; 55.7%); 16 patients reported a change to a psycho-social or psycho-oncological counseling appointment (2.6%: 20.3%); and three patients reported a change to care by nursing service (0.5%; 3.8%). Twenty-four patients (38.8%) of

**TABLE 1** | Patient demographic characteristics and clinical features.

| **Total sample (*N* = 621)** | | ***M*** | ***SD*** |
|---|---|---|---|
| | | 59.5 | 11.8 |
| | | ***n*** | **%** |
| Age (*n* = 595) | 18–40 | 39 | 6.6% |
| | 41–65 | 373 | 62.7% |
| | 66+ | 183 | 30.8% |
| Gender (*n* = 619) | Male | 147 | 23.7% |
| | Female | 472 | 76.3% |
| Education (*n* = 610) | Secondary general school-leaving certificate | 62 | 10.2% |
| | Intermediate school-leaving certificate | 159 | 26.1% |
| | University entrance qualification | 389 | 63.8% |
| Living situation (*n* = 603) | Lives alone | 111 | 18.4% |
| | Lives with another/others | 492 | 81.6% |
| | | ***M*** | ***SD*** |
| | | 0.26 | 0.63 |
| | | ***n*** | **%** |
| Minor-aged kids living at home (*n* = 621) | No | 514 | 82.8% |
| | Yes | 107 | 17.2% |
| Employment (*n* = 610) | Employed | 271 | 44.4% |
| | Self-employed | 41 | 6.7% |
| | Retired | 239 | 39.2% |
| | Unemployed | 59 | 9.7% |
| Health insurance (*n* = 615) | Private | 108 | 17.6% |
| | Statutory | 377 | 61.3% |
| | Statutory with private supplemental | 106 | 17.2% |
| | Co-insured free-of-charge | 24 | 3.9% |
| Type of cancer (*n* = 619) | Breast cancer | 310 | 50.1% |
| | Prostate cancer | 66 | 10.7% |
| | Colon cancer | 23 | 3.7% |
| | Lung cancer | 19 | 3.1% |
| | Other | 201 | 32.5% |
| Metastatic cancer (*n* = 615) | No | 414 | 67.3 |
| | Yes or suspected | 157 | 25.5 |
| | Do not know | 44 | 7.2 |
| Cancer phase (*n* = 612) | After diagnosis or during initial treatment | 197 | 32.2% |
| | Initial treatment completed | 245 | 40.0% |
| | Relapse/relapse treatment | 85 | 13.9% |
| | Advanced disease/palliative treatment | 68 | 11.1% |
| | Do not know | 17 | 2.8% |
| Setting for main treatment (*n* = 617) | Hospital inpatient | 31 | 5.0% |
| | Hospital outpatient | 187 | 30.3% |
| | Oncology practice | 160 | 25.9% |
| | Other | 239 | 38.7% |
| Observation period (*n* = 621) | Before second wave (Jul. 10–Nov. 1, 2020) | 185 | 29.8% |
| | Second wave (Nov. 2, 2020–Mar. 11, 2021) | 283 | 45.6% |
| | Third wave (Mar. 12, 2021–Jun. 30, 2021) | 153 | 24.6% |
| Sickened by COVID-19 (*n* = 603) | No or do not know | 596 | 98.8% |
| | Yes | 7 | 1.2% |
| Family, friend or acquaintance sickened by COVID-19 (*n* = 621) | No or do not know | 482 | 77.6% |
| | Yes | 139 | 22.4% |

those reporting a change in treatment reported more than one change. **Table 2** displays results of change in cancer treatment.

In regard to which socio-demographic and clinical features were associated with having a change in treatment, only the phase of treatment was statistically significant. Patients in the phase of treatment after diagnosis or during initial treatment were the group with the lowest percentage of changes in care (6.2%) and those reporting to be in the phase where initial treatment had been completed (e.g., follow-up care) had the highest (18.9%). Those in the relapse phase and those with advanced disease were in the middle (15.2 and 11.9% with changes, respectively). The odds of a patient having a change in care was 3.50 times greater in the phase after initial treatment was completed (95% CI 1.80–6.82, $p < 0.001$) and 2.68 times greater in the advanced disease phase (95% CI 1.10–6.53, $p = 0.030$), compared to those in the initial phase of treatment. The results are consistent with the finding above that most changes were to follow-up examinations. No other statistically significant associations were found among the sociodemographic and clinical factors (e.g., not age, form of health insurance, type of cancer, etc.) regarding a change in cancer care.

**TABLE 2 |** Change in care or to follow-up.

| Total sample (*N* = 621) | | *n* | % Entire sample | % Patients with change |
|---|---|---|---|---|
| Change to care during pandemic (*n* = 611) | No | 532 | 87.1% | |
| | Yes | 79 | 12.9% | |
| No. of changes (*n* = 78) | One | 54 | 8.7% | 69.2% |
| | Two or more | 24 | 3.9% | 30.8% |
| Type of tx change* | Operation | 10 | 1.6% | 12.7% |
| | Systemic therapy | 14 | 2.3% | 17.7% |
| | Radiotherapy | 1 | 0.2% | 1.3% |
| | Progress monitoring during treatment | 23 | 3.7% | 29.1% |
| | Follow-up after treatment | 44 | 7.1% | 55.7% |
| | Psycho-social or psycho-oncological counseling | 16 | 2.6% | 20.3% |
| | Nursing care | 3 | 0.5% | 3.8% |

*Multiple changes are possible.*

## Subjective Distress and Missing Contact With Others

In total, 30% of participants reported concern about being sickened or dying from a COVID-19 infection; a greater percentage (42%) reported worry that family or friends could be infected or die. One third (33%) were worried that as a consequence of the corona pandemic, the quality of their medical care would be impacted (see **Figure 2**). In terms of group comparisons, age, gender, type of cancer and observation period were predictor variables for concern of a COVID-19 infection. Gender, whether or not the patient had metastatic cancer, treatment phase, observation phase and whether a family member or friend had a confirmed COVID-19 diagnosis were covariates for worry concerning family and friends. However, after adjustment, gender was found to be a predictor for concern for others (AOR: 0.56; 95% CI: 0.36–0.86; $p = 0.008$), but not for concern for oneself. The odds of being concerned about a COVID-19 infection were less during the third observation period (i.e., during the third wave, but when vaccines were available; AOR: 0.54; 95% CI: 0.31–0.92; $p = 0.023$), and the odds of being concerned for others were higher during the second

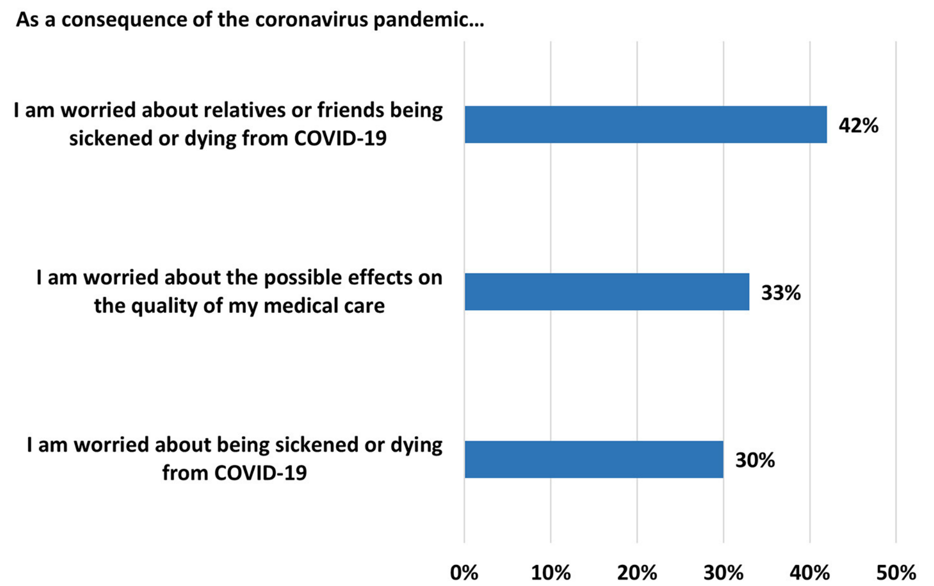


**FIGURE 2 |** Percent of agreement or strong agreement to subjective concerns during the pandemic.

**TABLE 3 |** Logistic regression of associated factors for patient worry regarding being sickened or dying from COVID-19[a].

| Variables | Category | Total, *N* | Worry COVID-19 (Self)[b] *n* (%) | Unadjusted results | | Adjusted results | |
|---|---|---|---|---|---|---|---|
| | | | | Odds ratio 95% CI | *P*-value | Odds ratio 95% CI | *P*-value |
| Age | 18–40 | 39 | 18 (46.2) | – | – | – | – |
| | 41–65 | 372 | 110 (29.6) | 0.49 (0.25–0.96) | 0.036 | 0.58 (0.29–1.16) | 0.121 |
| | 66+ | 181 | 50 (27.6) | 0.44 (0.22–0.90) | 0.025 | 0.66 (0.31–1.42) | 0.292 |
| Gender | Male | 145 | 33 (22.8) | 0.62 (0.40–0.96) | 0.033 | 0.74 (0.39–1.40) | 0.351 |
| | Female | 471 | 151 (32.1) | – | – | – | – |
| Type of cancer | Breast cancer | 310 | 102 (32.9) | – | – | – | – |
| | Prostate cancer | 65 | 10 (15.4) | 0.37 (0.18–0.76) | 0.006 | 0.40 (0.14–1.08) | 0.072 |
| | Colon cancer | 22 | 8 (36.4) | 1.16 (0.47–2.87) | 0.739 | 1.50 (0.56–4.01) | 0.421 |
| | Lung cancer | 19 | 3 (15.8) | 0.38 (0.11–1.34) | 0.133 | 0.27 (0.06–1.21) | 0.086 |
| | Other | 200 | 61 (30.5) | 0.90 (0.61–1.31) | 0.570 | 0.98 (0.63–1.53) | 0.939 |
| Observation period | Before second wave (Jul. 10–Nov. 1, 2020) | 184 | 56 (30.4) | – | – | – | – |
| | Second wave (Nov. 2, 2020–Mar. 11, 2021) | 281 | 100 (35.6) | 1.26 (0.85–1.88) | 0.250 | 1.38 (0.90–2.10) | 0.139 |
| | Third wave (Mar. 12, 2021–Jun. 30, 2021) | 153 | 29 (19.0) | 0.54 (0.32–0.89) | 0.016 | 0.54 (0.31–0.92) | **0.023** |

[a]*I am worried that I could be sickened or die from the coronavirus infection.*
[b]*Agree to strongly agree. Bold value indicates p < 0.05.*

**TABLE 4 |** Logistic regression of associated factors for patient worry regarding relatives and friends being sickened or dying from COVID-19[a].

| Variables | Category | Total, *N* | Worry COVID-19 (Others)[b] *n* (%) | Unadjusted results | | Adjusted results | |
|---|---|---|---|---|---|---|---|
| | | | | Odds ratio 95% CI | *P*-value | Odds ratio 95% CI | *P*-value |
| Gender | Male | 144 | 46 (31.9) | 0.57 (0.39–0.85) | 0.006 | 0.56 (0.36–0.86) | **0.008** |
| | Female | 471 | 212 (45.0) | – | – | – | – |
| Metastatic cancer | No | 411 | 186 (45.3) | – | – | – | – |
| | Yes or suspected | 156 | 57 (36.5) | 0.70 (0.48–1.02) | 0.062 | 0.70 (0.43–1.15) | 0.157 |
| | Do not know | 44 | 14 (31.8) | 0.56 (0.29–1.10) | 0.091 | 0.57 (0.28–1.18) | 0.132 |
| Phase of treatment | After diagnosis or during initial treatment | 196 | 70 (35.7) | – | – | – | – |
| | Initial treatment completed | 243 | 118 (48.6) | 1.70 (1.16–2.50) | 0.007 | 1.58 (1.06–2.36) | **0.026** |
| | Relapse/relapse treatment | 85 | 36 (42.2) | 1.32 (0.79–2.22) | 0.292 | 1.64 (0.92–2.91) | 0.092 |
| | Advanced disease/palliative treatment | 67 | 27 (40.3) | 1.22 (0.69–2.15) | 0.502 | 1.53 (0.77–3.02) | 0.222 |
| Observation period | Before second wave (Jul. 10–Nov. 1, 2020) | 184 | 69 (37.5) | – | – | – | – |
| | Second wave (Nov. 2, 2020–Mar. 11, 2021) | 281 | 141 (50.2) | 1.68 (1.15–2.45) | 0.007 | 1.82 (1.22–2.74) | **0.004** |
| | Third wave (Mar. 12, 2021–Jun. 30, 2021) | 152 | 50 (32.9) | 0.82 (0.52–1.28) | 0.380 | 0.80 (0.50–1.29) | 0.354 |
| Family, friend or acquaintance sickened by COVID-19 | No or do not know | 478 | 190 (39.7) | – | – | – | – |
| | Yes | 139 | 70 (50.4) | 1.54 (1.05–2.25) | 0.026 | 1.34 (0.89–2.02) | 0.162 |

[a]*I am worried that family or friends could be sickened or die from the coronavirus infection.*
[b]*Agree to strongly agree. Bold value indicates p < 0.05.*

observation period (i.e., during the second wave; AOR: 1.82; 95% CI: 1.22–2.74; $p = 0.004$). As for worry that the pandemic would affect the quality of patients' medical treatment, age, having minor-aged children living at home, and type of health insurance were retained for multivariate analysis. However, after adjustment, only type of health insurance was statistically significant. Patients with statutory insurance were more likely to report concern regarding the quality of their medical treatment (AOR: 2.35; 95% CI: 1.37–4.04; $p = 0.002$). Although not statistically significant, patients in the 18–40 age group were more than twice as likely to report concern regarding the quality of care than those in the age group 66 and older (AOR: 2.18; 95% CI: 1.00–4.77); $p = 0.052$. **Tables 3–5** show results of these logistic regression analyses.

With regard to how restrictions during the pandemic affected patients, almost three quarters of patients reported they missed public outings and personal contact with family, friends, colleagues, and neighbors (**Figure 3**). Examining group

**TABLE 5 |** Logistic regression of associated factors for patient worry regarding effects of the pandemic affecting the quality of medical treatment[a].

| Variables | Category | Total, *N* | Worry quality of care[b] *n* (%) | Unadjusted results | | Adjusted results | |
|---|---|---|---|---|---|---|---|
| | | | | Odds ratio 95% CI | *P*-value | Odds ratio 95% CI | *P*-value |
| Age | 18–40 | 39 | 20 (51.3) | – | – | – | – |
| | 41–65 | 372 | 125 (33.6) | 0.48 (0.25–0.93) | 0.031 | 0.54 (0.27–1.10) | 0.092 |
| | 66+ | 180 | 49 (27.2) | 0.36 (0.18–0.72) | 0.004 | 0.46 (0.21–1.00) | 0.052 |
| Minor-aged kids at home | No | 511 | 159 (31.1) | – | – | – | – |
| | Yes | 106 | 44 (41.5) | 1.57 (1.02–2.41) | 0.039 | 1.28 (0.79–2.08) | 0.313 |
| Type of insurance | Private | 105 | 20 (19.0) | – | – | – | – |
| Health insurance | Statutory | 376 | 143 (38.0) | 2.61 (1.54–4.43) | <0.001 | 2.35 (1.37–4.04) | **0.002** |
| | Statutory with private as supplement | 106 | 30 (28.3) | 1.68 (0.88–3.20) | 0.116 | 1.69 (0.88–3.25) | 0.113 |

[a] *I am worried that the effects of the pandemic could affect the quality of medical treatment.*
[b] *Agree to strongly agree. Bold value indicates p < 0.05.*

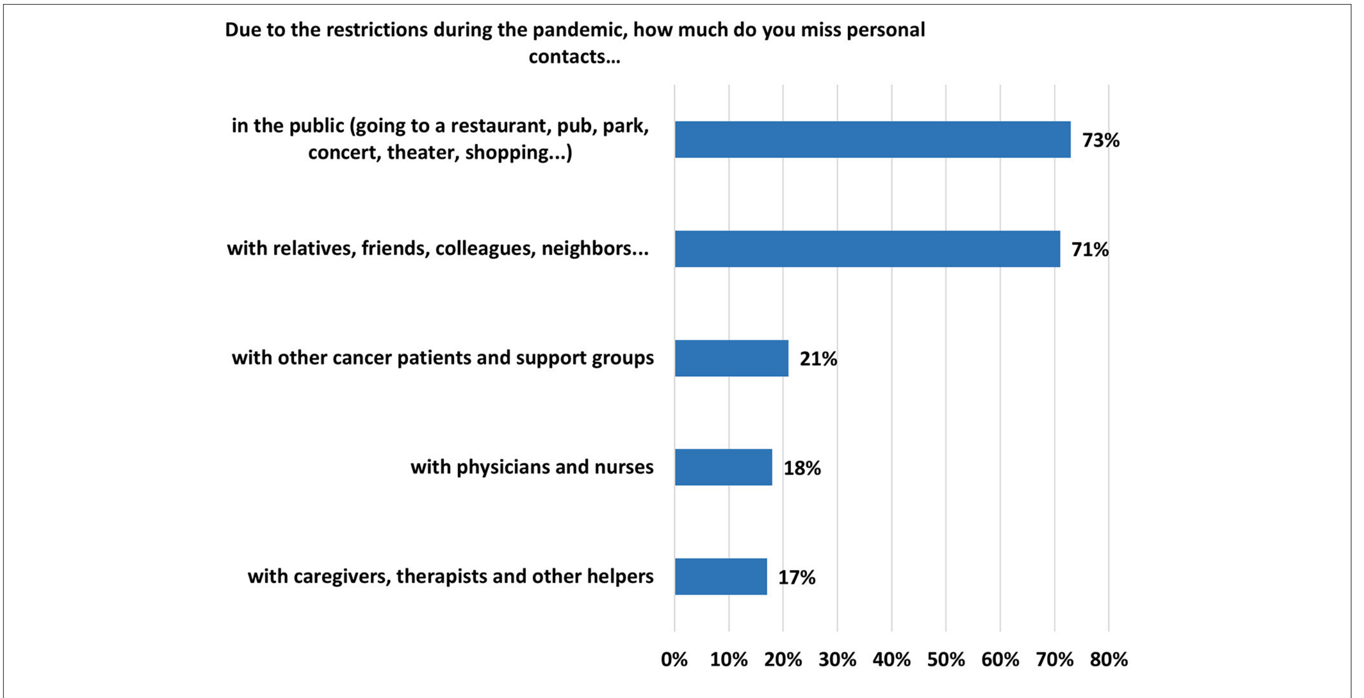


**FIGURE 3 |** Agreement or strong agreement to missing personal contacts due to restrictions during the pandemic ("miss it quite a bit or very much").

comparisons for patients missing contact with others outside the home due to COVID restrictions, age, gender, employment status, type of cancer, having a family or friend sickened by COVID-19, and the time point in the pandemic were adjusted. Only gender (AOR: 0.46; 95% CI: 0.24–0.88; $p = 0.019$) and observation period (second wave: AOR 3.20; 95% CI: 2.03–5.04; $p < 0.001$; third wave: AOR: 2.56; 95% CI: 1.53–4.28; $p < 0.001$) were statistically significant. See **Table 6** for results of the logistic regression analysis.

## Anxiety and Depression

Internal consistency for the HADS was high for the anxiety and depression items ($\alpha = 0.87$ and 0.88, respectively). The mean anxiety score was 8.2 (*SD*, 4.4) and the mean depression score was 6.8 (*SD*, 4.5). A total of 339 respondents (54.6%) exceeded criteria for having symptoms of anxiety when including borderline cases (score $\geq$ 8). For symptoms of depression, 241 participants (38.8%) exceeded criteria.

**Table 7** shows group comparisons for those who reported symptoms of anxiety. For the multivariate analysis, age, gender, level of education, having children under age 18 living at home, employment status, type of cancer, whether the cancer was metastatic were adjusted. Other factors included if there was a change in cancer care, subjective worry over being infected with COVID-19 or having family or friends infected, concern for the quality of medical care, and missing contact with others. Results indicated that patients with an intermediate school leaving certificate were more likely to report symptoms of anxiety (AOR:

**TABLE 6 |** Logistic regression of associated factors for patient missing contacts with relatives, friends, work colleagues, neighbors[a].

| Variables | Category | Total, *N* | Missing Contact[b] *n* (%) | Unadjusted results Odds ratio 95% CI | Unadjusted results *P*-value | Adjusted results Odds ratio 95% CI | Adjusted results *P*-value |
|---|---|---|---|---|---|---|---|
| Age | 18–40 | 39 | 31 (79.5) | – | – | – | – |
| | 41–65 | 373 | 272 (72.9) | 0.70 (0.31–1.56) | 0.379 | 0.68 (0.29–1.61) | 0.381 |
| | 66+ | 182 | 118 (64.8) | 0.48 (0.21–1.10) | 0.081 | 0.83 (0.30–2.32) | 0.724 |
| Gender | Male | 147 | 80 (54.4) | 0.39 (0.26–0.57) | <0.001 | 0.46 (0.24–0.88) | **0.019** |
| | Female | 471 | 356 (75.6) | – | – | – | – |
| Employment status | Employed | 271 | 204 (75.3) | – | – | – | – |
| | Self-employed | 40 | 29 (72.5) | 0.87 (0.41–1.83) | 0.705 | 0.79 (0.35–1.78) | 0.565 |
| | Retired | 239 | 158 (66.1) | 0.64 (0.44–0.94) | 0.023 | 0.71 (0.41–1.26) | 0.243 |
| | Unemployed or not employed | 59 | 38 (64.4) | 0.59 (0.33–1.08) | 0.089 | 0.68 (0.35–1.36) | 0.277 |
| Type of cancer | Breast cancer | 310 | 235 (75.8) | – | – | – | – |
| | Prostate cancer | 66 | 30 (45.5) | 0.27 (0.15–0.46) | <0.001 | 0.54 (0.23–1.28) | 0.159 |
| | Colon cancer | 22 | 16 (72.7) | 0.85 (0.32–2.25) | 0.745 | 1.27 (0.42–3.88) | 0.671 |
| | Lung cancer | 19 | 16 (84.2) | 1.70 (0.48–6.00) | 0.408 | 2.22 (0.59–8.34) | 0.236 |
| | Other type | 201 | 140 (69.7) | 0.73 (0.49–1.09) | 0.125 | 0.82 (0.50–1.33) | 0.414 |
| Observation period | Before second wave (Jul. 10–Nov. 1, 2020) | 185 | 105 (56.8) | – | – | – | – |
| | Second wave (Nov. 2, 2020–Mar. 11, 2021) | 282 | 217 (77.0) | 2.54 (1.70–3.80) | <0.001 | 3.20 (2.03–5.04) | **<0.001** |
| | Third wave (Mar. 12, 2021–Jun. 30, 2021) | 153 | 116 (75.8) | 2.39 (1.49–3.82) | <0.001 | 2.56 (1.53–4.28) | **<0.001** |
| Family, friend or acquaintance sickened by COVID-19 | No or do not know | 481 | 327 (68.0) | – | – | – | – |
| | Yes | 139 | 111 (79.9) | 1.87 (1.18–2.95) | 0.007 | 1.59 (0.97–2.60) | 0.065 |

[a]*How do you feel about the limitations of personal encounters due to the Corona pandemic? Personal contacts with relatives, friends, work colleagues, neighbors.*
[b]*Miss it extremely to miss it quite a bit. Bold value indicates p < 0.05.*

1.83; 95% CI: 1.17–2.85; $p = 0.008$) compared to those with a higher education (university entrance qualification). In addition, those who reported worrying about the quality of their medical care were more likely to report symptoms of anxiety (AOR: 2.76; 95% CI: 1.75–4.35; $p < 0.001$).

For factors potentially associated with depression, living alone vs. living with another/others and whether the cancer had spread were predictor variables (see **Table 8**). In addition, having a change in cancer care, worry of a COVID-19 infection for oneself or family or friends, and worry over quality of cancer care were included in the multivariate analysis. Similar to those reporting symptoms of anxiety, worry over the quality of care (AOR: 2.15; 95% CI: 1.43–3.23; $p < 0.001$) was associated with depression. In addition, having a change in cancer care (AOR: 2.18; 95% CI: 1.26–3.76; $p = 0.005$) and worry over family or friends being infected (AOR: 1.76; 95% CI: 1.12–2.74; $p = 0.013$) were associated factors, although being worried about oneself was not. Finally, those who did not know whether the cancer was metastatic were more likely to report symptoms of depression (AOR: 3.06; 95% CI: 1.53–6.12; $p = 0.002$).

# DISCUSSION

This study aimed to investigate how, over the course of a year, the pandemic affected cancer patients in terms of them receiving medical, follow-up care or psycho-oncological counseling. We presented the rates of changes made to care. Specifically, was there a change to care during the pandemic? For which type of cancer care was the change (or changes) made? We also looked at demographic and clinical features to identify possible sub-populations vulnerable to changes in care. Secondly, we examined the status of the study population's mental health, namely anxiety and depression, but also subjective distress unique to the pandemic (e.g., concerns about being infected, about family or friends being infected, or about the effects of the pandemic worsening the quality of cancer care), and missing contact with others. We compared those who had changes to care vs. those who did not. In addition, we explored subgroups vulnerable to psychological burden—regardless of changes to care—by comparing demographic and clinical features, as well as considering the phase of the pandemic.

## Changes to Cancer Care

Overall, 79 respondents (12.9%) reported a change to a treatment, examination or care plan. After comparing demographic and clinical factors, only the phase of treatment was associated with such changes. When comparing those who reported at least one change in planned cancer care with those who did not, the highest proportion of change occurred for patients reporting to be in the phase where initial treatment had been completed (18.9%). In comparison, those in the phase after diagnosis or who were in the process of receiving initial treatment had the least proportion of change (6.2%). Upon closer examination of

**TABLE 7 |** Logistic regression of associated factors for symptoms of anxiety[a].

| Variables | Category | Total, *N* | Yes[b] *n* (%) | Unadjusted results | | Adjusted results | |
|---|---|---|---|---|---|---|---|
| | | | | Odds ratio 95% CI | *P*-value | Odds ratio 95% CI | *P*-value |
| Age | 18–40 | 39 | 26 (66.7) | – | – | – | – |
| | 41–65 | 373 | 218 (58.4) | 0.70 (0.35–1.41) | 0.322 | 0.90 (0.40–2.06) | 0.813 |
| | 66+ | 183 | 82 (44.8) | 0.41 (0.20–0.84) | 0.015 | 0.89 (0.32–2.46) | 0.826 |
| Gender | Male | 147 | 64 (43.5) | 0.56 (0.38–0.81) | 0.002 | 0.85 (0.44–1.63) | 0.625 |
| | Female | 472 | 274 (58.1) | – | – | – | – |
| Education | Secondary general school-leaving certificate | 62 | 28 (45.2) | 0.76 (0.44–1.31) | 0.323 | 1.05 (0.54–2.03) | 0.884 |
| | Intermediate school-leaving certificate | 159 | 103 (64.8) | 1.70 (1.16–2.49) | 0.006 | 1.83 (1.17–2.85) | **0.008** |
| | University entrance qualification | 389 | 202 (51.9) | – | – | – | – |
| Minor-aged kids at home | No | 514 | 267 (51.9) | – | – | – | – |
| | Yes | 107 | 72 (67.3) | 1.90 (1.23–2.95) | 0.004 | 1.36 (0.80–2.30) | 0.263 |
| Employment status | Employed | 271 | 163 (60.1) | – | – | – | – |
| | Self-employed | 41 | 26 (63.4) | 1.15 (0.58–2.27) | 0.690 | 1.29 (0.58–2.83) | 0.529 |
| | Retired | 239 | 110 (46.0) | 0.56 (0.40–0.80) | 0.001 | 0.67 (0.38–1.17) | 0.157 |
| | Unemployed or not employed | 59 | 33 (55.9) | 0.84 (0.48–1.48) | 0.550 | 0.84 (0.42–1.69) | 0.631 |
| Type of cancer | Breast cancer | 310 | 181 (58.4) | – | – | – | – |
| | Prostate cancer | 66 | 23 (34.8) | 0.38 (0.22–0.66) | 0.001 | 0.70 (0.28–1.72) | 0.434 |
| | Colon cancer | 23 | 11 (47.8) | 0.65 (0.28–1.53) | 0.326 | 0.54 (0.18–1.59) | 0.263 |
| | Lung cancer | 19 | 10 (52.6) | 0.79 (0.31–2.00) | 0.622 | 1.10 (0.35–3.44) | 0.864 |
| | Other type | 201 | 112 (55.7) | 0.90 (0.63–1.28) | 0.552 | 0.96 (0.60–1.53) | 0.867 |
| Metastatic cancer ($n = 615$) | No | 414 | 231 (55.8) | – | – | – | – |
| | Yes or suspected | 157 | 74 (47.1) | 0.71 (0.49–1.02) | 0.064 | 0.79 (0.51–1.24) | 0.307 |
| | Do not know | 44 | 32 (72.7) | 2.11 (1.06–4.22) | 0.034 | 2.08 (0.94–4.61) | 0.070 |
| Change in cancer care | No | 532 | 273 (51.3) | – | – | – | – |
| | Yes | 79 | 61 (77.2) | 3.22 (1.85–5.59) | <0.001 | 1.77 (0.94–3.31) | 0.076 |
| Worry about corona infection | No | 433 | 208 (48.0) | – | – | – | – |
| | Yes | 185 | 129 (69.7) | 2.49 (1.73–3.59) | <0.001 | 1.43 (0.85–2.40) | 0.178 |
| Worry about family/friends corona infection | No | 357 | 187 (45.2) | – | – | – | – |
| | Yes | 260 | 150 (73.9) | 2.15 (1.55–3.00) | <0.001 | 1.24 (0.78–1.99) | 0.363 |
| Worry about possible effects on quality of medical care | No | 414 | 167 (46.8) | – | – | – | – |
| | Yes | 203 | 170 (65.4) | 3.44 (2.38–4.96) | <0.001 | 2.76 (1.75–4.35) | **<0.001** |
| Missing contact with relatives, friends, etc. | No | 182 | 83 (45.6) | – | – | – | – |
| | Yes | 438 | 255 (58.2) | 1.66 (1.17–2.35) | 0.004 | 1.31 (0.87–2.00) | 0.199 |

[a]*Hospital Anxiety and Depression Scale—Anxiety.*
[b]*Anxiety score ≥ 8. Bold value indicates $p < 0.05$.*

those who reported changes in care and who were in the phase after initial treatment was completed, 72% reported a change in follow-up care, 20% a change in psycho-social counseling; yet, to a smaller extent, some reported changes to a planned operation, to systemic treatment, to radiotherapy, or to progress monitoring during treatment. This indicates that patients reporting changes in treatment may have been considering treatments that were planned months prior to completing the survey. The survey item asks if a change in treatment occurred during the pandemic; however, the exact date of reported change was not captured. It could be that the patient was in the phase after initial treatment when answering the questionnaire, but when responding to questions about change in treatment was considering an earlier time in the pandemic when she or he was in the initial phase, or the change may have occurred in the 4 months of the pandemic before the current study began. However, of the patients who took the survey during the first observation period (July 10-November 1, 2020), 17.6% reported a change in cancer care; 11.9% in the second period (November 2, 2020–March 11, 2021); and 9.3% in the third (March 12-June 30, 2021). This indicates that changes in care decreased over time.

With regard to the types of changes to cancer care and occurrence, our results are in line with those of a survey of German comprehensive cancer centers, starting at the end of March 2020, where most changes occurred earlier in the pandemic and mostly concerned follow-up appointments and counseling, while acute care was much less affected (reductions from 10 to 20%) (26). A survey of gynecological cancer patients

**TABLE 8 |** Logistic regression of associated factors for symptoms of depression[a].

| Variables | Category | Total, *N* | Yes[b] *n* (%) | Unadjusted results | | Adjusted results | |
|---|---|---|---|---|---|---|---|
| | | | | Odds ratio 95% CI | *P*-value | Odds ratio 95% CI | *P*-value |
| Living situation | Lives alone | 111 | 51 (45.9) | 1.45 (0.96–2.19) | 0.081 | 1.42 (0.90–2.22) | 0.130 |
| | Lives with others | 492 | 182 (37.0) | – | – | – | – |
| Metastatic cancer | No | 414 | 152 (36.7) | – | – | – | – |
| | Yes or suspected | 157 | 59 (37.6) | 1.04 (0.71–1.52) | 0.848 | 1.08 (0.71–1.64) | 0.714 |
| | Do not know | 44 | 28 (63.6) | 3.02 (1.58–5.76) | 0.001 | 3.06 (1.53–6.12) | **0.002** |
| Change in cancer care | No | 532 | 188 (35.3) | – | – | – | – |
| | Yes | 79 | 50 (63.3) | 3.16 (1.93–5.15) | <0.001 | 2.18 (1.26–3.76) | **0.005** |
| Worry about corona infection | No | 433 | 148 (34.2) | – | – | – | – |
| | Yes | 185 | 91 (49.2) | 1.86 (1.31–2.65) | <0.001 | 1.00 (0.62–1.61) | 0.991 |
| Worry about family/friends corona infection | No | 357 | 111 (31.1) | – | – | – | – |
| | Yes | 260 | 128 (49.2) | 2.15 (1.54–2.99) | <0.001 | 1.76 (1.12–2.74) | **0.013** |
| Worry about possible effects on quality of medical care | No | 414 | 124 (30.0) | – | – | – | – |
| | Yes | 203 | 115 (56.7) | 3.06 (2.16–4.33) | <0.001 | 2.15 (1.43–3.23) | **<0.001** |

[a]*Hospital Anxiety and Depression Scale—Depression.*
[b]*Anxiety score* $\geq 8$. *Bold value indicates* $p < 0.05$.

in 16 European Union countries, conducted in May 2020, found that 36% had a change in their care plan, and 71% were concerned about cancer progression if there was a change in care (27). In a US survey of ovarian cancer patients, of the 43% who were in active treatment during the first 2 weeks of April 2020, 33% had a delay in some component of their cancer care, 26% specific to a planned surgery. Notably, delays in care were predictive of anxiety and depression (28). As these aforementioned studies occurred in the spring of 2020, during the initial phase of the pandemic, they cannot be directly compared to the results of our study, which began in July 2020. Partially overlapping with the timing of our study, the organization Cancer Australia reported a decrease in diagnostic and therapeutic services from March to May 2020 in contrast to the previous year; however, there was a partial recovery by June and a full recovery by September, excluding a few surgical procedures for breast, colorectal, and melanoma cancers (29).

## COVID-19 Related Concerns

Apart from changes to care, survey participants expressed worry about issues caused by the pandemic and its ensuing restrictions. Women were more likely to report worry regarding family and friends getting sick or dying, as well as missing contact with relatives and friends. Furthermore, concern about being infected was highest during the period of the second wave (November 2020 to March 2021) and lowest during the third wave (March to June 2021). This finding may be explained due to the first observation period (June to October 2020) occurring after the first initial higher infection rate had receded and restrictions on contact had been loosened. Regarding the third wave, although not addressed on the survey, COVID-19 vaccines were available during this observation period and presumably may have offered patients who were vaccinated some peace of mind. Interestingly, patients with statutory vs. private insurance were more worried that the pandemic could negatively impact the quality of their medical care. This corresponds to findings that privately insured patients have easier access to innovative medications, have shorter waiting times for appointments, and receive more time with physicians (30–32). Thus, some patients may view patient care with statutory health insurance as "worse" than that of private insurance. It's worth reiterating, we found no significant difference regarding change in care and insurance type (11% private insurance vs. 13% with statutory).

## Anxiety and Depression

More than half of survey participants (54.6%) reported symptoms for anxiety (HADS-A score $\geq 8$) and 38.8% reported symptoms for depression (HADS-D score $\geq 8$). Worry about possible negative effects of the pandemic on medical care was associated with anxiety symptoms. Of those who reported having symptoms of anxiety, 73.9% reported being concerned about the quality of their medical care vs. 45.2% who did not indicate concern over care. Aside from COVID-related factors, those who had attained an intermediate school-leaving certificate (leaving school after grade 10) were more likely to report symptoms of anxiety compared to those with a higher level of education (65 vs. 52% with a university entrance qualification). Interestingly, 45% of those with the lowest level of education (secondary general school-leaving certificate; leaving school after grade 9) reported symptoms of anxiety. Taken together, these findings make it difficult to draw conclusions about education level and anxiety for this study. For those reporting depressive symptoms (38.8% of study sample; HADS-D score $\geq$8), patients who had effective changes to care were more susceptible, but also those who reported worry about the quality of care. Patients who did not know if the cancer had metastasized were also more likely to report symptoms of depression.

Similar to our results, Frey et al. (28), found that 51.4% of their sample reported symptoms of anxiety and 26.5% symptoms of depression. Age (younger than 65) was predictive of greater cancer worry, anxiety, and depression and delay in cancer care was predictive of anxiety and depression. A survey conducted in the EU with gynecological cancer patients found that having experienced modifications of care due to the pandemic predictive of high depression scores (27). A study conducted in China also found that worry over cancer management due to COVID-19 was a predominant risk factor for psychological stress (33). Ayubi et al. conducted a meta-analysis of studies mostly occurring during the first 6 months of 2020, evaluating the level of depression and anxiety in cancer patients during the COVID-19 pandemic. Compared to control groups, cancer patients had higher anxiety levels. Studies using the HADS had an overall prevalence of 28% for depression (HADS-D $\geq$ 8), and a prevalence of 36% for anxiety (HADS-A $\geq$ 8) (22). Compared to before the onset of the pandemic, cancer patients had higher anxiety levels. Females and younger people reported higher mental burden (34). With regard to mental health in the general population in Germany during the pandemic, Bäuerle et al. (35) also found increased prevalence of anxiety (44.9%), depression (14.3%), psychological distress (65.2%) and COVID-19-related fear (59%).

### Limitations and Advantages

Our study had some limitations. The study began in July 2020, after the initial spike in incidence rates and after the first government imposed restrictions had been eased. Therefore, we were unable to capture changes in treatment as well as reactions to the pandemic writ large during and after the initial "lockdown" in March 2020. In addition we did not have baseline depression and anxiety measures pre-pandemic for our study sample. Thus, it is difficult to judge what symptoms are attributable to the pandemic and to what degree, aside from comparing data to other pre-pandemic studies. Another limitation of this study is the use of a non-population-based convenience sample.

Limitations in terms of the online administration via email should also be taken into consideration. While there is some concern over the ethics of recruitment via email (36, 37), the crux of the argument seems to stem over unwanted solicitation (i.e., spam). For the present study, the email invitation is sent as a response to an email initiated by the potential participants. The anonymity of the survey is explicitly stated in the invitation to the questionnaire and in the participant information. Further, data protection is explained in the participant information to address confidentiality.

Lastly, questions addressing the psychological distress unique to the pandemic were self-developed. These items were not developed to be aggregated into a single scale score. Therefore, there is no measure of internal consistency. Furthermore, we conducted cognitive pre-tests to qualitatively study and increase the validity of the items. However, various types of validity (such as construct validity) have not been assessed quantitatively. It might therefore be the case that some confounding factors that are not addressed by our survey influenced the responses to our self-developed items.

Despite some limitations, the current study provides detailed insight into the actual (i.e., changes in services) and perceived (e.g., psycho-social) burdens of a broad range of patients and disease conditions in real time over the course of 1 year. As of this writing, other publications examining the effects of the pandemic covered only the early phase. Moreover, in contrast to clinical research and face-to-face interviews, a "contact-free" online survey has obvious advantages during a pandemic. In addition, we had easy, yet controlled access to the group of interest. Our sample was well characterized, which allowed detailed analyses of subgroups.

## CONCLUSIONS AND FUTURE DIRECTIONS

Our results indicate that the majority of cancer patients contacting the Cancer Information Service during the COVID-19 pandemic did not experience a change in primary cancer treatment. Of those with changes, appointments regarding follow-up care were more likely to be rescheduled or canceled. This indicates that most patients in our study received the initial medical treatment that they were scheduled to receive. However, the level of anxiety and psycho-social burden of cancer patients during the pandemic remained high, particularly for those patients who experienced a change in their care. Identifying risk factors of depression and anxiety among patients with cancer during the COVID-19 pandemic is crucial for taking adequate measures and for allocation of appropriate services. We found that patients who had a change in cancer care were more than twice as likely to have symptoms of depression as those with no changes. Studies suggest that psychological distress may lead to higher rates of mortality in cancer patients (38). This compounded with the effects of a potential delay in medical care (8) may decrease the odds of survivorship. Another factor predicting both anxiety and depression was worry that the pandemic would lessen the quality of their medical care. One survey respondent wrote in the comment section of the survey, "As a cancer patient, one feels relatively left alone after the end of the initial treatment. I am waiting 14 weeks for the follow-up treatment. There is only Corona, all other diseases are no longer important. There are many questions that no one answers…" Clear and open communication between doctors/oncologists and their patients might help assure patients that they will receive the proper care they need. While some delays in treatment and follow-up care may be to prevent the patient from exposure to the coronavirus, this should be expressly communicated to the patient.

Research on the COVID-19 pandemic's impact on both physical and mental health is important (and not lacking), but it is also crucial to continue research into non-COVID medical conditions to identify disparities, gaps, shortcomings and vulnerable groups so that health care management can address respective needs and ascertain equitable care to all patients. The provision of appropriate psychological support for those in need and the provision of transparency and comprehensible information are crucial. An implication of our study for health care services and policy makers is the need to assess and to attend to cancer patients' medical needs, with added emphasis on patients' psychological and social well-being. This applies particularly in situations where the system is strained and prioritization is necessary.

Future analyses will address in more detail the changes made to cancer care and examine the financial impact of the pandemic on cancer patients.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

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

## AUTHOR CONTRIBUTIONS

RE and AG: drafted the manuscript and literature review. EK: data processing. RE: data analysis. AG and JU: cognitive pretesting. All authors were involved in the conceptualization of this study, design of the questionnaire, and contributed to this 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/fpubh.2021.788598/full#supplementary-material

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# Survey Responses of School Closures During the COVID-19 Outbreak in Taiwan

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**Background:** Taiwan faced a surge of COVID-19 infections in May 2021. Because new cases were quickly increasing, parents called for school closures. A national parent group used an online survey to collect opinions about upcoming school closings planned by the Ministry of Education. This study evaluated the results of the survey for all respondents and investigated the level of viral transmission following school closures among students in Taiwan.

**Methods:** An online survey titled "Survey of Opinions of School Closures during the Current COVID-19 Outbreak" (SOSC-COVID-19) was designed by the national parent association and then distributed to members of the community throughout Taiwan *via* local parent groups from May 17 to 18, 2021. The survey included an open-ended respondents' opinions about school closures. Differences among regions and socioeconomic scores (SES) were analyzed with chi-square tests.

**Results:** A total of 8,703 completed survey forms data were analyzed. Nearly all respondents (7,973, 91.6%) approved of school closures; there were no differences of opinions inside and outside municipalities or by regional SES scores. Only 8.4% of respondents were opposed to any type of school closure, believing parents should decide whether their child attended school, which also did not vary with region or SES score. Qualitative feedback from parent and teacher responders indicated students' health and economic impacts were additional concerns that influenced their choice of whether the government or parents should decide about school closures. On the afternoon of May 18, 2021, the government of Taiwan closed all schools. Although a spike in new cases of COVID-19 occurred among students 10 days after school closures, over the next 40 days new cases declined, falling to zero by July 5th.

**Conclusions:** Despite the inability of nationwide school closures to completely halt transmission of the virus within families during the COVID-19 outbreak, school closures helped to impede transmission between students.

**Keywords: school closures, survey, COVID-19, parents, outbreak**

# INTRODUCTION

On March 12, 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome caused by the virus known as SARS-CoV-2 to be a pandemic (1). Many countries attempted to control this pandemic disease, now referred to as COVID-19, by imposing nationwide school closures, which several countries continue to enforce. School closures can be a useful intervention during a pandemic, based on experiences with influenza (2). However, no data are available on the effectiveness of school closures specifically because they were part of a broad range of quarantine and social distancing measures to reduce the spread of COVID-19. Studies have concluded that the combination of quarantine and social distancing was effective in controlling the epidemic in mainland China (3) and Hong Kong (4), but the relative contribution of school closures was not assessed.

Taiwan has Mostly been spared from the impact of COVID-19 infections with an infection rate of <10 cases per week since the beginning of the pandemic in 2020. The alpha variant of SARS-CoV-2 in Taiwan was first reported for two cases on December 31, 2021. Then, on April 20, 2021, a small outbreak occurred, which became worse during the week of May 17, 2021, with a surge of new cases, most were the alpha variant. The infection rate increased to more than 900 cases per week, during which time the COVID-19 vaccination rate was only 0.93 per 100 people (5). Most of the cases were centered in Taipei and New Taipei; therefore, the mayors of these cities announced the closing of all kindergartens, elementary schools, and junior and senior high schools on May 17 and most universities also closed.

However, parents elsewhere in the country were also concerned about the rising number of cases. Although local areas had the option to close schools, there were no nationwide criteria. To determine if parents would support a decision by the Ministry of Education (MOE) to close schools nationwide, a national parent group designed a survey to collect parents' opinions of school closures, which was distributed on May 17, 2021.

The primary aim of this study was to determine if there were regional differences in parents' opinions regarding school closures during the outbreak of COVID-19 in May 2021. This study also investigated the effects of the school closures in reducing further viral transmission among students. The parental opinions of school closures and the effect of school closures on transmission of COVID-19 in Taiwan could be used to guide school systems in other countries, especially as outbreaks of the new variants of the virus occur.

# METHODS

## Design

The SOSC-COVID-19 was a cross-sectional survey sent to regional parent organizations in 20 districts throughout Taiwan. Regional leaders promoted the survey through social media, which provided a link to the online survey. The link was available to anyone in the community and was active between 5:00 p.m. on May 17, 2021, and 10:00 a.m. on May 18, 2021.

## Participants

The internet survey was dependent upon a convenience sample of participants to gather opinions of parents with school-aged children, and other individuals in Taiwan about school closures. In Taiwan, 85–90% people over 16 years-old have access to mobile phones and the Internet (6). The only inclusion criteria were access to the Internet *via* a smartphone or computer. Because responding to the survey required the ability to read, those who were unable to read Chinese were unable to participate.

## Ethical Considerations

This study was approved by the Ethics Committee of Taipei Hospital, Ministry of Health and Welfare (TH-IRB-0021-0017). All procedures were in accordance with the ethical standards of this committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## The Survey

The National Alliance of Parents Organization in Taiwan developed an online survey, titled "Survey of Opinions of School Closures during the Current COVID-19 Outbreak" (SOSC-COVID-19), which was designed on May 17, 2021, and asked the question, "Who should decide about school closures in Taiwan during the current COVID-19 outbreak?" (**Figure 1**). This was a critical time point at which a record high of 333 new COVID-19 cases were reported (which were corrected to 535 cases later). National Alliance of Parents Organization disseminated the SOSC-COVID-19 from May 17 to 18, intending to unofficially send the survey results to the central government (**Figure 2**). Respondents also had the option of indicating if they were a parent, teacher, student, or other. In addition, they had the option of responding to an open-ended question, "Do you have any opinions you would like to share about why you made your decision about school closures?"

## School Closures and Viral Transmission Among Students

To investigate the effects of the school closures in reducing further viral transmission among students, data were obtained for locally acquired new cases of COVID-19 for students in Taiwan between May 11 and July 9, 2021. These data were available from the Ministry of Education of Taiwan.

## Data Analysis

Quantitative data were analyzed using SPSS version 28.0 for Windows (Armonk, NY: IBM Corp). Descriptive statistics were used for frequency ($n$, %). Chi-square tests assessed the differences between participants' opinions. Statistical significance was set to $p < 0.05$ for all statistical comparisons.

Because the survey only asked who should decide school closures, qualitative data were collected about what influenced the choice made by the responders. The use of open-ended questions provides data that is more diverse than is possible with a forced response as respondents have an opportunity to offer more authentic opinions (7). The authors read through the opinions and sorted them according to support for government school closures or support for parental choice. Opinions

**Figure 1 Who should decide about school closures in Taiwan during the current COVID-19 outbreak?**

The Ministry of Education is considering school closures to help reduce the spread of COVID-19 during the current surge of cases.

Please respond to the following statements about who should make decisions about school closures by indicating if you agree or disagree. All responses will remain anonymous

| **Statement** | Agree | Disagree |
|---|---|---|
| 1. School closures should be initiated by the central government. | ☐ | ☐ |
| 2. School closures should be initiated by each local government. | ☐ | ☐ |
| 3. There should be no school closures. Parents should decide about their children's school attendance. | ☐ | ☐ |

Additional information (optional):

Please indicate the region in which you live: ____________________

Please indicate which of the following describes your status†:

| Status | Yes |
|---|---|
| Parent | ☐ |
| Teacher | ☐ |
| Student | ☐ |
| None of the above | ☐ |

Do you have any opinions you would like to share about why you made your decision about school closures?

**FIGURE 1 |** The survey designed by the National Alliance of Parents Organization in Taiwan, "Survey of Opinions of School Closures during the Current COVID-19 Outbreak" (SOSC-COVID-19). †If participants selected "parents" as well as "teacher" or "student", they were given the status of parent.

were read and categorized by weighting which opinions most frequently fell into a category, which was based on the reason given for their decision.

# RESULTS

## Participant Characteristics

A total of 8,712 participants filled in the online SOSC-COVID-19 survey from May 17 to 18, 2021. However, three surveys were incomplete, and six respondents completed the survey more than once. Thus, data were analyzed for 8,703 participants. The sample loss rate was 0.1%.

The geographical and economic distribution of respondents to the survey is shown in **Table 1**. The largest groups of respondents were from the inner municipalities of Taichung City ($n = 2,013$, 23.1%), Taoyuan City ($n = 1,352$, 15.5%) and Kaohsiung City ($n = 1,173$, 13.5%) and the outer municipality of Changua County ($n = 1,774$, 20.4%). The two cities where school closures were

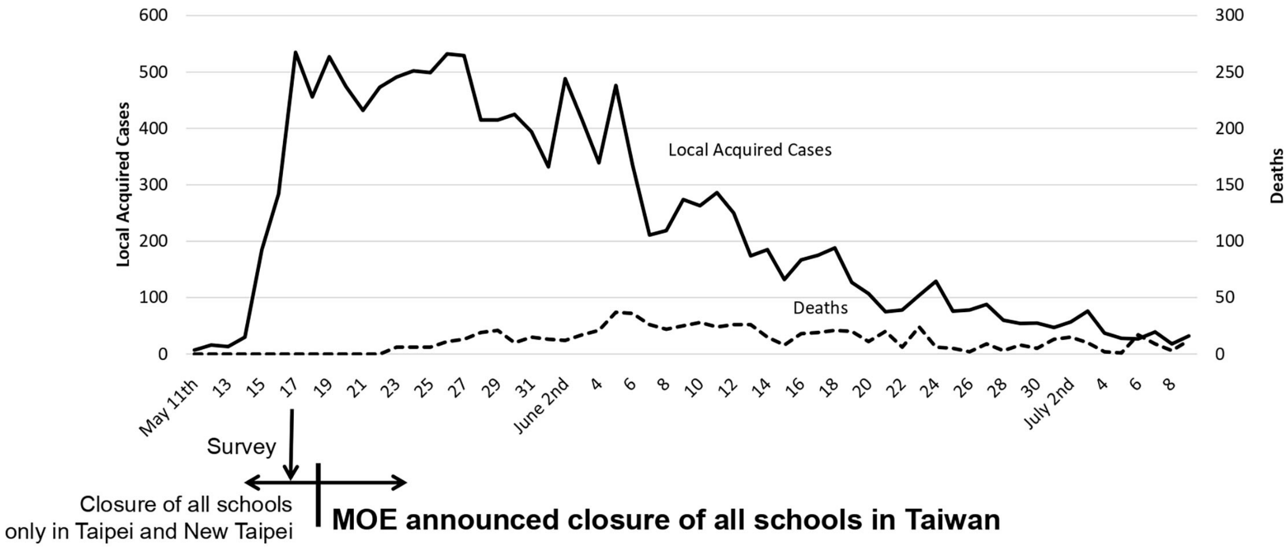


**FIGURE 2 |** Number of new daily local acquired COVID-19 cases and the timing of the survey of SOSC-19. Data excludes 1–10 imported cases per day (Ministry of Health and Welfare).

already announced (Taipei City and New Taipei), are inner municipalities and only a small number of surveys were received ($n = 150$, 1.7% and $n = 169$, 1.9%, respectively).

The socioeconomic status (SES) scores reported by the National Development Council were calculated by the incomes and employment opportunities for each region (8) (see **Table 1**). A total of 7,992 participants (91.8%) lived in areas with SES scores above 40. All inner municipalities have SES scores > 41. A total of 711 participants (8.2%) lived in areas with SES scores $\leq$ 40 (with income <NT800,000/USD 28,500 per family annually and less employment opportunity); these respondents represented 19.8% of the outer municipalities.

## Quantitative Survey Results

Most respondents (74.2%) indicated they were parents ($n =$ 6,457); 1,494 were teachers (17.2%); 377 were students (4.3%); 4.3% responded "none of the above". **Table 2** shows the responses to the survey grouped by all participants, inner and outer regional municipalities, and according to SES scores $\leq$40 and >41. Respondents overwhelmingly agreed that the government should be allowed to make the decision about school closures (91.6%). 52.5% felt the decision should be made by the central government and 39.1% felt it should be a local government decision. Only 730 participants (8.4%) felt parents should be allowed to make the choice about school attendance ($\chi^2 = 4.011$, $p = 0.001$). **Figure 3** shows the distribution of responses to the three statements in the survey for all participants. There were no significant differences in responses on school closures between respondents inside and outside municipalities ($\chi^2 = 4.184$, $p = 0.123$) or by SES scores ($\chi^2 = 3.93$, $p = 0.14$) (**Table 2**).

## Qualitative Survey Results

After reading through all responses voiced in the open-ended question, most opinions involved concerns about how closures affected students' health, economic impacts to families, and why they did or did not support school closures. Categories, descriptions, and opinions are summarized in **Table 3**.

### Concerns About Students' Health

Many respondents mentioned they were worried children would be infected with the virus if the schools were not closed. One parent from the Changhua district wrote, *"New cases of COVID-19 increased rapidly in the last several days, and it will be too late if the school is not closed now. The students can go back to school when the pandemic subsides."* Both teachers and parents supported school closures because they were concerned COVID-19 would be transmitted during classroom sessions or when students were eating without masks. A Taoyuan teacher wrote, *"Children will not tolerate wearing masks in hot weather and will be at risk of infection. We should avoid gathering in classrooms to reduce the risk of infection."* A parent from Taichung City said, *"Children spend a long time in school. They take off their masks when eating lunch, which will increase the risk of infection."*

Parents also worried about infection during transportation to schools and the sequelae of CPVID-19. A New Taipei parent wrote, *"Some students take the bus and Taipei Mass Rapid Transit (MRT), and they could be infected by COVID-19-infected classmates. It would be good to suspend classes as soon as possible."* A Taichung parent said, *"Children can develop severe pulmonary fibrosis from a COVID-19 infection, and then they will have no future at all! Please suspend classes as soon as possible!"*

### Economic Impacts

School closures carry high social and economic costs for communities. Employed parents are more likely to miss work when schools close to take care of their children. A Taichung parent wrote, *"Not every parent can take care of children during school closures. There should be supporting measures."* A

Changhua parent wrote, "*Schools should provide help to children without support, because not every family can take care of children during school closures, and this will cause problems.*"

Parents from areas with SES scores > 41 had concerns about the economic impact and challenges that low-income families (≤40) would face, which was expressed by a parent from New Taipei who wrote, *"Please provide more support to low-income families. If the parents take care of children and cannot go to work during school closures, they will lose their jobs and have no income."* A Single parent from an area with a low SES score (Hualien County) said, *"Some single-parent families cannot provide computers or smartphones. It is not good for children to be alone at home during school closures. Instead, it causes social problems."* A Taipei parent, who did not support nationwide school closures, was opposed due to concern about families for whom online teaching equipment was not affordable.

**TABLE 1 |** Geographic and economic distribution of respondents to the online SOSC-COVID-19 survey in Taiwan (*N* = 8,703).

| Region | SES score[a] | *n* (%) |
|---|---|---|
| **Inner municipality** | | |
| Taichung city | > 41 | 2,013 (23.1%) |
| Taoyuan city | > 41 | 1,352 (15.5%) |
| Kaohsiung city | > 41 | 1,173 (13.5%) |
| Tainan city | > 41 | 246 (2.8%) |
| New taipei city | > 41 | 169 (1.9%) |
| Taipei city | > 41 | 150 (1.7%) |
| **Outer municipality** | | |
| Changhua county | >41 | 1,774 (20.4%) |
| Hsinchu county/city | >41 | 734 (8.4%) |
| Chiayi county/city | >41 | 114 (1.3%) |
| Penghu, lianjiang and kinmen county | >41 | 88 (1.0%) |
| Yilan county | >41 | 73 (0.8%) |
| Miaoli county | >41 | 67 (0.8%) |
| Keelung city | >41 | 39 (0.4%) |
| Pingtung county | ≤40 | 486 (5.6%) |
| Nantou county | ≤40 | 88 (1.0%) |
| Yunlin county | ≤40 | 78 (0.9%) |
| Taitung county | ≤40 | 31 (0.4%) |
| Hualien county | ≤40 | 28 (0.3%) |

*SES, socioeconomic status.*
[a]*SES ≤ 40 = income <NT800,000/USD 28,500 per family annually and less employment opportunity.*

### Reasons for Who Should Make the Decision About School Closures

Most respondents believed school closures should be decided by the central government because of the nationwide impact of the COVID-19 outbreak. A teacher from Hsinchu County wrote, *"A decision by either the central or local government to close schools is acceptable."* A parent from Kaohsiung City wrote, *"There should be a unified standard by the central government. There will be inconsistent actions if school closures are not announced by the central government."* However, a parent in Changhua County commented, "*The central government should provide standards of school closures, and the local government should make decisions according to the standards*." Parents from the inner municipality of Taipei City (SES > 41) and the outer municipality of Yunlin County (SES ≤ 40) reported school closures should be decided by the local government because they were better able to address issues specific to each region, whereas the central government had multiple interests to juggle. One parent from Yunlin County said, "*It would be too late if the school closures were decided by the central government. The chief of the local government can judge and decide when to close the school in time* [to halt the spread of the virus]."

The reason respondents believed parents should make the decision was explained by a teacher from the inner municipality of Taoyuan City who wrote, "*Every family situation is different*". A parent from the outer municipality of Yilan County wrote, "*Even if school closures are not announced by the government, the parents should make the decision themselves. Do not overthink the situation.*"

## School Closures and Viral Transmission Among Students

Nationwide school closures are useful in preventing the spread of COVID-19 among students. MOE announced the closing of

**TABLE 2 |** Responses to the SOSC-COVID-19 survey about initiating school closures by group: all respondents, regional municipalities, and SES scores above or below 40.

| Group | Closure initiated by government | | No closure | $\chi^2$ | *p* |
|---|---|---|---|---|---|
| | Centrally | Locally | Parental choice | | |
| | *n* (%) | *n* (%) | *n* (%) | | |
| All respondents (*N* = 8,703) | 4,573 (52.5%) | 3,400 (39.1%) | 730 (8.4%) | 4.011 | 0.001 |
| **Regional municipalities** | | | | | |
| Inner (*N* = 5,103) | 2,701 (52.9%) | 1,955 (38.3%) | 447 (8.8%) | 4.184 | 0.123 |
| Outer (*N* = 3,600) | 1,872 (52.0%) | 1,445 (40.1%) | 283 (7.9%) | | |
| **SES scores** | | | | | |
| ≤40 (*N* = 711) | 350 (49.2%) | 302 (425%) | 59 (8.3%) | 3.93 | 0.14 |
| >41 (*N* = 7,992) | 4,223 (52.8%) | 3,098 (38.8%) | 671 (8.4%) | | |

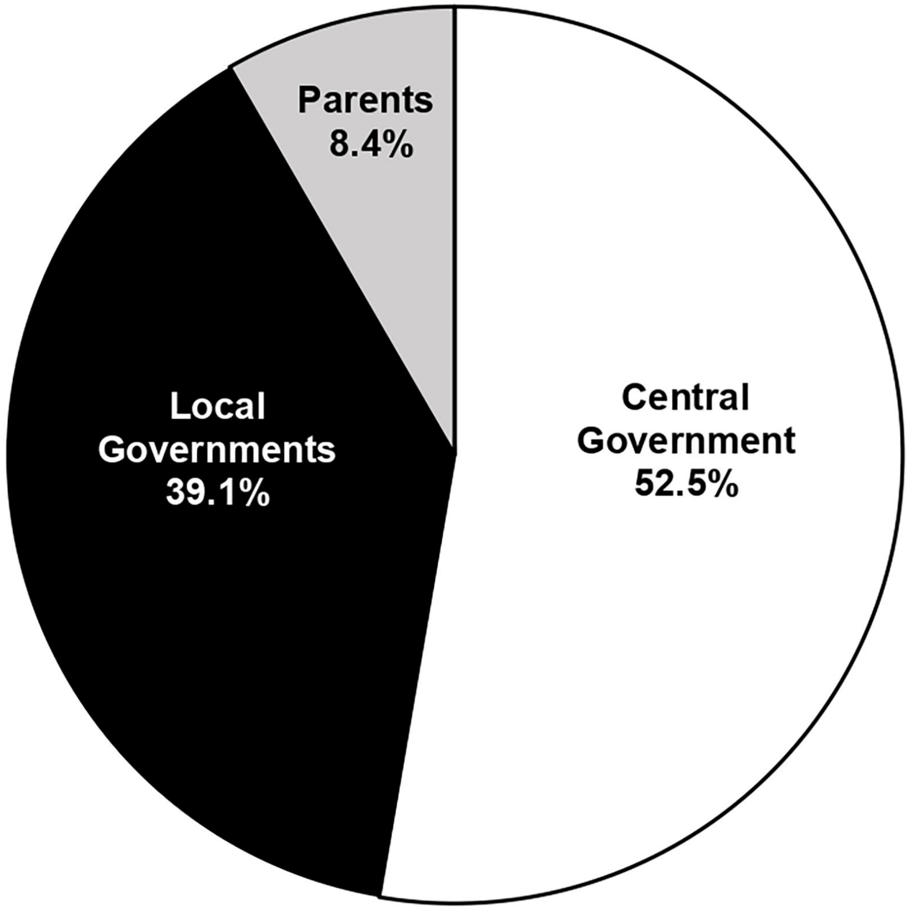


**FIGURE 3 |** Pie chart illustrating of who should decide about school closures obtained from the Survey of Opinions of School Closures during the Current COVID-19.

all schools on May 18, 2021. On May 19, 2021, nationwide level 3 epidemic prevention and control measures were implemented (**Supplementary Table S1**), without the need to initiate a nationwide full lockdown.

The initiation of Level 3 prevention and school closures began while the surge was increasing and there was an initial increase in newly diagnosed cases in Taiwan. However, cases began to decline significantly ∼21 days later, as shown in **Figure 2** (around June 6, 2021). The impact of school closures on viral transmission also benefited students. Cases of newly diagnosed COVID-19 among students initially increased from a rate of more than 10 cases per day to 47 cases on May 27. However, by June 6, 2021, new cases hovered around 15 per day with no new cases reported after July 5, 50 days after school closures (**Figure 4**). Most students who contracted COVID-19 were university students (205 cases, 30.7%, from April 20 to July 9).

## DISCUSSION

Although the initiation of school closures to suppress transmission of COVID-19 impacts all families, they tend to have the greatest effect on families with low-income (9). However, in our study, respondents in areas with SES scores $\leq$ 40, an indicator of low-income, were as equally supportive of school closures as respondents from areas scoring >41. This suggests concern for reducing transmission and the health of the student population outweighed other considerations of respondents, regardless of economic status, thus prompting a call for school closures. Though nationwide school closures cannot stop transmission within families, this intervention can reduce transmission among students during COVID-19 outbreaks, which could have an indirect effect on prevention of transmission from children to families.

### Decisions About School Closures

Nearly all respondents indicated that school closures should be announced by central or local governments. The anonymous feedback indicated both parents and teachers supported giving government control of this decision because of the crucial nature of the COVID-19 outbreak and concern about students' health. A report proposed the implementation of a set of public, comprehensible, and data-driven criteria for school closures during the COVID-19 pandemic (9). The most common measures used are new case rates and test positivity rates, primarily at the county level in the United States (10). Taiwan implemented measures for school closures in local areas but did not have nationwide criteria for school closures (11). Thus, criteria for nationwide school closures should be implemented to avoid unplanned school closures during outbreaks.

**TABLE 3 |** Summary of feedback: categories, description, and opinions.

| Category | Description | Opinions |
|---|---|---|
| 1. Students' health | Risks of COVID-19 infections for children if schools remain open. | • Schools should be closed immediately.<br>• Children would be safer not going to schools. |
| 2. Economic concerns | School closures would impact the family economics. | • Families needed financial support from governments.<br>• Children needed online learning support from the governments. |
| 3. Reasons for decisions | Support of government closures | • Standards to close schools should be set by the central government.<br>• Decisions to close schools should be at the local level because there are differences among school districts. |
| | Support for parental choice | • Parents should be allowed to decide. It is not proper to close the schools nationwide.<br>• Every family situation is different, let parents make the decision to suspend school attendance. |

## Nationwide School Closures Were Useful Interventions for COVID-19 Transmission in Schools

Many students infected by classmates or friends in the first few days of the outbreak went on to infect family members and others who contacted them (12). In one notable case that led to a cluster of outbreaks was one unknowingly infected individual transmitting COVID-19 not only to a group of friends who sang together at a karaoke parlor, but also the transmission of the virus to students in an adjacent room (13). These infected university students subsequently passed the virus to their roommates in university dormitories and their families, with a total of 9 individuals ultimately testing positive.

Following school closures, in combination with nationwide Level 3 epidemic prevention and control measures, new COVID cases and deaths decreased (**Figure 2**) and control measures were reduced to Level 2 on July 27, 2021. Data from MOE indicated the closing of schools on May 18, 2021, coincided with a reduction in the number of new cases of COVID-19 among students to zero 50 days after school closures. The comparison of the decline in COVID-19 cases among the total population of Taiwan (**Figure 2**) with COVID-19 cases among students over the same 50-day period (**Figure 4**), suggests the nationwide school closures had the greatest benefit for preventing transmission among students.

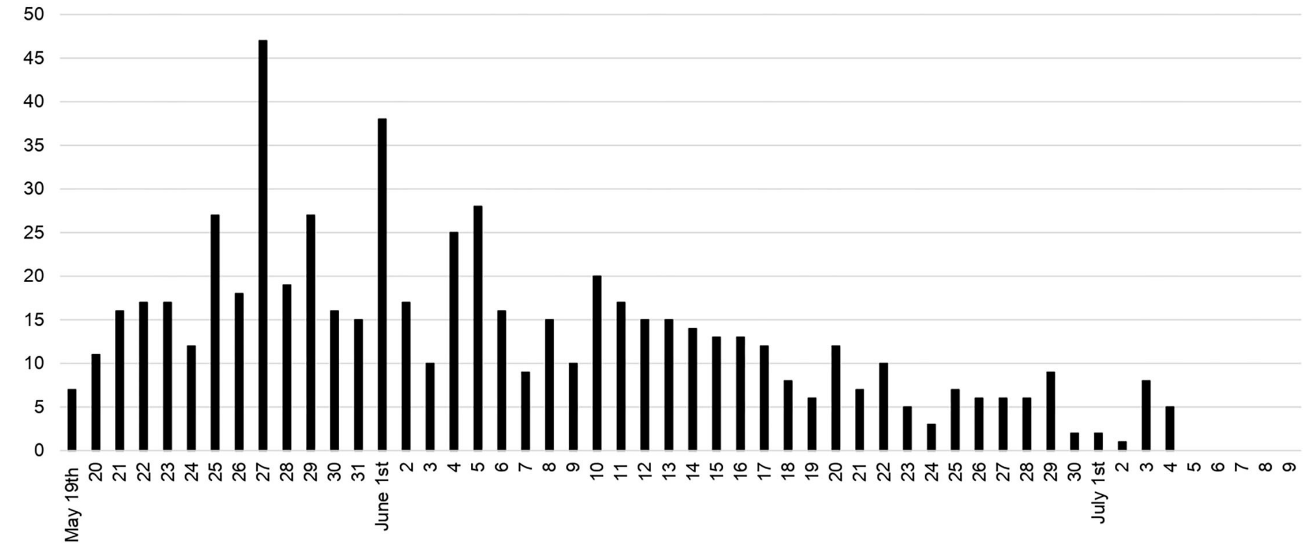


**FIGURE 4 |** Number of new daily cases of COVID-19 among students in Taiwan following closures of all schools in Taiwan (Ministry of Education).

Several theoretical reasons could explain why school closures might be less effective for preventing the spread of COVID-19 compared with previous influenza outbreaks. Children contribute more to influenza transmission than do adults (14), but transmission in schools was low or absent during the previous coronavirus (SARS) outbreaks (15). It was reported school closures is predicted to be insufficient to mitigate (never mind suppress) the COVID-19 pandemic in isolation (16), there is no strong evidence available for the effectiveness of school closures for COVID-19 (17). Children appear to represent a lower proportion of COVID cases than would be expected for the size of their population, however, it might be due to children largely remaining asymptomatic or having a mild form of the disease (18). Children who contracted COVID-19 in school can easily pass the virus to other children as well as to adults. A granddaughter returned to Tainan from New Taipei, and infected her grandmother in Tainan (19). Data from Taiwan support our findings that the implementation of nationwide school closures further contributes to prevention of infection among students and lowering the risk of infection to families.

### Additional Measures to Suppress the Spread of COVID-19

The combination of preventive measures implemented in Taiwan suppressed the wave of COVID-19 transmission in May 2021, even as Australia, Vietnam, and Singapore were struggling with an uptick of the virus at the same time. These measures included strict border controls, close health monitoring, and quarantine measures for people entering Taiwan (20). Second, Taiwan doubled down on longstanding strategies of masking, quarantine measures, and contact tracing, and provided quarantine facilities, which significantly reduced transmission of the virus within families. Contact tracers leveraged activities by maintaining written records or canning a QR code provided by an app from their phones. Third, authorities banned indoor dining in the early days of the outbreak.

### Public Health Interventions and Effective Strategies Are Necessary to Help Parenting Difficulties

The feedback from parents about concerns for children's health and economic problems, including availability of online learning support, are similar to reports from parents in the United States, who worried about the impact of closures on their children's daily routines, the spread of COVID-19, and demands of online schooling (21). Parents in the United States also reported high levels of depression, anxiety, parental burnout, and increased negative emotions, such as anger and worry (22). Our findings provide additional confirmation that school closures during COVID-19 are stressful for parents. Public health interventions should address parenting-specific stressors and effective strategies for managing parenting difficulties to mitigate their deleterious impact.

### Limitations

Our findings have some limitations. The critical surge in COVID-19 cases prompted the survey to be rapidly designed and processed on May 17, 2021. Therefore, the validity and reliability of the survey was not analyzed. Although the survey results were useful in transmitting the message to MOE that 91.6% of respondents wanted schools closed immediately, the survey lacked demographic information. A follow-up survey with demographic information will be conducted in the future. Only 3.6% participants were from Taipei and New Taipei, where school closures had already been announced. Although 85–90% of Taiwanese over 16 years of age use mobile phones and have access to the Internet, few respondents (8.2%) were from low-income areas of Taiwan and few of these respondents provided any personal feedback. A lack of Internet access would limit receiving information through social media channels as well as the ability to complete the online survey in the short period of time.

## CONCLUSIONS

The SOSC-COVID-19 was disseminated in response to the desire of parents to close schools. The survey results were sent to the MOE for reference; however, the decision was made prior to the MOE receiving the survey results. Although school closures addressed the concerns expressed by parents in the survey's feedback, no information is available as to how the closures impacted learning loss of children and economic stability of families, which should be examined with future studies.

School closures carry high social and economic costs for communities. Their impact is particularly severe for the most vulnerable and marginalized children and their families (23). Schools are essential for children's learning, health, safety and wellbeing (24), and are particularly vital for children primary school age children (25). The consequences of school closures could be felt for decades and are contributing to even wider inequality, particularly for girls (25). Working parents are more likely to miss work when schools close to take care of their children, which results in wage loss and possibly job loss (23). Future research should collect information to estimate the scale of learning loss and economic harms during school lockdowns moving forward.

## 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 Taipei Hospital, Ministry of Health and Welfare. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

T-YH designed and disseminated the survey. K-YC collected the data and processed the analyses. WC conceived the study, wrote the manuscript, and took primary responsibility for communication with the journal and editorial office throughout the submission, peer review, and publication processes. 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.2022.726924/full#supplementary-material

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**Conflict of Interest:** T-YH was a volunteer of National Alliance of Parents Organization.

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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# Comprehensive Analysis of the COVID-19: Based on the Social-Related Indexes From NUMBEO

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**Background:** The COVID-19 has been spreading globally since 2019 and causes serious damage to the whole society. A macro perspective study to explore the changes of some social-related indexes of different countries is meaningful.

**Methods:** We collected nine social-related indexes and the score of COVID-safety-assessment. Data analysis is carried out using three time series models. In particular, a prediction-correction procedure was employed to explore the impact of the pandemic on the indexes of developed and developing countries.

**Results:** It shows that COVID-19 epidemic has an impact on the life of residents in various aspects, specifically in quality of life, purchasing power, and safety. Cluster analysis and bivariate statistical analysis further indicate that indexes affected by the pandemic in developed and developing countries are different.

**Conclusion:** This pandemic has altered the lives of residents in many ways. Our further research shows that the impacts of social-related indexes in developed and developing countries are different, which is bounded up with their epidemic severity and control measures. On the other hand, the climate is crucial for the control of COVID-19. Consequently, exploring the changes of social-related indexes is significative, and it is conducive to provide targeted governance strategies for various countries. Our article will contribute to countries with different levels of development pay more attention to social changes and take timely and effective measures to adjust social changes while trying to control this pandemic.

**Keywords: COVID-19, time series analysis, social-related Indexes, climate, k-means clustering algorithm**

## INTRODUCTION

The outbreak of COVID-19 has been accompanied by an exponential increase of new infections and a growing death count. The WHO has reported over 440 million diagnosed infections, and more than 5.98 million patients lost their lives worldwide as of 6 March 2022 (1). This sudden pandemic has hit the medical assistance systems of many countries hard and has disrupted the normal public order (2).

Many countries made different containment and targeting strategies (3), and country-based mitigation measures will influence the occurrence and development of COVID-19 (4). When it comes to public hygiene interventions, Hong Kong, which is more liberal, trends to voluntary and stepwise action instead of implemented strict compulsory testing and isolation (5). Meanwhile, the Austrian government is revising and submitting a bill to force all residents to receive COVID-19 vaccine in order to reduce the risk of infection and the spread of the disease (6). The Changning District of Shanghai has mainly adopted some strategies to prevent and control COVID-19, such as focusing on key populations and key areas, standardizing the workflow, and investigation and closed-loop management to control new cases (7). The Ethiopian government made tremendous efforts to control COVID-19, such as limiting public gathering, closing borders, and restricting transportation (8). Certainly, the degrees of severity of the pandemic in different countries vary. It is mostly dependent on government policies, detection intensity, mass awareness of prevention, vaccination status, medical facilities, traffic propagation rate, and supervision (9–11).

As one of the most severe pandemics in the last eight decades, there is a link between the grave circumstances of COVID-19 and diverse societal levels. The impact of COVID-19 on the economy should be recognized. There is a drastic effect on the worldwide economy, with an estimated loss of more than 1 trillion dollars (12). Some researchers claimed that the effect of this pandemic on sector fluctuations was greater than the global financial crisis (13). In terms of quality of life, Chinese researchers confirmed that COVID-19 has aggravated mild stress, but improved social and family support for residents (14). Research on Korean adults shows that their lifestyle has changed and that their daily activities are restricted. In addition, the quality of life and mental health declined (15). The epidemic has a greater impact on children and adolescents in Germany, especially minors in families with difficult domestic life or immigrant background (16). The control of COVID-19 is also closely related to the medical supplies and treatment services. The rapid establishment of the Fire God Mountain hospital and the Thunder God Mountain hospital had provided patients with timely suitable rescue and treatment environments in Wuhan, China (17). The challenges and pressing actions for the United States especially highlights the problem of continuous improvement and optimization of the supply chain of health care in the United States (18). In addition to reducing disease transmission, COVID-19 mitigation strategies have also reduced urban road traffic, resulting in indirect benefits air quality, traffic noise, and accidents (19). To slow down the transition, most countries recommended that people reduced aggregation activities. Some countries even released prisoners by means of parole and probation. However, it would lead to a degree of destruction of social security and stability (20).

We select nine social-related indexes from NUMBEO. These indexes include quality of life index, climate index, health care index, safety index, cost of living index, and so forth. We utilize the time series model (21). The differences between the forecast and actual values of 2020 mid-year are predicted and compared. The D-value (the forecast of 2020 mid-year minus actual values of 2020 mid-year) of nine indexes are calculated. The cumulative incidence (CuI) and the score COVID-safety-assessment (SCSA) of selected country are collected. Correlation analyses between these two variables and the D-value are performed. It is valuable that we analyze the social conditions of many countries from a macro perspective about COVID-19. Countries with different development levels are facing diverse situations. No matter to what extent the COVID-19 is, the impacts of COVID-19 and the changes in social-related aspects should not be ignored. We aim to find out which index in countries is more affected by COVID-19. This will help countries with different levels of development pay more attention to social changes and take timely and effective measures to adjust social changes while trying to control this pandemic. Moreover, social stability is more conducive to the implementation of epidemic prevention and control work.

## MATERIALS AND METHODS

### Nine Indexes of 52 Countries

We first searched for relevant social news and relevant social indicators through Google, Baidu, and other websites. After information screening, we initially selected the NUMBEO website. NUMBEO was quoted by numerous newspapers, magazines, and blogs [e.g., Time, BBC, People (China, in Chinese), and so on]. Then, after consulting relevant literature, we finally decided to select the NUMBEO website (22, 23). NUMBEO is the world's largest cost of living database. It is also a crowd-sourced global database of quality-of-life information that includes perceived crime rates, quality of health care, and pollution index, among many other statistics. The detailed introduction of each index was shown in **Supplementary Table 1**. It contributed data about cities and countries worldwide. The data provided by the website is public and can be downloaded directly without processing. We collected data published from 2014 to 2020 (24). After deleting countries with nine missing indexes and combining the national information provided in the data of SCSA, we finally selected 52 countries, including nine indexes, and SCCA data.

### Cumulative Incidence

The cumulative confirmed number of COVID-19 cases of 52 countries were obtained from Netease website from the first reported case to 1 July 2020 (25). The data from the Netease website were from official and media reports of various countries and regions. We collected the total population of the selected countries (26) to calculate cumulative incidence that indicated the severity of the epidemic.

$$\text{CuI} = \frac{\text{number of new cases}}{\text{total populaition}} \times 100\%$$

### SCSA

The data of SCSA was from the COVID-19 Regional Safety Assessment. It included Big Data Analysis of 200 Countries, Regions, and Territories that were published by the Deep Knowledge Group (27). The SCSA was based on the analysis of

130 quantitative and qualitative parameters and 11,400 data from 200 COVID-19 endemic countries around the world in June by the deep knowledge group.

## D-Value

The D-value of nine indexes is the forecast of 2020 mid-year minus actual values of 2020 mid-year.

D-value = (the forecast values of 2020 mid-year) - (the actual values of 2020 mid-year).

## Statistical Methods

### Time Series Models

The time series model tries to predict unknown data by modeling historical surveillance data (28–30). To solve the problem of data with a long time span and small quantity, several time series models, including the naive, simple average, and exponential smoothing, were employed in this study. The Naive method is suitable for data with high stability. The simple average method fits data with more stability. The exponential smoothing is suitable for forecasting data with no trend or seasonal pattern. A major advantage of these three methods was that they were suitable for processing simple and stable data in line with the characteristics of the data we collected (**Supplementary Figure 1** and **Supplementary Table 2**). The mathematical formulas were expressed as follows:

$$F_{t1} = A_{t1-1},$$

where $F_{t1}$ is the forecast value at the t moment and $A_{t1-1}$ is the actual value at the moment of t1-1;

$$F_{t2} = \frac{\sum_{i=1}^{n} A_{t2-i}}{n},$$

where $F_{t2}$ is the forecast value at the t2 moment, i is the corresponding moment, n is the number of data, and $A_{t2-1}$ is the actual value at the moment of t2-1;

$$F_{t3} = F_{t3-1} + \alpha \left( A_{t3-1} - F_{t3-1} \right),$$

where $F_{t3}$ is the forecast value at the t moment, $A_{t3-1}$ is the actual value at the moment of t3-1, $F_{t3-1}$ is the forecast value at the moment of t3-1, $A_{t3-1}$ is the actual value at the moment of t3-1, and α smoothing coefficient whose value is between 0 and 1.

$$RMSE = \sqrt{\frac{1}{n} \sum_{t=1}^{n} (F_t - A_t)^2},$$

Based on the data of nine indexes of 52 countries from 2014 to 2019, we used three methods to predict 2020 data. By comparing the actual and forecast value in 2020, we selected the optimal model according to the root mean squared error (RMSE) to forecast the corresponding value in mid-year of 2020. Through comparing the difference between forecast and actual values in mid-year 2020, we used a paired-sampled *T*-test to find the indexes that were affected during COVID-19 pandemic.

**TABLE 1 |** Error measures obtained under the three time series models.

| Index | Naive method | Simple average method | Simple exponential smoothing method |
|---|---|---|---|
| Quality of life index | 2.52 | 4.36 | 2.64 |
| Climate index | 0.87 | 4.15 | 1.08 |
| Cost of living index | 1.45 | 3.17 | 1.46 |
| Health care index | 1.04 | 1.79 | 1.07 |
| Pollution index | 1.27 | 2.18 | 1.28 |
| Property price to income ratio index | 0.96 | 1.66 | 0.98 |
| Purchasing power index | 3.48 | 4.94 | 3.81 |
| Safety index | 1.26 | 2.14 | 1.34 |
| Traffic commute time index | 1.56 | 2.33 | 1.57 |

### K-Means Clustering Algorithm

To cluster the 52 countries and further explore the impact of COVID-19 on social-related indexes, we used the k-means clustering algorithm. The variables used to create patterns were the differences among these nine indexes and whether the countries were developed.

### Bivariate Statistical Analysis

We used the parametric test, Mann-Whitney U-test, and Pearson correlation analysis to find the indexes affected by COVID-19. All statistical analysis were performed by the Python (Version 3.7.9). The significance level set with $p$-value $< 0.05$.

# RESULTS

## Forecasting the Nine Indexes Using the Naive Model

The RMSE values of different methods were compared to judge the error of prediction effect. The naive method showed the best RMSE value. Hence, the naive method was the best model among the three time series models for our data. The results of RMSE of three methods are shown in **Table 1**. We used the naive model to forecast the nine indexes of the 52 countries (**Supplementary Figure 1** and **Supplementary Table 2**). It could be observed from **Table 2** that there was no significance between the actual and forecast value in 2020 of Climate Index (CI), Cost of Living Index (CLI), Health Care Index (HCI), Pollution Index (PI), and Traffic Commute Time Index (TCTI). Therefore, it can be said that COVID-19 has little impact on these indexes. There was significance in Quality-of-Life Index (QLI), Property Price to Income Ratio Index (PPIRI), Purchasing Power Index (PPI), and Safety Index (SI), indicating that during the COVID-19 pandemic, QLI, PPI, and SI were decreased, while PPIPI was increased.

## K-Means Analysis of the Data

It could be noticed from the results that there were 24, 26, and two countries in Cluster, ClusterII, and Cluster III, respectively. The three Clusters showed different characteristics. In Cluster I, the characteristics of the 24 developing countries were the decline

**TABLE 2 |** The results of paired Student's *T*-test for each index.

| Index | *t* | *p* |
|---|---|---|
| Quality of life index* | −4.76 | 1.65e−05 |
| Climate index | −0.98 | 0.33 |
| Cost of living index | −0.13 | 0.90 |
| Health care index | 0.78 | 0.44 |
| Pollution index | 0.83 | 0.41 |
| Property price to income ratio index* | 2.26 | 0.03 |
| Purchasing power index* | −11.90 | 2.44e−16 |
| Safety index* | −2.94 | 0.00 |
| Traffic commute time index | −1.66 | 0.10 |

*$p < 0.05$.

**TABLE 3 |** Clustering of 52 countries.

| | Countries | Indexes | Developed countries | Developing countries |
|---|---|---|---|---|
| Cluster I | 24 | dCLI dCI dPI | – | United Arab Emirates, Saudi Arabia, Lithuania, South Africa, Malaysia, Mexico, Hungary, Argentina, India, Serbia, Turkey, Romania, Bulgaria, Thailand, Brazil, Colombia, China, Philippines, Pakistan, Ukraine, Indonesia, Russia, Egypt, Iran |
| Cluster II | 26 | dPPI dPPIRI dPI | Switzerland, United States, Germany, Sweden Finland, Denmark, Canada, Australia, Austria, New Zealand, Japan, Norway, Netherlands, United Kingdom, Ireland, France, Belgium, Portugal, Spain, Czech, Republic, South Korea, Israe, Italy, Singapore, Greece | Croatia |
| Cluster III | 2 | dQI dSI dHCI | Poland | Chile |

of CLI and CI, and the increase of PI. Except for Croatia, all 25 countries in Cluster II were developed. In addition, developed countries had characteristics of having an increase of HCL and a decline of QLI and SI. Cluster III only included Poland and Chile, which had a decline of PPI and an increase of PPIRI and PI (**Table 3** and **Figure 1**).

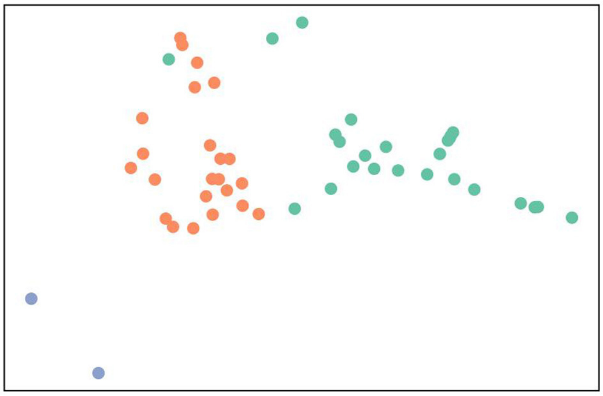

**FIGURE 1 |** Visual clustering map of 52 countries. Cluster I, Cluster II, and Cluster III was indicated by soft orange dots, lime green, and slightly blue, respectively.

**TABLE 4 |** Differences in nine indexes between developing and developed countries.

| Index | t/u | *p* |
|---|---|---|
| dQLI* | −2.10 | 0.04 |
| dCI | 277.00 | 0.06 |
| dCLI* | 3.28 | 0.00 |
| dHCI | −1.81 | 0.08 |
| dPI | 1.80 | 0.08 |
| dPPIRI | 288.00 | 0.41 |
| dPPI* | −3.42 | 0.00 |
| dSI* | −3.15 | 0.00 |
| dTCTI | 0.95 | 0.35 |

*$p < 0.05$.
*d of nine indexes is the forecast of 2020 mid-year minus actual values of 2020 mid-year.*

## Differences in Nine Indexes Between Developing and Developed Countries

Testing the normality of nine indexes, the distributions of the Difference of Climate Index (dCI) and the Difference of Property Price to Income Ratio Index (dPPIRI) is not normal. To analyze this problem, Mann-Whitney U test was used. The independent sample *t*-test was used to analyze the other seven indexes which were all subjected to normal distribution and variance homogeneity.

Compared with developed countries, under the influence of the COVID-19, the decline of QLI, PPI, and SI in developing countries were relatively small, while the decline of CLI in developing countries was large. The results showed that COVID-19 had a great impact on the QLI, PPI, and SI in developed countries, and a greater impact on CLI in developing countries (**Table 4**).

## The Relationship of Nine Indexes Between Developing and Developed Countries

The severity of the pandemic was expressed by cumulative incidence. For developing countries, the hypothesis was tested

**TABLE 5 |** The relationship between nine indexes, cumulative incidence, and the score COVID-safety assessment (SCSA) of countries.

| Indexes | Developing countries | | | | Developed countries | | | |
|---|---|---|---|---|---|---|---|---|
| | CuI | | SCSA | | CuI | | SCSA | |
| | Pearson | *P* | Pearson | *P* | Pearson | *P* | Pearson | *P* |
| dQLI | −0.06 | 0.77 | −0.34 | 0.10 | 0.09 | 0.68 | −0.08 | 0.71 |
| dCI | 0.14 | 0.51 | −0.49 | 0.01* | 0.32 | 0.12 | −0.43 | 0.03* |
| dCLI | 0.60 | 0.00* | −0.27 | 0.20 | −0.17 | 0.43 | 0.11 | 0.62 |
| dHCI | −0.12 | 0.57 | −0.57 | 0.00* | 0.02 | 0.93 | 0.22 | 0.28 |
| dPI | 0.16 | 0.45 | 0.06 | 0.80 | −0.53 | 0.01* | 0.36 | 0.08 |
| dPPIRI | 0.01 | 0.97 | 0.22 | 0.30 | 0.03 | 0.89 | 0.01 | 0.97 |
| dPPI | 0.12 | 0.57 | 0.18 | 0.39 | −0.39 | 0.06 | 0.15 | 0.47 |
| dSI | −0.18 | 0.41 | −0.08 | 0.73 | 0.00 | 0.98 | −0.06 | 0.77 |
| dTCTI | 0.08 | 0.71 | −0.19 | 0.38 | −0.10 | 0.65 | 0.10 | 0.62 |

**p-value < 0.01.*
*d of nine indexes is the forecast of 2020 mid-year minus actual values of 2020.*

with Pearson correlation statistics which showed that there was a significant relationship between the Difference of Cost-of-Living Index (dCLI) and cumulative incidence. The severity of the pandemic impacted on cost of living of residents. However, for developed countries, an inverse correlation between the Difference of Pollution Index (dPI) and cumulative incidence was observed (**Table 5**). Thus, it could be noted that climate conditions can affect the cumulative incidence.

The SCSA reflected the degree of control of the pandemic. For developing countries, there was a significant relationship between dCI, the Difference of Health Care Index (dHCI), and the SCSA. For developed countries, the link between dCI and the SCSA was statistically significant.

## DISCUSSION

Overall, in those countries affected by COVID-19, it can be considered that the quality of life of inhabitants has reduced, the purchasing power of residents of most countries has generally declined, and that the property price to income ratio has increased. Meanwhile, the safety of individuals is threatened (**Table 2**). From **Figure 1** and **Table 3**, the outstanding feature of each cluster that we can find is the degree of national development. Developed and developing countries show different distribution. These features guide us to conduct further hierarchical analysis on the basis of the level of national development.

In this pandemic, developing countries are less affected in the quality of life, purchasing power, and safety than developed countries (**Table 4**). The quality of life of people in developed countries have reduced in such a large-scale pandemic. Research shows that young Americans expressed that there was a decline in the quality of life and an increase in psychiatric distress (31). In our results, the per capital purchasing power of developed countries has declined more significantly than that of developing countries. Of course, this is not the case for all developed countries. Another study stated that more support was urgently needed to alleviate the loss of COVID-19 on the more vulnerable people in consideration of the possible duration of social distancing measures and the associated economic impacts (32). This situation is worthy of the attention of the state aid agencies and psychological counseling departments. Contrary to our result, the safety of society in overall developed countries might be worse in these results (33, 34). The difference might be due to our overall comparative analysis of the selected developing and developed countries. Meanwhile, countries that are seriously affected by COVID-19 should pay more attention to social security. Residents should understand and cooperate with the relevant work of the government to put an end to social disorder and reactionary behavior. In our research, the cost of the living level of developing countries is more severely affected than in developed countries. It has been demonstrated that in developing countries, COVID-19 affected the food security status and the stability of food supply chains (35, 36). It is necessary for local governments to pay attention to the quality of living goods and materials with the aim of alleviate the cost of living of residents.

As shown in **Table 5**, we found that as of 1 July 2020, the COVID-19 notification information shows that in developing countries, the cumulative incidence is positively correlated with the difference of cost-of-living index. There is no doubt that the quality of life of residents have been affected, as it is reflected in medical services, life consumption, work, study, and so on. People in developing countries are faced with heavy loss of family income, affecting their living expenses and quality of life (37, 38). While trying to control the epidemic, relevant governments should also pay attention to the living conditions of all citizens and strive to provide appropriate help and psychological counseling for the people at the bottom of society. In our results, the SCSA is negatively correlated with the health care of residents in developing countries. SCSA is quantified by many aspects of assessment. Moreover, the level of health care could best reflect the SCSA. In India (39), hospital beds and medical equipment were overrun in the face of the huge number of patients infected with COVID-19. People at risk should have confidence and hope for more complete medical facilities. It is important to highlight that good weather conditions are particularly important for the governance and control of the pandemic in our results. Some researches for COVID-19 indicated that temperature, combined with humidity, were the vital risk factors (40, 41). This is consistent with our results. As for the relationship between the climatic conditions and the spread of the virus, it is obviously a huge problem, which is still worthy of further study.

The more developed countries do have better medical facilities and sufficient financial resources, but the degree of development does not mean that they have a faster response and better rational response attitude. In our research, developed countries with aggravated environmental pollution have a higher cumulative incidence (**Table 5**). There is reason to believe that air pollution has a negative effect of COVID-19 (42–44). Meanwhile, poorer climatic conditions often lead to poor control in countries affected by COVID-19 (45–47). Consequently, countries with better development have the reason to think highly of environmental sanitation in order to reply the diffuse of COVID-19.

Through this research direction and data characteristics, we aim to explore the impact of COVID-19 on social-related levels in lots of countries from a macro perspective. The purpose is not to find differences, but to find changes in types of social-related indexes to further guide the formulation of related strategies and measures. We hope that the pandemic can be triumphed as soon as possible worldwide.

## CONCLUSION

We analyze the social conditions of many countries from a macro perspective. We utilize the three time series models to forecast values of 2020 mid-year. Then, by comparing the difference between the forecast and actual values, we aim to finding out which index in countries is more affected by COVID-19.

Our article will contribute to countries with different levels of development pay more attention to social changes and take timely and effective measures to adjust social changes while trying to control this pandemic. Moreover, it also will help countries to realize how social changes can emerge if measures regarding social changes and control pandemic crises are not effective and adjusted to the specific needs of the population.

Through our results, we find that COVID-19 has affected the lives of residents in many ways. On one hand, the quality of life, purchasing power, and safety of people have declined. On another, the property price to income ratio has risen. Our further research shows that the changes of social-related indexes in developed and developing countries are different, which is related to their epidemic control measures and severity. For developing countries, the higher CuI has a great impact on quality of life of residents, and the SCSA has a negative correlation with the health care situation. There is a correlation between CuI and environmental pollution during COVID-19. Last but not least, the influence of climate on the development and control of this pandemic deserves more detailed study. Consequently, exploring the changes of social-related indexes is significative, and it is conducive to provide targeted governance strategies for these countries affected by COVID-19.

There are limitations of this study to consider. First, in order to ensure the accuracy of the results and the reliability of the conclusions, the index data of some countries are relatively imperfect. We have to delete the countries where the data is missing and select 52 countries where the data is complete. Second, in this study, we find that climate index is related to the overall performance of epidemic control in both developed and developing countries. However, due to the different research focuses on this study, this important variable has not been further analyzed and discussed in detail. In the follow-up study, we hope to pay more attention to the influence of climate factors on the spread and control of COVID-19 and seek other databases and methods to specifically explore the economy, health care services, and other aspects of different countries are affected by COVID-19.

## 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

XG, RC, JJ, and SL had the original idea for the study, and with all co-authors, carried out the design. YY provided valuable insight regarding the methodological approach and organization of the manuscript. YM carried out the statistical analysis. YW, TF, JT, and BS reviewed the consistency of data included in the article. XG and RC wrote the first draft of the manuscript, performed the interpretation of the results, and wrote the final version of article in collaboration with SL and JJ. 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/fpubh.2022.793176/full#supplementary-material

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