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PHRP publishes original articles, review articles, brief reports, short communications, editorials, correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

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Editorial

How to deal with the Delta variant this fall

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The United Kingdom declared its "freedom day" on July 19, 2021, and coronavirus disease 2019 (COVID-19)-related lockdown measures were completely lifted. This controversial step was implemented even though the vaccine uptake rate has not reached the herd immunity level (primary vaccination rate, 69.48%; vaccination completion rate, 59.94%). However, a curious phenomenon that must be explained is that, in the United Kingdom, case levels have not rebounded because the herd immunity level of vaccination has not been reached, giving rise to multiple interpretations. Meanwhile, Israel was the first country to carry out wide-scale vaccinations against COVID-19, and its vaccination rate was very high (primary vaccination rate, 67.33%; vaccination completion rate, 62.46%) [1], which led to a complete lifting of social restrictions. However, the spread of COVID-19 in Israel has recently increased to the level of February 2021, so mandatory measures regarding social distancing and mask-wearing have been reintroduced, and third vaccinations for immune-suppressed patients are being promoted.

Although the United States (US) has pushed ahead with vaccination, it has not reached the level of herd immunity due to vaccine hesitancy (primary vaccination rate, 58.72%; vaccination completion rate, 49.97%) [1]. The government eased anti-COVID-19 policies before the vaccination rate was high enough to protect the community, causing confusion and leading to the spread of the Delta variant in areas with many unvaccinated people, increasing the number of confirmed patients and deaths. In response, it has been necessary to reintroduce strengthened non-pharmaceutical interventions (NPIs) [2].

In the Republic of Korea, where vaccination has not yet reached the level of herd immunity (primary vaccination rate, 41.7%; vaccination completion rate, 15.4%), the scale of the fourth wave of the epidemic has expanded to the point that around 2,000 new cases are being reported daily. The burden of COVID-19 is increasing [3].

Globally, the Delta variant is dominating, challenging the effectiveness of vaccination. It is first necessary to confirm whether the main cause of the fourth wave of the epidemic in Korea is the Della variant. And whether the fourth wave is related to loosened measures during summer vacation and the exhaustion of health workers.

First of all, raising the vaccine uptake rate is an urgent priority above all else. Even if variants of COVID-19 with novel mutations are spreading in the community, the current vaccines can alleviate the burden on the medical system by reducing the overall hospitalization and mortality rates. Therefore, securing vaccines is very important and private medical institutions must provide immunization services to promptly raise the vaccination rate.

In a situation where outbreak clusters are continuing and many cases involve an unclear

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contact history, NPIs remain an effective preventive measure until the vaccination complete rate rises to 60% or more. Misguided messaging can cause confusion among the public, like in the US. The introduction of premature mitigation policies without evidence and in the absence of a high vaccine uptake rate will lead to an absolute increase in the number of patients, which will increase the number of fatalities.

Third, mutations have resulted in an increased transmission rate, meaning that the expanded reproduction ratio has changed from 2–3 to 4–6; thus, the vaccination rate required to establish herd immunity is likely to increase to 80% ($1-1/R_0$). In addition, children under 12 years of age (about 5.72 million people, as of 2015 in the Republic of Korea) cannot currently be vaccinated. Therefore, if the Delta variant becomes predominant, herd immunity will be difficult to achieve. In particular, children under the age of 12 should be protected by wearing a mask and social distancing. It is urgently necessary to take rapid steps to vaccinate family members of unvaccinated children and teachers to block the epidemic in schools, as children can transmit the infection.

Fourth, although peer review has not been conducted, initial findings suggest that the Alpha and Beta variants present higher rates of severe infection and mortality than the original strain of COVID-19, and the Delta variant is even worse in this regard [4]. A Canadian research report has suggested that an increase in mortality and a shortage of intensive care units may occur nationwide due to the prevalence of the Delta variant. Therefore, wearing masks and social distancing in unvaccinated risk groups as NPIs should be more rigorously implemented, along with preparing ICU beds.

Fifth, variants cause re-infection and breakthrough infections, which occur even after natural infection and vaccination. However, the hospitalization rate and mortality rate are reduced in patients who experience COVID-19 breakthrough infections. Since antibody titers can decrease from 6 months after vaccination, high-risk individuals who received the initial vaccination should take measures against re-infection in the fall. In other words, long-term care facilities that implemented early vaccination initiatives should consider revaccination, while simultaneously blocking the spread of the Delta variant by expanding monitoring and limiting visits.

Sixth, if vaccination uptake increases, the number of patients will naturally decrease. Nonetheless, even if the alert level is downgraded, there is a very high possibility of cluster outbreaks at mass gatherings, such as sports games and events. However, essential businesses and those related to normal life should create a couple of alternatives of ICT centered on rapid testing, contact tracing, and isolation rather than social distancing and movement restrictions.

Finally, international cooperation for securing vaccines is important. Ultimately, vaccinations must be carried out worldwide as a joint effort to prevent the emerging variants and cross-border transmission. The contribution of Korean industry to the scaled-up capability of vaccine production is important, and vaccine aid for low- and middle-income countries with extensive travel to and from Korea is also necessary.

In response to COVID-19, individual liberty and human rights, economic losses, and the strictness of infection control must depend on vaccine uptake, the intensity of COVID-19 spread in the community, and the participation of the public. Political and policy considerations in decision-making are very difficult choices. Such decision-making is an art that requires an evidence-based scientific approach, including precise monitoring and surveillance, as well as simulations and modeling.

Notes

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Review Article

Scrutiny of COVID-19 response strategies among severely affected European nations

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ABSTRACT

Although the health care systems in Europe are considered the global benchmark, European nations were severely affected by the coronavirus disease 2019 (COVID-19) pandemic. This manuscript aimed to examine the strategies implemented to combat the COVID-19 pandemic by France, the United Kingdom, Spain, Italy, Germany, and Russia and their outcomes in terms of the number of cases, testing, and deaths. This is the first review of its kind that extensively analyzes the preparedness, mitigation, and response strategies against the COVID-19 pandemic adopted by these nations. This paper further suggests a strategic preparedness model for future pandemics. From the analysis, we found that a decentralized approach, prompt decision-making and timely execution, coordination between local health authorities, and public participation in the implementation of strategies could substantially reduce the case fatality rate. Nations with a high percentage of gross domestic product invested in the health sector, as well as more nurses, physicians, hospital beds, intensive care unit beds, and ventilators, better managed the pandemic. Instead, nations that postponed their pandemic response by delaying tracking, tracing, testing, quarantine, and lockdown were badly affected. The lessons learned from the present pandemic could be used as a guide to prepare for further pandemics.

Keywords: Coronavirus; COVID-19; Europe; Health policy; Pandemics

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Introduction

On December 31, 2019, health authorities from Wuhan, China informed the World Health Organization (WHO) about an increase in pneumonia cases of unknown origin. On January 7, 2020, Chinese health authorities detected the novel coronavirus as the causative agent of the pneumonia cases, and the virus was initially named "2019-nCoV," which was later renamed

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as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease as coronavirus disease 2019 (COVID-19). Owing to the virulence and the contagious nature of the virus, the WHO declared the novel coronavirus outbreak a public health emergency of international concern on January 30, 2020 [1,2]. With the steep rise in infections outside China, the WHO declared the outbreak to be a pandemic on March 11, 2020 [3].

On January 24, 2020, France was the initial country in the European Union (EU) to report a coronavirus case [4]. Since then, there has been a steady rise in the number of cases in the EU countries. As of March 10, 2021, a total of 35,636,156 cases had been reported from the EU, wherein 846,378 people succumbed to the illness [5]. The European lifestyle of taking a summer holiday abroad and "mass movement" of holidaymakers soon after the relaxation of draconian lockdown measures has been a significant factor in spreading the disease. While some countries were hit harder during Europe's first wave, the second wave was felt more widely and included countries that largely escaped the initial outbreak. Although vaccination against COVID-19 started in December 2020, COVID-19 maintains its foothold in EU countries.

Nations that prudently executed surveillance, quarantine, lockdown, and isolation were able to tame the virus, whereas those that delayed were severely affected by the pandemic [6]. The Global Health Security (GHS) index ranks countries based on their preparedness to counteract epidemics and related capabilities. It was believed that the nations that ranked top in the GHS index would manage the pandemic well, but the real scenario was different. This review aimed to examine the COVID-19 containment strategies employed by the worst-affected European countries and their impact on COVID-19 management, which could guide other nations in planning their strategies against upcoming pandemics.

Materials and Methods

A thorough literature search was performed to retrieve the containment strategies of the selected nations between January 2020 and February 2021, using Science Direct, Scopus, MEDLINE, Google Scholar, and the official websites of the WHO and the concerned nations. The keywords were COVID-19, pandemic, SARS-CoV-2, preparedness, and containment strategies. Among the European nations, the most affected countries (Russia, Germany, Spain, France, Italy, and the United Kingdom [UK]) were selected. The available data from these countries included COVID-19 cases (date of the positive index case, number of tests performed, number of positive cases, and deaths), mitigation (availability of human resources, personnel protective equipment arranged, number of hospital beds including critical care beds with facilities for mechanical ventilation and other strategies) and response (screening and isolation facilities, implementation of lockdown, public relations, and restricted travel). Since mortality is a precise appraisal of the progression and outcome of a pandemic [7], with which the management strategy of a nation can be evaluated, the death rate (per million population) was fixed as the primary endpoint for evaluating the outcome of measures taken by these 6 selected nations.

Preparedness and Containment Strategies

The victory of a nation over a pandemic strongly depends upon the existing health care system (in terms of health infrastructure, early mobilization of available resources, services rendered by trained health care professionals), expertise in dealing with an emergency, and the early mitigation strategies adopted. The response of each nation to the pandemic in terms of identifying the severity, reducing the incidence of infections and the mortality rate, supporting health care professionals, and safeguarding vulnerable populations exhibits the preparedness of the nation for managing the pandemic. Adequate preparedness not only reduces the strain on the health care system, but helps to cope promptly with the health consequences of the pandemic.

France

France reported the index COVID-19 case on January 24, 2020, which was also the primary case reported in the EU as a whole [8]. Unchecked communal gatherings, transmission of infection through sailors and airline carriers, and local municipal elections paved an easy way for the infection to spread among the French population [8,9]. On January 27, 2020, a health crisis center was established and the Pasteur Institute developed a rapid diagnostic kit. With the aim of preparing the health care system to face a pandemic of global concern, on February 13, 2020, the organization plan for the response of the health system (ORSAN) was activated [10]. On March 5, 2020, gatherings of more than 5,000 people in enclosed spaces were banned, and the number of people permitted to gather was further reduced in the following days. A ban of ships carrying more than 100 people calling in or anchoring in inland and territorial waters came into force on March 14 [11]. A lockdown was imposed on March 17, 2020 and later extended until May 11, 2020 (Figure 1A) [12]. Commonly employed preventive strategies, such as physical distancing, personal hygiene, limitation on public gatherings, use of face masks in public spaces, periodic ventilation of closed spaces, and isolating

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cases with symptoms and testing them as early as possible, were enforced by the health authorities [13]. With the successful implementation of these containment measures, the number of cases per day was limited to 120 on May 17, 2020.

By the end of July 2020, people's complacency regarding hygiene measures during the summer and lifting of restrictions led to the emergence of the second wave, and France reported its highest number of COVID-19 cases on November 7, 2020 (86,852 cases) since the beginning of the pandemic [14]. At the end of June 2020, the incidence rate, effective reproduction number (R), and reverse transcription-polymerase chain reaction (PCR) positivity rate were 5.14 (per 100,000 population), 0.99, and 1.44% respectively, but by the end of November 2020, these values increased to 491 (per 100 000 population), 1.4, and 20%, respectively [15]. With the surge in coronavirus cases, further restrictions were imposed on public movement and social gatherings, such as night curfews, lockdowns, and border closure to nations outside the EU. As of March 10, 2021, France still has weekend lockdown measures in place in active circulation zones. Witnessing a resurgence of coronavirus cases, hospitals were geared up with more intensive care unit (ICU) beds to accommodate new cases [16]. On March 10, 2021, France had a total of around 3.9 million coronavirus cases, or approximately 60,624 cases per million population (Figure 1B) [5].

Germany

Germany was not among the EU countries initially hit by COVID-19. Germany reported its index case on January 27, 2020. Taking heed from other severely hit countries, Germany's risk-averse attitude and proactive behavior presumably enabled limited draconic measures in the country compared to other EU countries. By mid-March, stringent measures to contain the pandemic were enforced, including a "contact ban" that delimited public assemblage to 2 people (outside families), physical distancing measures of at least 1.5 meters, and shutdown of schools and non-essential businesses [17]. However, a curfew was never imposed. Travelers arriving in the country from high-risk nations had to quarantine for a fortnight and were urged to furnish information about potential exposure along with their contact information. Borders to adjoining countries were closed on March 15, and a lockdown was imposed until April 19, 2020 [17].

The German government made it mandatory for all health care providers to notify any suspected cases of COVID-19 to local public health authorities within 24 hours. Germany's national pandemic plans were in accordance with the guidelines of the Robert Koch Institute (RKI), and they mandated the publication of periodic situation reports for national and international public health zones. Having a response plan in place and being a federalized country allowed the government to counteract the pandemic quickly. Protocols for testing, case detection, contact tracing, and treatment strategies were prepared even before the index case was reported [18]. Having laboratories with proficiency, accreditation, and machinery to conduct PCR assays and announce diagnoses, Germany scaled up their testing capacity.

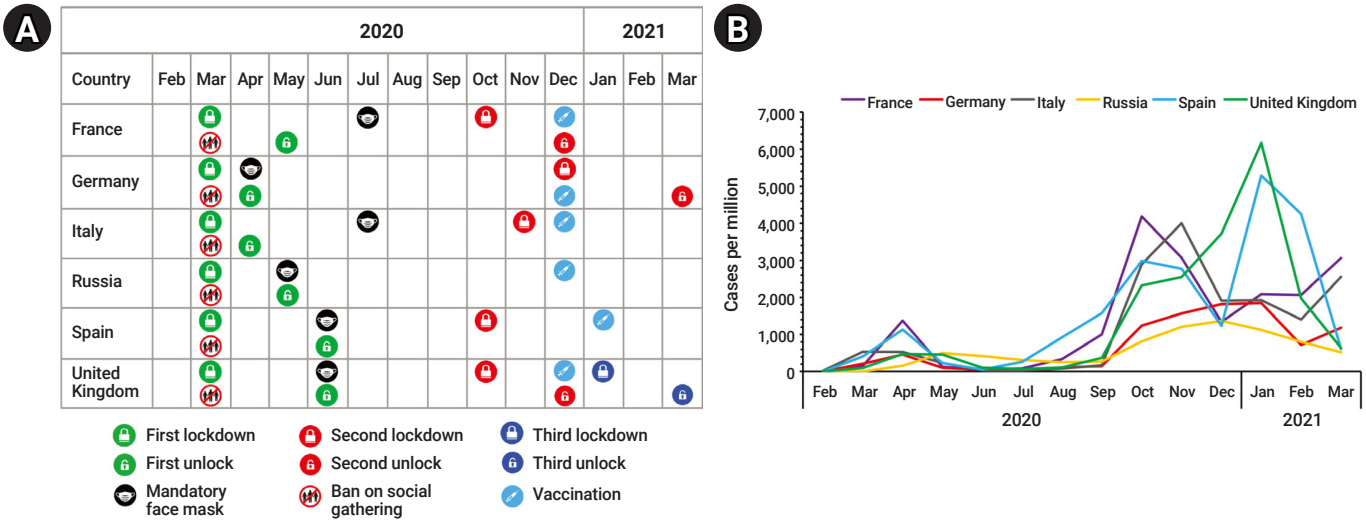

Figure 1. (A) Timeline comparing containment measures against coronavirus disease 2019 (COVID-19). (B) Timeline comparing coronavirus cases per million population among the selected nations.

Testing was made free of cost to everyone upon medical or epidemiological indication through the Coronavirus Relief Bill. As of March 10, 2021, Germany reported 30,164 cases per million population and 873 deaths per million populations, which signifies the quality of Germany's health care system (Table 1).

United Kingdom

The UK refers to a political union between England, Wales, Northern Ireland, and Scotland. The UK reported its index case of COVID-19 on January 31, 2020, even though screening for travelers from Wuhan, China started by late January at Heathrow airport [19]. Upon early reports of the outbreak from Wuhan, Public Health England, the main agency responsible for health advice and directives, raised the risk level of the pandemic from "very low" to "low" and subsequently to "moderate" following declaration of the outbreak as a public health emergency of international concern [20]. The governmental response against the pandemic was based on the national pandemic influenza plan of 2011, which delivers data about the expected impact of the pandemic and provides certain norms to aid in planning the pandemic response [21]. Later, written guidelines were made available at all airports for unwell travelers, and people returning from affected countries were advised to self-isolate for a fortnight if they developed flu-like symptoms [21]. Authorities urged the public to refrain from non-essential travel and to avoid social gatherings. On February 10, the government enacted the Health Protection (Coronavirus) Regulations-2020 act, which provided discretionary powers to the authorities to impose quarantine under threat of legal proceedings and to impose restrictions on people and situations leading to spread of the virus. The government-imposed closure of public places (pubs, restaurants, indoor sports and other leisure facilities) under the provisions of these regulations, and hospitals started drive-through testing centers for COVID-19 [22].

Although the UK initiated testing for detecting coronavirus cases in January 2020, it conducted very few tests until the middle of March. As of March 31, 2020, the country's testing rate were only up to 5,000 tests in a day; a much lower figure than in other European countries [23]. A lockdown was not imposed until March, 2020; later, a "stay at home" order was announced to save lives and protect the National Health Service (NHS) staff. The government passed the Coronavirus Act-2020 on March 19, which granted the government power to regulate areas of health service, social care, and public activities including local councils [24].

Until March 3, 2020 a definitive action plan was not drafted by the government despite witnessing early spread of virus throughout February. A public health information campaign with the slogan "Catch it, bin it, kill it" was launched to limit the spread of the virus within the country by facilitating behavior change among the public [25]. The 2020 UK local elections were postponed for a year on March 13 as a precautionary measure. On April 2, the government announced a "five-pillar" strategy to scale up virus testing in the UK, which included intensifying swab testing in public labs and NHS hospitals, nationwide surveillance, and capacity-building, to have 100,000 tests a day. Although the UK enforced containment measures against the spread of COVID-19, the months preceding September observed some relaxations in imposed restrictions, including the reopening of higher schools, which led to a resurgence of infections during September. Owing to all these factors, the government was forced to impose a second lockdown (Figure 1A). On December 14, 2020, the health authorities of the UK reported a new SARS-CoV-2 variant, "SARS-CoV-2 VUI 202012/01" (variant under investigation, year 2020, month 12, variant 01), to the WHO; this variant is much more transmissible than the previous strain [26]. As of March 10, 2021, the UK reported 4,234,924 cases and 124,987 deaths from COVID-19. Notably, the UK has the highest deaths per million among the nations investigated herein (Table 1).

Spain

The first case of COVID-19 was confirmed in Spain on January

Table 1. COVID-19: incidence, CFR, and recovery Index of selected nations

GHS rank	Country	Deaths per million population	CFR (%)	Recovery index
2	United Kingdom	1,834	2.9	66.79
11	France	1,370	2.3	60.30
14	Germany	873	2.8	72.62
15	Spain	1,539	2.1	54.38
31	Italy	1,669	3.4	58.66
63	Russia	622	2.0	70.38

Data as on March 10, 2021 (source: http://www.worldometers.info).
COVID-19, coronavirus disease 2019; CFR, case fatality rate; GHS, Global Health Security.

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31, 2020, after a German traveler tested positive in La Gomera, Canary Island. Shortly thereafter, all direct flights from affected nations to Spain were canceled from March 10 to March 25, 2020, and a lockdown was imposed on March 14, 2020, which was later extended through June 21 (Figure 1A). Borders were closed, and all non-essential employees were asked to stay at home from March 30 to April 9, 2020 to flatten the curve and contain the pandemic [27]. A COVID-19 diagnostic application, CoronaMadrid, was developed by the Spanish government; this self-assessment application encouraged COVID-suspected nationals to perform an assessment when they thought they had COVID-19 symptoms. People received instructions and recommendations about COVID-19, through the same application [28]. On October 20, 2020, Spain became the first European nation to report 1 million cases. With the resurgence of coronavirus cases after an initial decline, stringent measures were employed, including a partial lockdown (October 21, 2020), declaration of emergency (October 25, 2020), imposition of overnight curfew, and reinforced quarantine. Spain still dominates the EU in the number of coronavirus cases per million population (67,963) (Table 1) [29]. The scarcity of ICU beds, ventilators, and numerous health care workers falling ill led to a high death rate (1,539 deaths per million population) [29]. Among the 6 European countries analyzed, Spain still has the lowest recovery index (54.38) (Table 1).

Russia

The world's largest country by area, Russia reported its index COVID-19 case on January 31, 2020 [30]. Russia prepared for the ongoing pandemic through repurposing existing facilities, building new hospitals, procuring the requisite diagnostic and resuscitation equipment, and embarking upon intense and swift retraining of their health care workers. When the outbreak began, the health administration created more than 1,77,000 beds exclusively for COVID-19 patients, including 25,000 ICU beds [31]. In collaboration with the Russian health authorities, the Ministry of Defense created 800 multifunctional bedded medical centers in several regions of Russia to treat COVID-19 patients. Around 2,000 highly skilled doctors, nurses, and other medical staff were deployed at various medical centers. The national government allocated 8.8 billion Russian rubles (approximately 120 million United States dollars) to set up these infectious disease centers [32].

In an unprecedented measure, Russia suspended all national and international regular flights except rescue flights bringing Russian citizens by March 27, 2020 [33]. Trains to China and North Korea were also suspended and work visas to Chinese citizens stopped being issued on February 19, 2020. On March 30, in a bid to curb the spread of COVID-19, Russia closed its borders completely except for goods and cargo [34]. In October 2020, owing to the surge in coronavirus cases, a night-time curfew was implemented and the use of face masks was made mandatory. A nationwide aggressive testing regimen was put in place, which was later appreciated by the WHO. On December 15, 2020, the nation started a vaccination program against COVID-19 to halt the rise in cases (Table 2). On March 10, 2021, Russia had conducted more than 113 million COVID-19 tests (779,571 tests/million population) [29]. Russia has 29,873 cases per million population (Table 1) [29]. Among the severely affected European countries, Russia has the lowest death rate, with 622 deaths per million population and a case fatality rate (CFR) of 2%, which is the lowest among the nations studied (Table 1) [35].

Italy

COVID-19 entered Italy on January 31, 2020, through 2 Chinese tourists. With the identification of the primary coronavirus cases, a state of emergency was declared and all flights to and from China were suspended. Since the first confirmed case, emergency medical number-112 was designated exclusively for COVID-19, and the emergency medical team performed a primary assessment, screening, counseling, or hospitalization based on the situation at hand.

Table 2. COVID-19 vaccination status in the selected nations

Country	Start date (mm/dd/yyyy)	Vaccine manufacturer	Population vaccinated (million)	Doses administered per 100 people
United Kingdom	12/12/2020	Pfizer/BioNTech, AstraZeneca, Moderna	23.77	35.02
France	12/27/2020	Pfizer/BioNTech	5.97	8.80
Germany	12/27/2020	Pfizer/BioNTech	8.16	9.74
Spain	01/04/2021	AstraZeneca	4.85	10.37
Italy	12/27/2020	Pfizer/BioNTech	5.78	9.56
Russia	12/15/2020	Sputnik V	6.69	4.59

Data as on March 10, 2021 (source: ourworldindata.org).
COVID-19, coronavirus disease 2019.

Initially, Italy did not screen contacts linked to confirmed cases or recent travelers to outbreak regions until they showed symptoms. By February, partial quarantine was imposed on identified clusters, and on March 9, 2020, a quarantine was imposed all over the country. A nationwide lockdown came into force from March 10 until April 13, 2020 (Figure 1A). As a primary initiative, all the residents of Vò (a commune in Italy) were screened, including those who did not have symptoms, which allowed them to quarantine and reduce the spread of the virus. Technological advances, specifically artificial intelligence-powered robots, were deployed in hospitals to screen and care for patients.

With a loosening of containment strategies, Italy witnessed a second wave of the pandemic by July 2020. Shortly thereafter, a state of emergency was declared, use of face masks was made mandatory in public gatherings, and demonstrations and meetings were banned. The health system was restructured and expanded with the installment of sophisticated ICU beds. Millions of doses of flu vaccine were procured to be distributed among the public [36]. All schools and universities remained closed from October 15, 2020 until October 30, 2020. By the end of October, a regional lockdown was imposed in affected areas. Although vaccination was started on December 27, 2020, it was not sufficient to control the increasing number of coronavirus cases, as the initial doses of vaccines were administered to health care workers and immuno-compromised people. On March 10, 2021, Italy had 51,711 cases per million population and a high CFR of 3.4% (Table 1) [29]. It is predicted that the situation will further deteriorate with the invasion of newer virus strains (e.g., the UK, Brazilian, and South African variants) and scarcities in vaccine supply [37].

Discussion

The actual response of each country to COVID-19 did not correlate well with their respective GHS index (Table 1). It was predicted that the nations occupying the top positions in the GHS index would perform better during a pandemic. However, in the real scenario, the nations with well-established primary health care that employed advanced health technology with transparent communication demonstrated a remarkable performance. This was also evident in their respective global COVID-19 recovery index (GCI). The daily recovery status of patients from COVID-19 is taken into consideration to evaluate the GCI [38]. Germany and Russia stood high among the nations studied in terms of the GCI (Table 1). The measures followed by these nations could serve as a guide for other nations in the present and upcoming pandemics.

Until the end of July 2020, France maintained the number of coronavirus cases under control, whereas there was an upsurge in the number of cases starting in August 2020 [39]. Digital technology was aptly employed, wherein precise data regarding the pandemic were procured and communicated with the public, and contact tracing was reinforced with the help of technology. Amidst the upsurge of coronavirus cases, numerous religious meetings and municipal elections were held, leading to a further escalation of cases [9]. Even though there was a change in the political structure after elections in July 2020, the health care policies pertaining to social care remained unchanged. France experienced one of the world's worst outbreaks of COVID-19 in the spring, and cases increased after the first phase of the lockdown (March 16, 2020 to May 11, 2020). Despite the exquisite French public health system, the operation of top-down, centralized control measures slowed their response to the fast-moving crisis. Owing to their shortage in the logistic capacity in terms of scanty accredited laboratories and reagents for testing; widespread testing could not be practiced, resulting in 1370 deaths per million population (Table 1) [5]. The number of physicians per 1,000 population was also very low (3.3 per 1,000 population) when compared to France's counterparts (Figure 2). In a recent study published, only 31% of persons with having COVID-19-like symptoms sought medical care despite governmental recommendations [40]. France hopes to contain the spread of pandemic through its vaccination program [41].

The index case of coronavirus in Germany was reported from Munich, which is home to a biosafety level-3 lab that had the capacity to perform PCR testing shortly after China released the genetic sequence of the coronavirus. By the time initial clusters of cases were brought under control, protocols were established and in place for diagnosing, isolating, and treating COVID-19 patients safely. Germany was quick to lockdown (Figure 1A) and scaled up its testing capacity, and then repeatedly adapted this program to respond to changes in the epidemic dynamics. Widespread testing is acknowledged as the primary reason for a lower number of deaths per million population (873 deaths) in Germany, as it enabled the detection and management of cases at an earlier stage. The decentralized approach to managing a pandemic was a good way to deal with a quickly changing pandemic. This was accomplished by collaborating with local health authorities through the RKI, which tailored responses according to local needs. Being the fourth-largest economy in the world, Germany spends roughly 11% of its gross domestic product (GDP) on health care (Figure 2) [42]. In the EU, Germany has the highest number of hospital beds (8.3), nurses (13.2) and physicians (4.2) per 1,000 people (Figure 2) [43,44]. When COVID-19 arrived in Germany, ICU bed capacity was increased from 12,000 to 40,000

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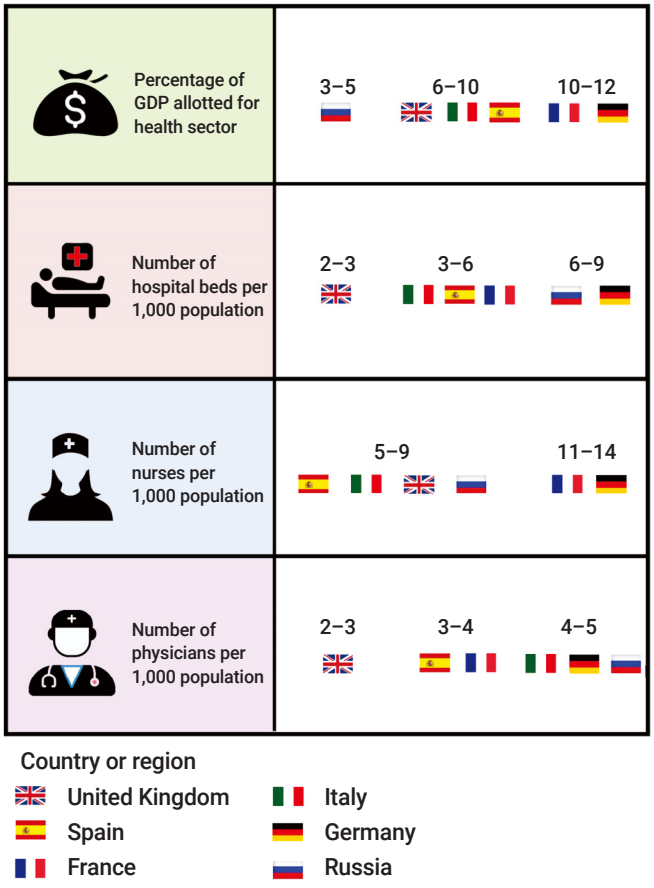

Figure 2. Existing health system capacities of the selected nations.
GDP, gross domestic product.

beds quickly. This is considered the primary reason why Germany achieved a brilliant recovery index (72.62) (Table 1), which was the highest among the nations studied. Citizens and permanent residents of Germany are covered through health insurance. Endowed with ample human resources and physical infrastructure, Germany possesses a robust health care system, which—in combination with the rapid initial advances that were made after the detection of COVID-19—augmented Germany's efficacious containment strategies. The restrictions imposed by the government were wholeheartedly accepted by the public and became vital in curtailing the progression of the pandemic. The federal system of the government focused on collecting and analyzing the data and transparently communicating outcomes to the people, leading to unusual levels of public support. Judicious decision-making at the highest level of the government, relying on expert advice from scientists mixed with the trust that the public holds in the government, enabled Germany to manage the crisis swiftly.

The GHS index ranks countries based on their preparedness for epidemics and related capabilities. Although the UK occupies the second position in GHS ranking among all 195 nations, the UK's health system was overstretched well before the pandemic hit the UK (Table 1). Among the UK's 19 counterpart nations, the UK had the third-lowest number of available hospital beds per 1,000 population [45]. The nation believed in and propagated herd immunity as a permanent solution to contain the pandemic, despite the WHO's warning regarding tracking, tracing, and isolating COVID-19 cases. In response to widespread criticism regarding the government's delayed approach to initiate mass testing and tracing of infected COVID-19 cases, attempts were made to increase the testing capacity [46]. With the nation's precarious delay in combating the pandemic, the CFR rose to 11.56%, which was much higher than the global average and the average among the UK's European counterparts. The health care capacity in terms of beds was also very low (2.5 per 1,000 population) when compared to the other selected nations (Figure 2). Although a contact tracing app was developed through the NHS in the first week of May 2020, alleging security reasons, its implementation was suboptimal [47]. However, since September 2021, with the resurgence of the second wave of the virus and the emergence of the mutated variant (UK strain), the government was forced to tighten containment measures, including lockdowns, after a phased easing of imposed restrictions. On December 2, 2020, with the arrival of the Pfizer/BioNTech vaccine against COVID-19, the UK was the first country to approve a vaccine for use in humans. By December 8, an immunization program was launched [48]. As of February 26, 2021, 3 vaccines have been approved to be used in the UK, which has announced the goal of vaccinating all UK nationals by the end of July 2021 (Table 2).

The COVID-19 pandemic tested the integrity, strength and pandemic preparedness of the Spanish health care system. A health alert and emergency coordination center was established in 2004, with the aim of identifying and controlling situations causing health crises (national and/or international) that significantly affect the public health [49]. The response towards the COVID-19 pandemic signifies the importance of scrutiny of the Spanish health care system, which was believed to be a strong health sector. The increase in the number of cases was attributed to the letdown of both societal and governmental norms. Basic infection control measures, like social distancing and use of face masks, were erroneously not followed during the initial phases of the pandemic [50]. The latest survey results from the WHO and Spain's Carlos III Institute of Health revealed that almost half of the Spanish citizens still believed that there was only a low to medium risk of contracting the virus

through social gatherings [51].

The economic crisis of 2008 debilitated Spain's public health and health system capacity. The health care system was shrunken, leading to a severe reduction in the number of health care providers. The health care system operated with an extremely low level of personnel (5.9 nurses per 1,000 population), whereas the EU is reported to have 9.3 nurses per 1,000 population (Figure 2) [52]. A decentralized health care system under 17 autonomous communities [53] and the presence of a significant proportion of the elderly population resulted in a mortality rate of 1,539 per million population (Table 1). Moreover, studies have suggested that Spain might have underestimated the infection and mortality rates due to the negligence in reporting and lack of a robust testing strategy [54]. The use of low-quality testing kits is also considered a reason for the upsurge in the number of cases.

Since Russia shares China's land boundaries, Russia had the potential to become a major focus of epidemic spread. With the advent of COVID-19 in China, numerous systematic steps were implemented by the Russian Federation, including administrative, organizational, technical, sanitary, and hygienic measures. These initiatives have given Russia to prepare to handle the situation, divert human and fiscal resources, and boost the health care system's readiness to deal with the epidemic. Russia is the only nation in which the public health service is kept accountable for its citizens' sanitary and epidemiological welfare. The system is well equipped with approximately 100,000 trained professionals, including epidemiologists, researchers, scientists, and technicians. The sanitary-epidemiological service succeeded in preventing the primary transmission of COVID-19 from mainland China, which further provided adequate time to prepare and reorganize the health care facilities to combat the pandemic. Airports, railway stations, and other public transport facilities were well equipped with sanitary quarantine centers (SQC), in which epidemiologists worked relentlessly to check the occurrence of any infectious disease in the Russian Federation. SQCs played a pivotal role in the prevention of the spread of COVID-19 in Russia [55].

The Russian health care system's response towards COVID-19 was deeply ingrained through its historical inheritance of the Semashko health system (named after Dr. Nikolai Semashko, one of the major founders and organizers of the public health system in the Soviet Union), which already emerged victorious by successfully delivering universal health coverage to the Russian citizens by 1930. The Semashko tradition has made the therapeutic health care system inclined towards institutional-based medical services. Consequently, Russia's physician-to-population ratio (4 per 1,000 population) and available hospital beds (7.1 per 1,000 population) have been quite high in comparison to its European counterparts for decades (Figure 2) [56]. This has helped the Russian health care system launch a better institutional response during the pandemic. Other judicious responses like timely border closure, the long experience of the public health care system in controlling infectious diseases like plague, enhanced testing capacity, economic stimulus measures, low population density across the country, and digitalization in public health may have effectively limited the fatality rate compared to other nations. The overall governmental measures against COVID-19 met the requirements of quality, availability, and provision of health care services, drugs, and other consumables. The endurable investment in health care and the prudent implementation of measures combating COVID-19 helped Russia take the upper hand over the pandemic by limiting the CFR to 2% (Table 1) with a recovery index of 70.38 (Table 1).

Although Italy was placed in the 31st position in the GHS index ranking, the Italian health system occupies the second position in overall health system performance among 191 countries. The Italian constitution ensures the right to health and free medical to all its citizens, based on the principles of universality, equality and equity through Article 32. Health care in Italy is delivered through 3 different levels of health services: primarily through collective preventive and public health (including preventive measures through vaccinations and health promotion campaigns); secondly through district assistance with health and social health activities and services (e.g., outpatient services, home care, rehabilitation, and old age homes); and thirdly through hospital services [57]. With expenditures of 8.8% of the GDP on health, Italy has not been able to provide adequate health care to the public due to the increasing number of elderly people (Figure 2). Moreover, the Italian health care system relies on a triage policy, wherein critically ill patients receive health care rapidly, whereas less critically ill patients have to wait for their turn. Unfortunately, the majority of the COVID-19 patients are either asymptomatic or have mild to moderate symptoms. During the early stage of the pandemic, the Italian health care system failed to identify these patients, which resulted in a surge of COVID-19 cases. This strategy stressed the already exhausted health care system and caused the situation to deteriorate. Furthermore, the highly decentralized health care delivery system, lack of proper testing strategy, shortages in the supply of personal protective equipment for health care providers, lack of preparation to face a pandemic, and lack of proper protocols for the initial management of COVID-19 patients made the situation arduous [58,59].

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What Steps Can Nations Follow?

Owing to increased encroachment into wildlife habitats, the COVID-19 pandemic will not be the last time a virus would threaten human existence [60]. The unprecedented COVID-19 pandemic has challenged existing health care systems and revealed their efficiency (or lack thereof). The nations that were able to contain the virus have reiterated the perennial truth that multi-level coordinated and comprehensive strategies are imperative to combat any outbreak from progressing into a pandemic. It is imperative to note that a reasonable proportion of GDP investment in health, including the health system capacity in terms of the number of physicians, nurses, and hospital beds served as a feature demarcating nations' pandemic responses (Figure 2). Hence, nations could adopt sensible efforts for capacity-building and resource allocation for the health sector.

The strategies ought to pay due attention to all phases of the preparedness and response framework (prevention, preparedness, response, and recovery) (Figure 3). In the academic curriculum, emphasis should be placed on the significance of having a balanced human ecosystem and the repercussions that could result from encroachment into wildlife. Biosafety labs should be relentlessly monitored and reinforced to prevent any accidental or intentional entry of viruses into the outside world. As a dilemma exists regarding the origin of SARS-CoV-2, the recent G7 summit reiterated the need for a better understanding of the origin of the virus [61]. The public must be educated and should incorporate health behavior practices into day-to-day life. All of these steps could prevent pandemics.

During the preparedness phase, epidemiological institutes should be built, which could help with the swift identification of a virus and its characteristics. It is imperative for every nation to have tailored pandemic preparedness plans, and the plans should be tried out during inter-pandemic periods to evaluate their efficiency and flaws. As primary health centers (PHCs) remain the initial contact between patients and the health care system, PHCs should be

Figure 3. Global strategic model for future pandemics.
PHC, primary health center.

fostered. Boosting industrialization could help nations to be independent in fulfilling their needs [62,63]. Dependence on other nations for commodities resulted in exportation and importation of the virus on a global scale.

In the response phase of a pandemic, communicating "what is unknown" along with "what is known" to the general public would ensure their cooperation and trust towards the government. A nation needs to act in accordance to its pandemic preparedness plan or in accordance to evidence-based practices [64,65]. Resources should be mobilized in accordance to priorities and needs. Active surveillance should be carried out to identify all cases. Adequate investment in technology would help with all these response strategies.

Immunization and health behavior reforms, such as hand washing, mask wearing, and social distancing, could curtail transmission. An economic relief package would ameliorate the downswing in business and trade. These measures are key in the recovery phase of the pandemic.

Limitations

Written health care policies of the described nations were not explored in detail. Most of the data retrieved were from online sources and the ground reality may vary. However, this was a meaningful appraisal of the COVID-19 pandemic preparedness and response strategies of the most strongly affected European countries.

Conclusion

Although the strategies in combating the pandemic were identical among European countries, the timing and rigor of their execution led to differences in the number of coronavirus cases and CFR. Nations with a centralized, government-run health care system and a decentralized local health care execution fared better in response to the surge in coronavirus cases. The responses were directed and backed by timely political will. Furthermore, in many nations, early adoption of stringent containment strategies reduced the transmission speed. None of the EU countries were completely prepared to deal with the COVID-19 pandemic, as had been widely predicted. Nations with a robust health care infrastructure, sufficient health care human resources, and a high percentage of GDP invested in the health sector will effectively combat future pandemics.

Notes

Ethics Approval

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

All data generated or analyzed during this study are included in this published article. For other data, these may be requested through the corresponding author.

Authors' contributions

Conceptualization: AI, SS; Data curation: JJ, NK, RS, MD; Writing–original draft: SS, AI, RVR, SJ, SMA, ASN; Writing–review & editing: NK, RS, MD.

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Review Article

COVID-19 prediction models: a systematic literature review

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ABSTRACT

As the world grapples with the problem of the coronavirus disease 2019 (COVID-19) pandemic and its devastating effects, scientific groups are working towards solutions to mitigate the effects of the virus. This paper aimed to collate information on COVID-19 prediction models. A systematic literature review is reported, based on a manual search of 1,196 papers published from January to December 2020. Various databases such as Google Scholar, Web of Science, and Scopus were searched. The search strategy was formulated and refined in terms of subject keywords, geographical purview, and time period according to a predefined protocol. Visualizations were created to present the data trends according to different parameters. The results of this systematic literature review show that the study findings are critically relevant for both healthcare managers and prediction model developers. Healthcare managers can choose the best prediction model output for their organization or process management. Meanwhile, prediction model developers and managers can identify the lacunae in their models and improve their data-driven approaches.

Keywords: COVID-19; Data science; Forecasting; Healthcare management; Models

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Introduction

Healthcare refers to the organized provision of medical care to people and communities. It constitutes the efforts made by qualified and licensed practitioners to preserve or achieve physical, mental, or emotional well-being. Healthcare and medical facilities are regarded as making a significant contribution to the promotion of individuals' health and well-being. The healthcare industry is responsible for manufacturing and distributing the drugs and services needed to safeguard, cure and sustain well-being. Providing healthcare for patients affected by coronavirus disease 2019 (COVID-19) has been challenging, especially in India and in Karnataka in particular. Several studies have been performed to understand the spread of COVID-19 and to deal efficiently with COVID-19 patients. The motivation of this study was

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to collate the available information on various prediction models and to choose accurate models for anticipating the number of cases. Many governments have collected and are trying to analyze data to be better equipped for providing healthcare to COVID-19 patients. The COVID-19 pandemic challenged healthcare facilities, with the sheer number of cases resulting in an acute shortage of capacity that constrained healthcare services [1]. A study was conducted to identify the best social media platform that can be employed for sentiment analysis and data mining, and the reported methods of data extraction and methodological consideration provide a basis for planning future studies [2]. State-of-the-art techniques for COVID-19 prediction algorithms are based on commonly used data mining and machine learning techniques to benefit the healthcare sector [3]. The management of the healthcare system focuses on the overall governance of public health services, including the appropriate and effective use of clinical infrastructure facilities, with a view to attaining the highest benefits for human health.

With the worldwide spread of the COVID-19 pandemic, which causes potentially severe respiratory illness, healthcare systems are facing challenges in order to provide appropriate treatment to support patients. In accordance with the goals of healthcare, there are several factors and aspects of the medical sector that must be actively planned and organized.

Adopting a multi-criteria decision framework, such as the Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) method, is an effective approach to prioritize COVID-19 patients that facilitates detection of the health conditions of asymptomatic carriers and helps stakeholders tackle the complex problem of COVID-19 [4–6]. The TOPSIS framework was developed based on machine learning and multiple-criteria decision-making via the subjective and objective decision by opinion score method to provide effective care and prevent the extremely rapid spread of COVID-19 from affecting patients and the medical sector [3].

Based on the findings of the systematic literature review (SLR), it is recommended that healthcare systems and stakeholders should use the best prediction model to forecast the number of cases and make the necessary arrangements for imposing social distancing and lock-down measures during the pandemic.

The present study provides insight into various prediction models and how to choose the best model in terms of maximizing accuracy and minimizing errors. This information will be vital in decision-making for government, the healthcare sector and other stakeholders. The findings of this study have implications for the quality of healthcare management. The health system is expected to perform well in all aspects of satisfying the needs of the customers whether those customers are patients, attending physicians, employers, or functional departments within an organization. The current study presents an SLR of papers published from January 2020 to December 2020. The study applied a specific set of inclusion and exclusion criteria to generate comprehensive tables reviewing the literature that contain information about various COVID-19 prediction models, the characteristics considered in prediction, sample size, and model accuracy.

Spread of COVID-19 (World-wide Scenario)

Pandemics are caused by pathogenic microorganisms (e.g., bacteria, viruses, parasites, and fungi) that tear through populations. The bubonic plague of the 14th century infected over 50 million people in Europe and the Spanish flu of 1918 infected a fifth of the world's population. Pandemic influenza, also termed H1N1 influenza/novel influenza/'swine flu,' ravaged populations worldwide in more recent years [7].

COVID-19 is an infectious disease that affects the human respiratory system. In December 2019, the illness was first reported in Wuhan, the capital of China's Hubei province. At the end of December 2019, a number of patients were admitted to hospitals with an initial pneumonia diagnostic test showing an unknown etiology. Since then, COVID-19 has spread around the globe. At the time of writing this paper (July 26, 2021), 90,698,044 cases of the virus had been recorded worldwide. COVID-19 was formally declared a global pandemic on March 11, 2020 by the World Health Organization (WHO). The top countries affected by COVID-19 are classified in terms of cases reported, deaths, and recovered cases (Table 1). The United States of America (USA), India, Brazil, Russia, France, United Kingdom, Turkey, Argentina, Colombia, and Spain are the top 10 countries affected by COVID-19. On January 13, 2020, the first case outside China was identified in Thailand [8,9]. The first case of COVID-19 was reported in the USA on January 23, 2020 [10].

Spread of COVID-19 in the Indian Context

India, which is the second most populated country after China, is the country in South Asia with the most COVID-19 cases. On January 30, 2020, India recorded the first case of the disease. Since then, cases have increased significantly and dramatically. In order to reduce the transmission of COVID-19, the government of India announced a nationwide lock-down starting on March 25, 2020, which continued

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Table 1. Top 10 most affected countries by coronavirus disease 2019

Country	Cases reported	Death	Recovered case
United States	35,689,184	629,072	29,652,042
India	31,619,573	423,965	30,781,263
Brazil	19,880,273	555,512	18,595,380
Russia	6,265,873	158,563	5,608,619
France	6,103,548	111,824	5,696,559
United Kingdom	5,856,528	129,654	4,508,650
Turkey	5,704,713	51,253	5,449,253
Argentina	4,919,408	105,586	4,557,037
Colombia	4,776,291	120,432	4,567,701
Spain	4,447,044	81,486	3,711,200

This data is as of July 29, 2021 from Worldmeter (https://www.worldometers.info/coronavirus/).

for about 2 months. The number of COVID-19 cases as of July 31, 2021 has reached 197,548,856 confirmed cases and 4,213,071 cases. Within India, Karnataka is the second most strongly affected territory. In the early stages of the global pandemic, Karnataka registered fewer cases than most other Indian states. It was among the early states to deploy new equipment and tools as part of its infrastructure and containment initiatives. The first case in Karnataka was reported on March 9, 2020. The number of COVID-19 cases reported in Karnataka is 928,792 confirmed cases, 906,593 recovered cases and 12,142 deaths (as of January 11, 2021). The government of Karnataka incorporated a gradual lock-down, closing shops and offices, and shutting down inter-district and interstate journeys as part of the initiative to contain the outbreak. The period from March 24 to April 14, 2020 was phase 1 of the lock-down, with the strict restrictions on travel and social interaction. The second phase was from April 15 to May 3, and the third phase lasted from May 4 to May 17 [11]. Bengaluru, the capital of Karnataka, had more infections than other parts of the state. On March 9, 2020, the first COVID-19 case was identified in Bengaluru. As of January 11, 2021, the number of COVID-19 infections in Bengaluru amounted to 392,581 confirmed cases, 382,166 recovered cases, and 4,347 deaths. In terms of controlling the virus, Bengaluru has implemented various curfews, public awareness campaigns, and rigorous reverse-transcription polymerase chain reaction tests. The mapping of containment zones and predictive modeling conducted by *Bruhat Bengaluru Mahanagara Palike* (a local body) were vital factors for successfully controlling the pandemic (Figure 1).

COVID-19 is primarily transmitted by close contact with the droplets spread by sneezing, coughing, and talking to an infected person [12]. The initial stages in COVID-19 transmission have been attributed to human exposure in the wet animal market in Wuhan, where live animals are frequently sold, and it is speculated that this wet market was likely the main source of COVID-19 [13]. Efforts are being made to search for transitional carriers from which the infection might have spread to humans; however, regardless of the original source, COVID-19 has shown an unprecedented degree of horizontal spread. Person-to-person transmission takes place by close contact or through droplets spread by an infected person's cough or sneeze [14].

WHO Definitions of Key Parameters

Confirmed case: A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Positive case (same as confirmed case): A person with laboratory confirmation of COVID-19.

Active cases: The value obtained by subtracting the number of recovered cases and the number of deaths from total number of positive cases.

Recovered cases: Those cured of COVID-19 and discharged from a healthcare facility, also referred to as "discharged."

Death: For surveillance purposes, a COVID-19 death is characterized as a death resulting from a clinically compatible disease in a likely or confirmed case of COVID-19, unless there is a specific alternative cause of death that cannot be attributed to COVID-19 (e.g., trauma). There should be no time of full healing between sickness and death.

Symptoms: A moderate case is defined a confirmed case with fever, respiratory symptoms and radiographic evidence of pneumonia, whereas a case involving dyspnea or respiratory failure is defined as a severe case

Objectives

Owing to the wide spread of COVID-19 and its devastating effects on humans, several research groups have investigated various aspects of the virus, such as its epidemiological characteristics, socio-economic effects, and factors and

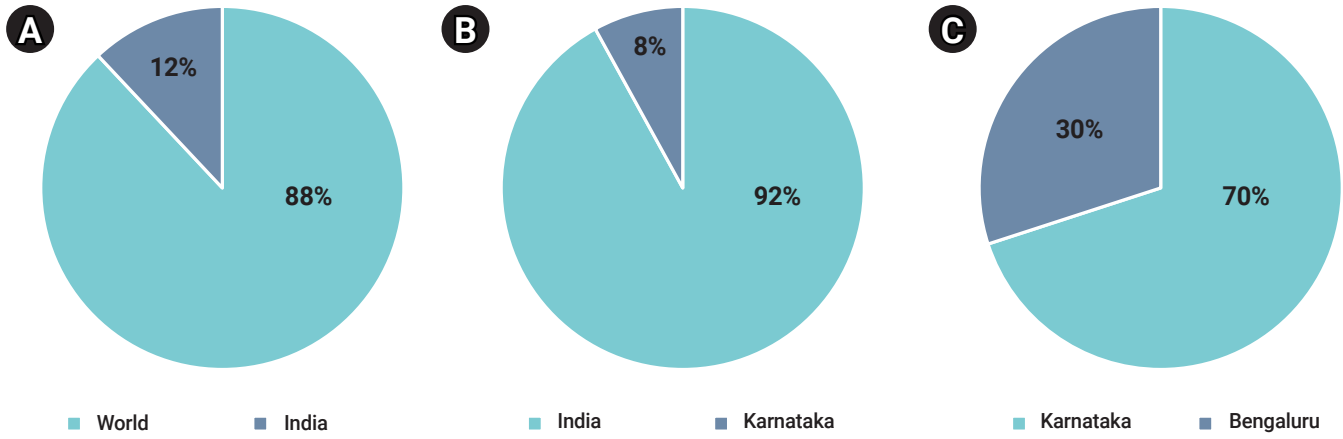

Figure 1. Region-wise comparison of coronavirus disease 2019 (COVID-19) cases (as of January 2021), presenting the percentage share of COVID-19 cases reported as of January 2021. (A) World vs. India COVID-19 cases. (B) India vs. Karnataka COVID-19 cases. (C) Karnataka vs. Bengaluru COVID-19 cases.

parameters aiding the spread of the virus. The present work is an SLR with the following objectives: (1) To systematically review the prediction models that have been developed for COVID-19; (2) To analyze the various COVID-19 prediction models that are currently available; (3) To synthesize and extract useful results and conclusions about the COVID-19 prediction models.

Methods

An SLR is a supplementary methodology used to help evaluate studies by capturing principal analyses on the basis of specific criteria. An SLR is carried out on the basis of previous similar studies through a systematic review. The purpose of an SLR is to summarize the studies carried out and to identify gaps between previous studies and current studies.

Okoli [15] stated that an SLR is "a systematic, explicit, detailed and repeatable approach to identify, assess and analyze the existing body of work by researchers, scholars and practitioners." According to Tranfield et al. [16], an SLR is considered as a "fundamental scientific activity." Moher et al. [17] presented a checklist for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The objective of this SLR was to understand further the mechanisms and analyses used in prediction models for COVID-19 infections. The research time period for this study was from December 2020 to January 2021. This study was conducted in 4 phases: (1) the development of literature search strategies, (2) the formulation of inclusion and exclusion criteria, (3) quality assessment, and (4) analysis and conclusion.

Research Questions

The wide spread of the COVID-19 pandemic has resulted in illness and loss of life on a global scale. Research teams have worked on various models to understand the spread of the virus and make data-driven predictions. For the purpose of this SLR, we articulated a research question (RQ) to help focus on the main issue. The motivation and RQs of this study were as follows:

Motivation: To identify methods, techniques, models that support the prediction of COVID-19 infections.

RQ1: What factors support the prediction of COVID-19 infections?

RQ2: What methods and techniques are followed in data-driven modeling for predicting COVID-19 infections?

Inclusion and Exclusion Criteria

Current search engines provide a high level of recall, which leads to a large number of irrelevant resources being retrieved. Therefore, for effective results, a researcher must follow a systematic search strategy. This stage of an SLR screens the literature to find the relevant literature on the basis of particular criteria. In this study, 3 inclusion and exclusion criteria for identifying relevant content and restricting irrelevant content were adopted. The first inclusion criterion was the type of document: only published documents were included, whereas manuscripts under review and unpublished manuscripts were excluded. The domain (i.e., the subject area identified for the study) was the second screening criterion; the authors included documents containing prediction models developed for or used in the COVID-19 domain, while other documents were excluded. The last screening criterion was the language in which the document was released. In order

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to avoid confusion and complexity related to translation, only documents available in English were included, while documents in other languages were excluded (Table 2).

Databases and Search Strategies

The terms were searched in several databases (Google Scholar, Scopus, Publish or Perish, and Web of Science [WoS]). The search terms are as follows: prediction models, COVID-19, Coronavirus, SARS-CoV, SARS-CoV-2, healthcare, healthcare system, survival model, medical care. Various combinations of the search terms were used to retrieve resources in particular databases. Some of the search strings used are as follows—"Prediction models" AND "COVID-19"; "COVID-19 Datasets" AND "Prediction modeling"; "Predictive Analysis" AND "COVID-19 data" OR "Predictive Analysis" AND "Corona Virus".

After applying the inclusion and exclusion criteria, 1,196 documents were retrieved, of which 47 were duplicates. Therefore, a total of 1,149 documents continued to the second stage of scrutiny and quality assessment (Table 3). The percentage shares of articles from various databases in the initial, screening, and acceptance stages of the document selection process are illustrated.

In the initial phase, out of the total number (i.e., 1,196 documents) of retrieved documents, Google Scholar accounted for 77%, Scopus contained 17%, and WoS had 6% (Figure 2A). After the initial screening, 62 documents were included for further consideration. During the screening phase, 52% of the initially included documents were retrieved from Google Scholar. Out of the remaining 30%, Scopus and WoS had an 18% share each (Figure 2B). Out of the total accepted documents, 70% were retrieved from Google Scholar, 14% from Scopus, and 16% from WoS (Figure 2C).

The present study focused on publications dealing with COVID-19 prediction models across the world. This review was conducted in January 2021. The country of a research/case was defined by the affiliations of authors in the paper, and a limited research level was observed for several countries (e.g., Canada, Chile, France, Jordan, etc.). Given our

Table 3. Document selection

Database	Initial	Screened	Accepted
Google Scholar	910	33	21
Scopus	210	19	4
Web of Science	76	10	5
Total	1,196	62	30
Duplicates	47	0	0
Total selected	1,149	62	30

Table 2. Inclusion-exclusion criteria

Criteria	Inclusion	Exclusion
Document type	Published documents	Under review, unpublished or upcoming documents
Domain	Prediction models of COVID-19	Other than prediction models of COVID-19
Language	English	Other than English

COVID-19, coronavirus disease 2019.

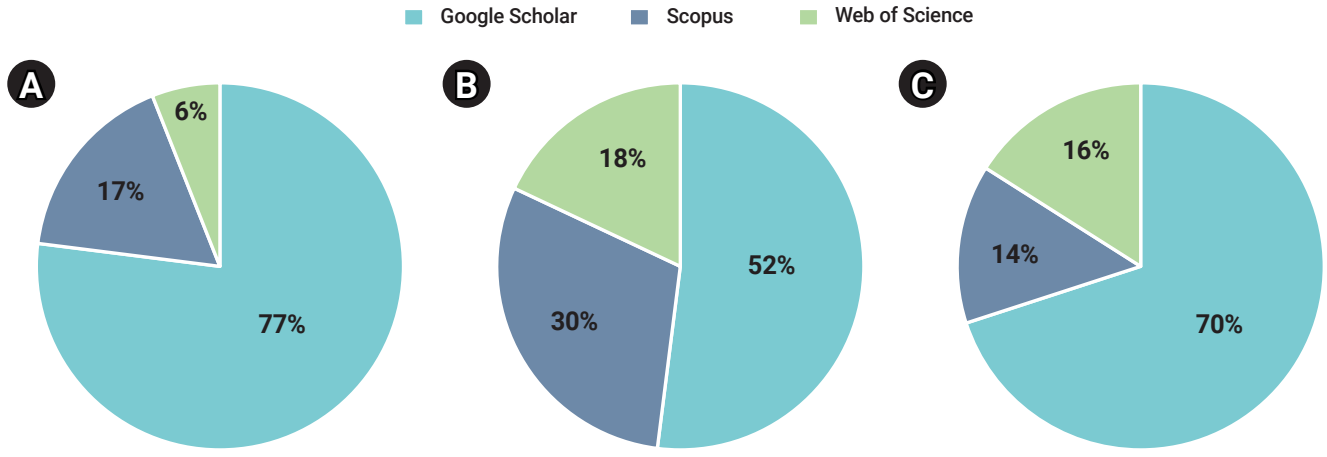

Figure 2. Database's percentage share of COVID-19 cases reported as of January 2021.
(A) Document selection (initial). (B) Document selection (screened). (C) Document selection (included). Document selection was carried out based on selection criteria.

particular focus on the spread of the pandemic in India, the highest number of publications was from India and China (Figure 3).

Quality Assessment and Coding

Quality evaluation of a phenomenon is conducted as a systematic way to avoid biases and errors. Thereby, an SLR includes quality assessment as an essential step. In this study, in the initial phase, 1,196 documents were chosen. Based on their titles, these documents were further analyzed and 62 documents were screened. The content was scrutinized on the basis of the title, abstract, introduction, and conclusion and 30 studies were finally selected for the review.

Related Literature

Prediction Models

A prediction model is a method of becoming aware of a future scenario beforehand based on available data. Predictive modeling mainly uses statistics to predict outcomes [18]. Forecasting in the COVID-19 pandemic allows medical professionals to better manage facilities and to validate the use of medical and financial resources. It is essential to systematically assess the predictive outcomes of 1 or more prediction models in order to analyze the prediction accuracy of a framework across different study populations, ecosystems, and locations and to assess the need for further developments or improvements of a model [19]. In this paper, we present a systematic review and analysis of these models as presented in the literature.

Related Works

Coronaviruses are among the main pathogens that predominantly affect the human respiratory system. The focus of the literature review was, therefore, to outline the predominant variables and methodology used in studies related to the spread of the virus. People with prevalent illnesses such as diabetes, hypertension, diabetes, stroke, heart, or kidney failure, as well as elderly people with impaired immune systems, are at an increased risk of infection [20]. Closed areas with low ventilation and airflow may increase the risk of infection. The spread of the virus is believed to occur through respiratory droplets from coughing and sneezing, as with other respiratory viruses, including influenza virus and rhinoviruses. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces [21].

Several reports have defined a series of variables in terms of quarantine facilities, laboratory testing facilities, and

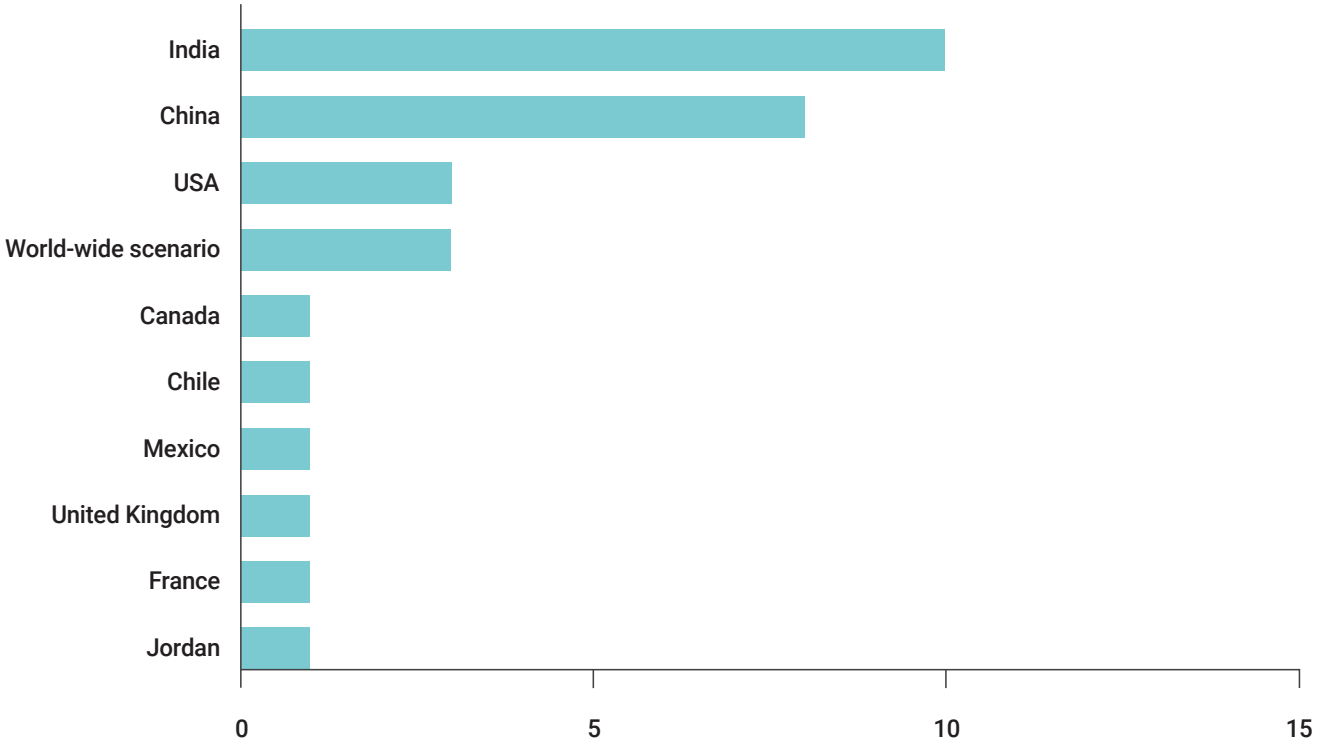

Figure 3. Total articles selected.
The blue bars represent the total number of articles included in this systematic literature review.

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healthcare capability, contributing to state preparedness to fight the pandemic. The most important and successful of these factors must be explored as an urgent solution to the pandemic. The availability of open data sets corresponding to different variables helps to accelerate studies and forge cooperation [22]. Environmental factors, such as pollution and basic sanitation, were considered in some studies. Several studies have also taken into consideration deaths due to COVID-19 and other demographic information [23, 24]. Other studies and theories have pointed to comorbidities as a key factor in the number of COVID-19 cases [25,26]. Without considering comorbidities, fatalities may be mistakenly interpreted as exclusively COVID-19 deaths. Researchers from many universities in the USA have successfully predicted COVID-19 deaths. One such study was conducted at Columbia University and the CDC (2020), in which "death" was used as an exponential function and a social distance parameter prediction was made using a susceptible-exposed-infectious-removed (SEIR) meta-population model.

Since the very beginning of the COVID-19 pandemic, numerous researchers have attempted to construct statistical models of the COVID-19 pandemic, as can be seen from a primary review of existing models. There are several differences in scope, assumptions, forecasts, the effects of interventions, and their impact on health services [27]. A PRISMA flow diagram based on the identification of studies from various databases, screening, and the eligibility and inclusion criteria is presented in Figure 4.

SLR on COVID-19

In the context of the COVID-19 pandemic, people across the world are using various methods to explore prediction models with the goal of addressing the problems caused by the pandemic. The motivation for this SLR was to help researchers across the world study the various prediction models that have been created by numerous authors from multiple countries by providing information on a comprehensive range of models in one place. A systematic review is a compilation of various studies related to a single topic. It aims to provide a comprehensive and unbiased review of all the relevant studies in a given field. Our SLR was conducted to determine which prediction models are currently available, and the objective of the study was to identify the various methods used to develop different types of prediction models and to conduct an effectiveness or quality assessment of the models, which helps to evaluate their accuracy. It is hoped that this SLR will help healthcare workers and researchers wisely and confidently choose accurate prediction models to facilitate healthcare management by arranging medical facilities and equipment. Researchers or scholars can enhance their research program by using this SLR to obtain up-to-date information on the various techniques used in prediction models, as well as their efficiency and accuracy. All currently available prediction models for COVID-19 were systematically reviewed and critically appraised. There are currently a number of diagnostic and prognostic models for COVID-19, all of which show moderate to excellent discrimination. To explore the different prediction models and find the best-suited model in terms of providing high accuracy while minimizing the burden on the healthcare system and improving care for patients, both the diagnosis and prognostic evaluation of diseases need to be improved. This study will influence decision-makers in various aspects.

The selected papers deal with different techniques used to build predictive models for the spread of COVID-19. Various techniques are used for the modeling and to present results. Quantitative assessments were also evaluated based on the papers' presentation of the percentage success/accuracy rate or error rates in statistical and regression models. This SLR sums up the research work of different prediction model developers in detail. In this SLR of prediction models related to the COVID-19 pandemic, we identified 30 studies with various prediction models. Among the 30 papers, the most cited ones were found to be those authored by Chinese researchers, followed by papers authored by Indian researchers and then papers authored by USA-based researchers (Table 4) [12,28–56].

To identify the likelihood of future results based on historical data, predictive analytics uses data, statistical algorithms, and different techniques such as machine learning, autoregressive integrated moving average (ARIMA) models, SEIR models, and long short-term memory (LSTM) models. The present SLR also classified papers on the basis of the techniques used (Table 5) [12,28–56]. The most commonly used techniques used in predictive modeling and analysis were as follows:

Machine learning

Machine learning is a technique used in which computers evaluate a data set and learn from the insights they gather. An artificial neural network is simulated by the use of complex algorithms that allow machines to classify, interpret, and understand data, and then use the insights that have been obtained to solve problems or make predictions. Common examples of machine learning include classification models, forecasts, medical diagnosis, image processing, regression, chatbots, and recommendation engines. Machine learning

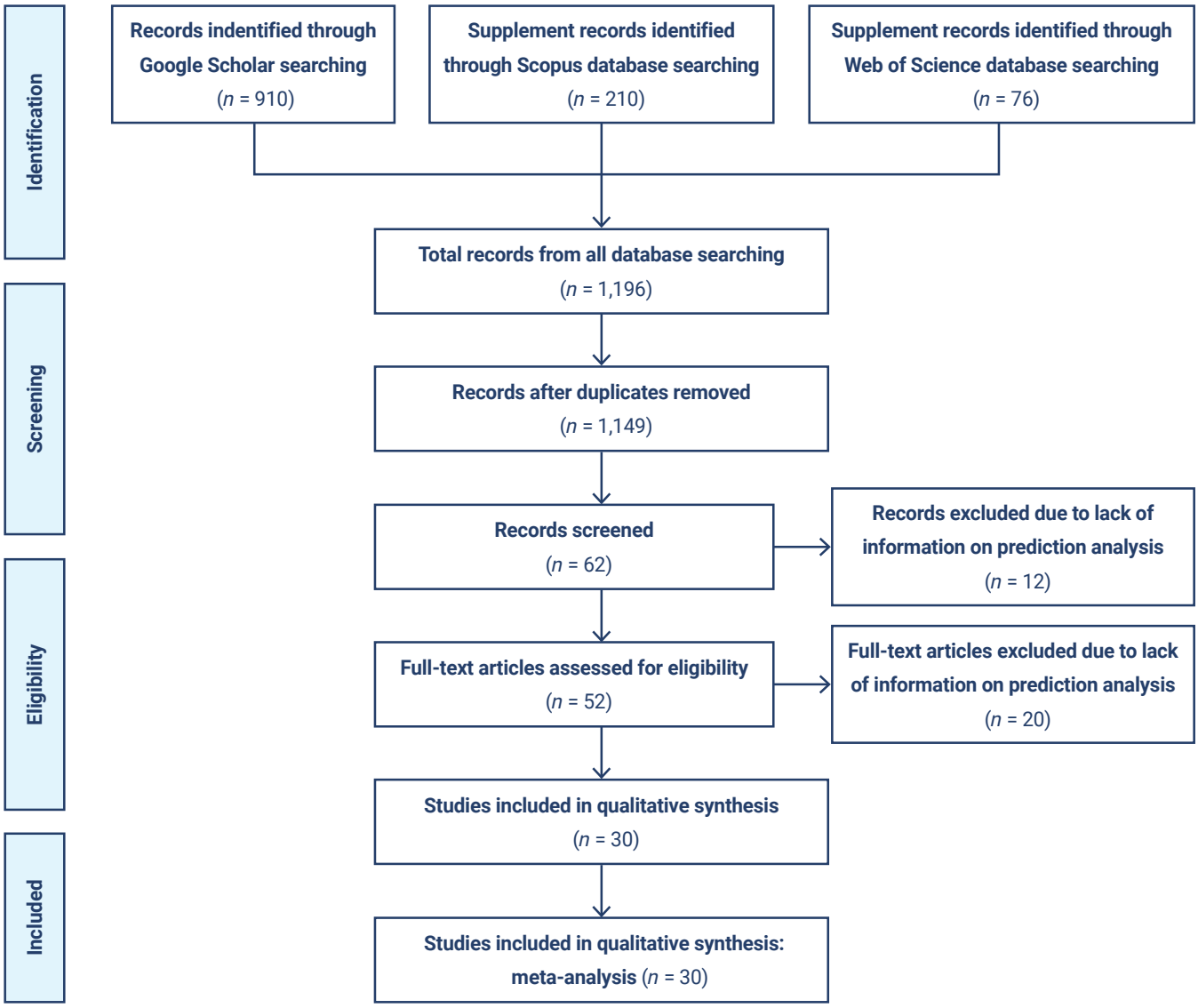

Figure 4. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

is a different branch of programming and is known to be an emerging technology.

ARIMA models

ARIMA models can be built in an array of software tools, including Python. These models are used in statistics and econometrics to measure events that happen over a span of time. ARIMA models predict future data in a series using past data. An ARIMA model can be constructed for any number series that display patterns and is not a random event series. For example, sales data from a footwear store would be an example of time series data because the data are collected over a period of time. One of the key characteristics is that the data are collected at constant, regular intervals [57].

SEIR models

SEIR models are commonly used for assessing infection data during the different phases of an infectious outbreak. SEIR models are among the most widely adopted mathematical frameworks to describe disease dynamics and forecast potential contagion scenarios. After an infectious disease outbreak, a SEIR model can be helpful in determining the efficacy of different interventions, such as lock-downs. These models are based on a series of complex ordinary differential equations that take into account the number of people who are sick, the pattern of people who recover over time after sickness, and the people who die [58].

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Table 4. Literature review

No.	Study	Objective	Type of model	Result	Quality assessment
1	Yang et al., 2020 [28]	To forecast COVID-19 patterns in China using a SEIR and AI model	SEIR model and AI model	· The model was effective in forecasting COVID-19 cases.	95% CI
2	Liang et al., 2020 [29]	To forecast the risk of critical illness at hospital admission and identify survival of COVID-19 patients	Statistical software: LASSO, logistic regression model	· The score gives an estimation of the probability of critical disease progression for a hospitalized patient with COVID-19.	AUC (accuracy) was 0.88, 95% CI.
3	Yan et al., 2020 [30]	Relieving clinical burden and potentially reducing the mortality rate of COVID-19	Machine learning tool: XGBoost	To predict patients with higher risk and potentially reduce mortality rate · Survival prediction accuracy was 100%. · Mortality forecast accuracy was 81%.	Overall accuracy was 0.90.
4	Gong et al., 2020 [31]	To predict the early detection of cases at high risk for progression to serious COVID-19	Statistical analysis	· Results helped in COVID-19 patient identification for effective management.	Training cohort: · AUC was 0.912, 95% CI. Validation cohort: · AUC was 0.853, 95% CI.
5	Chatterjee et al., 2020 [32]	To develop a stochastic mathematical model to predict COVID-19 cases	SEIR	· To help in healthcare preparedness and in allocations of resources. · The model suggested that herd immunity may be achieved when 55% to 65% of the population is infected.	R0 was 2.28, growth rate of the epidemic in India was 1.15.
6	Hu et al., 2020 [12]	To predict confirmed COVID-19 cases and group cities into clusters according to transmission pattern	AI	· AI-based prediction showed significant accuracy and may act as a powerful tool for helping healthcare planning and policymaking.	Average errors: • 6-Step (1.64%) • 7-Step (2.27%) • 8-Step (2.14%) • 9-Step (2.08%) • 10-Step (0.73%)
7	Tomar & Gupta, 2020 [33]	To predict new COVID-19 cases using LSTM based techniques	LSTM	· Prediction corresponded to the original information with a reasonable CI.	± 5% CI
8	IHME COVID-19 Health Service Utilization Forecasting Team & Murray, 2020 [34]	To predict deaths and requirements of total beds for hospitals due to COVID-19	Statistical model	· The model estimated that the number of COVID-19 deaths would range from 81,114 to 162,106 over the next 4 mo.	Not available.
9	Chimmula & Zhang, 2020 [35]	To track COVID-19 cases and to help government and policymakers prepare	LSTM, R0 method	· ARIMA	RMSE (45.70)
10	Pandey et al., 2020 [36]	To create a predictive model to assess the need for clinical treatment for patients	Machine learning models: SEIR, regression model	· Predictions will help check supply and medical assistance and help policymakers prepare.	RMSLE: · SEIR model was 1.52. · Regression model was 1.75. R0 between the 2 models was 2.02.

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Table 4. Continued

No.	Study	Objective	Type of model	Result	Quality assessment
11	Jehi et al., 2020 [37]	To develop a model for risk prediction for patients testing COVID-19 positive	Statistical prediction model: chi-square test	· Predictions could help direct healthcare preparedness.	C-statistic: · Development cohort was 0.863. · Validation cohort was 0.840.
12	Ardabili et al., 2020 [38]	To forecast the outbreak of COVID-19 using machine learning soft computing	Machine learning: logistic model	Correlation coefficient · Italy (0.997) · China (0.994) · Iran (0.997) · USA (0.999) · Germany (0.997)	RMSE · Italy (3358.1) · China (2524.44) · Iran (628.62) · USA (350.33) · Germany (555.32)
13	Sujath et al., 2020 [39]	To forecast COVID-19 pandemic using machine learning	Machine learning: LR, MLP	· 95% CI with LR and MLP	95% CI
14	Qi et al., 2020 [40]	To predict the hospital stay of COVID-19 patients	Machine learning: logistic regression, RF	· Predictions exhibited feasibility and accuracy for hospital stay for patients with pneumonia associated with COVID-19 infection.	LR model: · Sensitivity was 1.0. · Specificity was 0.89. RF model · Sensitivity was 0.75. · Specificity was 1.0.
15	Ghosal et al., 2020 [41]	To forecast the number of deaths due to COVID-19 in India	Multiple regression and LR, auto-regression technique	· The estimated mortality rate (n) at the end of the 5th and 6th weeks was 211 and 467.	Multiple R was 0.9903. R squared was 0.9807. Adjusted R squared was 0.9700. Standard error was 234.1358.
16	Hoertel et al., 2020 [42]	To develop a prediction model to identify patients needing professional care	Statistical analysis: Kaplan-Meier method, R Foundation for statistical computing	· Cox model predicted with a high accuracy ($p < 0.05$).	· AUC was 0.97. · Overall C-statistic was 0.963 (95% CI, 0.936-0.99).
17	Arora et al., 2020 [43]	To forecast the number of COVID-19 positive cases in 32 states and union territories of India using deep learning-based models	Deep learning: LSTM, RNN	· Model was highly accurate for short-term predictions (1–3 days) ahead.	· MAPE range < 3% · Weekly forecast, 4%–8%
18	Salgotra et al., 2020 [44]	To forecast COVID-19 outbreaks in India and use time series study and model on CC and DC in 3 states of India, Maharashtra, Gujarat, and Delhi	GEP model	· The model was highly effective in forecasting both reported cases and deaths around India.	· Lowest R value: 0.9881, DC in Delhi · Highest value: 0.9999, RC in India
19	Dutta & Bandyopadhyay, 2020 [45]	To validate the predicted outcome of COVID-19 cases using machine learning	LSTM, GRU	Accuracy level · Confirmed cases: 87% · Negative cases: 67.8% · Deceased cases: 62% · Released cases: 40.5%	RMSE · Confirmed cases: 30.15% · Negative cases: 49.4% · Deceased cases: 4.16% · Released cases: 13.72%
20	Zhao et al., 2020 [46]	To develop risk ratings based on clinical categories and to forecast COVID-19 ICU admission and mortality	Logistic regression: multivariable regression model	· Predictions will significantly assist the flow of COVID-19 patients and distribute resources accordingly.	· ICU admission: AUC was 0.74, 95% CI. · Predicting mortality: AUC was 0.82, 95% CI.

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Table 4. Continued

No.	Study	Objective	Type of model	Result	Quality assessment
21	Hernandez-Matamoros et al., 2020 [47]	To predict COVID-19 behaviors in order to make future plans and hence to forecast the progress of the virus	ARIMA	· The model was able to predict the behavior of spread of COVID-19 infection.	RMSE average of 144.81.
22	Alazab et al., 2020 [48]	To predict COVID-19 cases across the world using an AI-based technique	PA, ARIMA, LSTM	· PA delivered the best performance. · The model predicted COVID-19 cases and achieved an F-measure of 99%.	Accuracy: · Australia was 94.80%. · Jordan was 88.43%.
23	Parbat & Chakraborty, 2020 [49]	To predict the total number of deaths, recovered cases, cumulative number of confirmed cases, and number of daily cases	Vector regression model	The model: · Functioned well in fitting the total cases · Poor fit for the daily number of cases	RMSE: · Total deaths: 0.092142 · Total recovered: 0.174036 · Daily confirmed: 0.330830 · Daily deaths: 0.361727
24	Zhao et al., 2020 [50]	To predict COVID-19 confirmed cases using 6 rolling grey Verhulst models	Rolling Grey Verhulst model	· Predictions exhibited good accuracy. · Six models predicted S-shaped change characteristics consistently.	MAPE: training stage · Max (4.74%) · Min (1.80%) Testing stage · Max (4.72%) · Min (1.65%)
25	Achterberg et al., 2020 [51]	To evaluate a diverse range of forecast algorithms for COVID-19	Network-based forecasting	· The algorithm performed well in predicting COVID-19 cases and was superior to any other prediction algorithm.	NIPA · Hubei was 0.122. · The Netherlands was 0.038.
26	Fernandez et al., 2021 [52]	To develop a forecasting algorithm to consider patient survival	Logistic regression: multivariate logistic regression	· Patients that would be able to survive were classified by age, CRP, platelet count, and number of lung consolidations.	AUC was 0.8129. GOF: Hosmer and Lemeshow test, $p = 0.018$; 95% CI (0.773–0.853, $p < 0.001$)
27	Li et al., 2020 [53]	To develop a prediction model for identifying patients at an increased risk of COVID-19 death	Machine learning: autoencoder model, logistic regression, SVM, RF	· The model exhibited specificity and accuracy above 0.9.	Logistic regression, SVM, RF · Sensitivities below 0.4. · Autoencoder scores above a sensitivity value of 0.4.
28	Siwiak et al., 2020 [54]	To develop a global model for COVID-19 in terms of the number of infected cases	GLEAM	· Presented a percentage difference over time between the number of reported, confirmed cases and CI limits for different modeled predictions.	95% CI
29	Bhandari et al., 2020 [55]	To predict the progression of COVID-19 in India using ARIMA	ARIMA	· The COVID-19 forecast helps the government and policy makers to optimize resources and make decisions.	95% CI

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Table 4. Continued

No.	Study	Objective	Type of model	Result	Quality assessment
30	Muhammad et al., 2021 [56]	To forecast COVID-19 infection using machine learning	Machine learning: logistic regression, decision tree, support vector machine, naive Bayes, and artificial neutral network	· Decision tree model accuracy was 94.99%. · Support vector machine model sensitivity was 93.34%. · Naive Bayes model has a specificity of 94.30%.	RMSE: LMST (27.187) LR (7.562)

COVID-19, coronavirus disease 2019; SEIR, susceptible-exposed-infectious-removed; AI, artificial intelligence; CI, confidence interval; LASSO, least absolute shrinkage and selection operator; AUC, area under the curve; XGBoost, eXtreme gradient boosting; LSTM, long short-term memory; ARIMA, autoregressive integrated moving average; RMSE, root mean square error; RMSLE, root mean square logarithmic error; LR, linear regression; MLP, multilayer perceptron; RF, random forest; RNN, recurrent neural network; MAPE, mean absolute percentage error; CC, confirmed case; DC, death case; GEP, genetic evolutionary programming; RC, reported case; GRU, gated recurrent unit; ICU, intensive care unit; PA, prophet algorithm; NIPA, network inference-based prediction algorithm; CRP, C-reactive protein; GOF, goodness of fit; SVM, support vector machine; GLEAM, global epidemic and mobility framework.

Table 5. Classification of papers by the technique/tool used

No.	Study	Year	Country	Citation (January 2, 2021)	Model
1	Yang et al. [28]	2020	China	467	SEIR and AI model
2	Liang et al. [29]	2020	China	327	Statistical software
3	Yan et al. [30]	2020	China	194	Machine learning
4	Gong et al. [31]	2020	China	134	Statistical analysis
5	Chatterjee et al. [32]	2020	India	131	SEIR
6	Hu et al. [12]	2020	China	130	Artificial intelligence
7	Tomar & Gupta [33]	2020	India	129	LSTM
8	IHME COVID-19 Health Service Utilization Forecasting Team & Murray [34]	2020	USA	119	Statistical model
9	Chimmula & Zhang [35]	2020	Canada	99	LSTM
10	Pandey et al. [36]	2020	India	57	Machine learning
11	Jehi et al. [37]	2020	USA	45	Statistical analysis
12	Ardabili et al. [38]	2020	Worldwide scenario	41	Machine learning
13	Sujath et al. [39]	2020	India	41	Machine learning
14	Qi et al. [40]	2020	Worldwide scenario	41	Machine learning
15	Ghosal et al. [41]	2020	India	39	Regression model
16	Hoertel et al. [42]	2020	France	37	Statistical analysis
17	Arora et al. [43]	2020	India	34	LSTM, RNN
18	Salgotra et al. [44]	2020	India	34	GEP model
19	Dutta & Bandyopadhyay [45]	2020	India	33	LSTM, GRU
20	Zhao et al. [46]	2020	China	13	Logistic regression
21	Hernandez-Matamoros et al. [47]	2020	Chile	11	ARIMA
22	Alazab et al. [48]	2020	Jordon	9	PA, ARIMA, LSTM
23	Parbat & Chakraborty [49]	2020	India	9	Regression model
24	Zhao et al. [50]	2020	China	6	Grey Verhulst
25	Achterberg et al. [51]	2020	China	2	Network-based forecasting
26	Fernandez et al. [52]	2021	UK	2	AI
27	Li et al. [53]	2020	Worldwide scenario	1	GLEM
28	Siwiak et al. [54]	2020	India	1	ARIMA
29	Bhandari et al. [55]	2020	UK	-	Logistic regression
30	Muhammad et al. [56]	2021	Mexico	-	Machine learning

SEIR, susceptible-exposed-infectious-removed; AI, artificial intelligence; LSTM, long short-term memory; RNN, recurrent neural network; GEP, genetic evolutionary programming; GRU, gated recurrent unit; ARIMA, autoregressive integrated moving average; PA, prophet algorithm; GLEM, global epidemic and mobility.

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LSTM models

LSTM models are a type of recurrent neural network (RNN) used to predict new infection numbers over time by processing and forecasting several issues related to time series. With repeating modules like an RNN, an LSTM model has a chain-like structure, except that instead of a single neural network layer as in RNNs, an LSTM model has 4 layers that communicate in a slightly different manner, each of which performs its own special network role. In an LSTM cell, each repeating module has a cell state. Through using various gates in the cell, the LSTM cell has the power to add or subtract information to the cell state. There are 3 gates for the standard LSTM cell that control the sum of data input or output to/from the cell state and protect the cell state.

Regression models

Regression analysis is a method of quantitative research that is used in studies modeling and analyzing several variables, where a dependent variable and 1 or more independent variables are included in the relationship. In basic terms, regression analysis is a mathematical approach used to evaluate the existence of the relationship between a dependent variable and 1 or more independent variables [59]. The 2 most widely used regression analyses are: (a) Logistic regression: in logistic regression, an independent variable is used to estimate the dependent variable. (b) Support vector regression (SVR): SVR provides the flexibility to determine how much error is suitable in a model and to find an appropriate line (or hyperplane in higher dimensions) to match the results.

GLEM models

Global epidemic and mobility (GLEM) models are being used in a number of COVID-19 related studies and analyses. These models involve a stochastic computational framework that combines high-resolution demographic and mobility data across the globe to predict the epidemic distribution across the globe. The goal of the GLEM model is to optimize versatility in specifying the disease compartment model and configuring the simulation scenario. It allows the user to set a number of criteria, including compartment-specific features, transition values, and environmental effects [60].

Conclusion

This study identified the core literature on prediction models for COVID-19. The aim of this research was to review and analyze the articles in the literature related to prediction models for COVID-19. A prediction model is a method for predicting the future scenario based on present facts. This SLR was based on a manual search of 1,196 papers published from January to December 2020, out of which 30 documents were selected on the basis of inclusion and exclusion criteria. Our SLR was conducted to explore which prediction models are currently available, with the goals of identifying various methods used to develop different types of prediction models and to conduct an effectiveness or quality assessment of models, which helps in evaluating their accuracy.

Based on this review, it is critical for statistical methods to be extensively used to predict the spread of infection. The LSTM [35] approach was used to track COVID-19 cases and to help government officials and policymakers in preparedness, with a root mean square error (RMSE) of 45.72. An ARIMA [47] model was used to predict the spread of COVID-19 infection with an average RMSE 44.81, followed by machine learning, artificial intelligence, and hybrid models. Lastly, in a few of the studies, mathematical modeling and network-based forecasting were used. SEIR models are among the most widely adopted mathematical frameworks to describe disease dynamics and forecast potential contagion scenarios. This SLR provides detailed information about various COVID-19 prediction models that can be adopted by researchers. This information can be used by healthcare professionals and by local government bodies in order to make decisions for managing healthcare facilities accordingly.

Notes

Ethics Approval

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

Data for literature review was taken from Google Scholar, Scopus, and Web of Science. All data generated or analysed during this study are included in this published article. For other data, these may be requested through the corresponding author.

Authors' Contributions

Conception: all authors; Design: all authors; Supervision: RS, DRS; Literature review: SMS, NSK, PPM; Writing–original draft: all authors; Writing–review & editing: all authors.

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Original Article

The current status of sexually transmitted infections in South Korean children in the last 10 years

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ABSTRACT

Objectives: This study aimed to review the status of sexually transmitted infections (STIs) in children in South Korea between 2010 and 2019, as well as to establish guidelines for the prevention and management to reduce the incidence of STIs in children.

Methods: Data reports from 590 STI surveillance institutions in local health center, hospital-level medical institutions with urology or obstetrics/gynecology departments and public hospitals between 2010 and 2019 in the integrative disease management system of the Korea Disease Control and Prevention Agency as of December 2020 were analyzed.

Results: A total of 172,645 cases of STIs were reported over the 10-year period (2010–2019), of which 2,179 cases (1.26%) represented STIs in children below the age of 18 years. A higher incidence of infections was observed in girls (1,499 cases, 68.79%) than in boys (680 cases, 31.21%). The STIs that had the highest incidence were, in descending order, chlamydial infections (997 cases, 45.75%), gonorrhea (592 cases, 27.17%), condyloma acuminata (338 cases, 15.51%), genital herpes (250 cases, 11.47%), and chancroid (2 cases, 0.09%). In adolescents aged 14 to 17 years, chlamydial infections, genital herpes, and gonorrhea were most frequently reported. Condyloma acuminata, in particular, have been consistently reported in children below the age of 14 years.

Conclusion: Children must be protected legally and institutionally from sexual abuse. Specific management protocols for STIs in children must be established by local governments and associated organizations. National human papillomavirus vaccination programs should be expanded to include boys, and anti-STI educational efforts using modern media should be more activated.

Keywords: Adolescent; Child; Child welfare; Sexual offenses; Sexually transmitted infections

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Introduction

Incidents of child abuse have been reported in Korea on an ongoing basis, and social interest in the topic has been increasing due to media coverage. According to Article 3, Section 1 of

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the Child Welfare Act, a child is considered a person below the age of 18 years. Article 3, Section 7 defines child abuse as harm to the health or welfare of the child or physical, emotional, or sexual violence, or harassment inflicted by an adult, including the child's guardian, as well as the abandonment or neglect of a child by the child's guardian, that might impede the healthy development of a child.

Child abuse is broadly classified into physical abuse, emotional abuse, neglect, and sexual abuse [1]. Physical abuse refers to any non-accidental act in which an adult causes or allows the infliction of bodily harm to a child. Examples include bodily harm inflicted directly or through the use of a tool(s), force, or harmful substances. Emotional abuse refers to verbal insults, emotional threats, locking up a child, restraint, and other abusive behaviors towards a child by an adult and can also be termed verbal, mental, or psychological abuse. Other than offensive verbal abuse, emotional abuse can include not putting a child to bed or expulsion from the home without clothes. Neglect refers to the act of a guardian placing a child in a dangerous environment or failing to provide the child with essential food, clothing, shelter, necessary education, or medical attention [2]. Finally, sexual abuse refers to any sexual activity performed by an adult, including the child's guardian, against a child below the age of 18 years for the purpose of satisfying the adult's own sexual desire, specifically when the child does not consent to or is not old enough to legally consent to the sexual activity [3].

Sexual abuse can lead not only to physical disabilities, but also to a range of mental health problems such as mental disorders, cognitive disorders, and social maladjustment [4]. Hence, there is a pressing need for a national effort to prevent recurrence and new incidents. Current national efforts for the prevention of child abuse include regulation of the roles of the local governments by Article 22 Section 1 of the Child Welfare Act and Article 23 of the Enforcement Decree of the Child Welfare Act, the installation and operation of emergency telephone lines, and events and promotions pertaining to the designated annual Child Abuse Prevention Day (November 19). In addition, education about the duty to report child abuse, as well as counseling and education for perpetrators of child abuse, are recommended. Nevertheless, in cases of sexual abuse, which requires a close examination of clinical symptoms and continuing treatment by a clinician, Article 10 of the Act on Special Cases concerning the Punishment of Child Abuse and Article 34 of the Act on Protecting Children and Adolescents from Sexual Abuse offer vague criteria on the reporting of child abuse, making it difficult for representatives of the local government to understand and fulfill their duty to report cases.

The 7 types of sexually transmitted infections (STIs) that can be contracted from sexual abuse are classified as level 4 legal communicable diseases. Although epidemiological investigations are conducted for other level 4 communicable diseases such as hand, foot, and mouth disease with complications, influenza, rotavirus, respiratory syncytial virus, acquired immune deficiency syndrome, and novel communicable diseases [5], no epidemiological investigations are being conducted on STIs. Moreover, there might be limitations to conducting fact-based investigations due to prejudices and stigma regarding sexual activity. This study aimed to examine the incidence of STIs based on the number of cases reported in the sentinel surveillance systems over 10 years (2010–2019) and analyzed the high-risk age groups. These findings will help in suggesting national prevention and management guidelinesto reduce the incidence of STIs in children in the future.

Materials and Methods

Currently, patient reports for the 7 types of STIs are obtained through a sentinel surveillance system at select institutions. The STIs that require reporting of suspected or confirmed patients are gonorrhea, genital herpes, and condyloma acuminata, while the STIs that require reporting of confirmed cases are chlamydial infections, chancroid, and syphilis, and carriers of human papillomavirus (HPV) must also be reported [6].

Institutions that are a part of the STI surveillance system include local health center, clinic- or hospital-level medical institutions with urology or obstetrics/gynecology (OB-GYN) departments, and public hospitals. There is one designated institution for every 100,000 persons in cities, counties, and districts. In cities and counties with a population of less than 100,000, public health center is designated. Reports of patients and suspected cases from the previous week (Sunday to Saturday) are sent by web or fax to the local public health center within 7 days (every Tuesday) and then each province sends the reports to the Korea Disease Control and Prevention Agency each week (Figure 1). Data from the 590 STI surveillance institutions in local health center and clinic- or hospital-level medical institutions with urology or OB-GYN departments, and public hospitals reported between 2010 and 2019 in the integrative disease management system at the Korea Disease Control and Prevention Agency as of December 2020 were included. Furthermore, reports on syphilis, which had been reported for mandatory surveillance until December 31, 2019 were excluded.

Results

Total Number of Cases

In the last 10 years, 172,645 cases of STIs were reported, of which 2,179 were cases of STIs in children below the age of 18 years. Among them, the most commonly reported STIs were as follows: 997 cases (45.75%) of chlamydial infections, 592 cases (27.17%) of gonorrhea, 338 cases (15.51%) of condyloma acuminata, 250 cases (11.47%) of genital herpes, and 2 cases (0.09%) of chancroid. The incidence of chancroid has been decreasing each year since 2008; of the 4 cases reported in 2019, 2 were reported in individuals aged 17 years (Figure 2).

An assessment of the annual number of reported cases of STIs revealed the highest incidence of chlamydial infections across all the years and a steady increase each year. The incidence of gonorrhea, condyloma acuminata, and genital herpes was generally high, while the incidence of chancroid was lowest (Figure 3). As of 2015, there has been a general increase in STIs. Chlamydial infections have been increasing each year, while the incidence of gonorrhea peaked in 2016, decreased slightly thereafter, but increased once again in 2019. The incidence of genital herpes has been steadily increasing since 2012, while high numbers of cases of condyloma acuminata were reported in 2019.

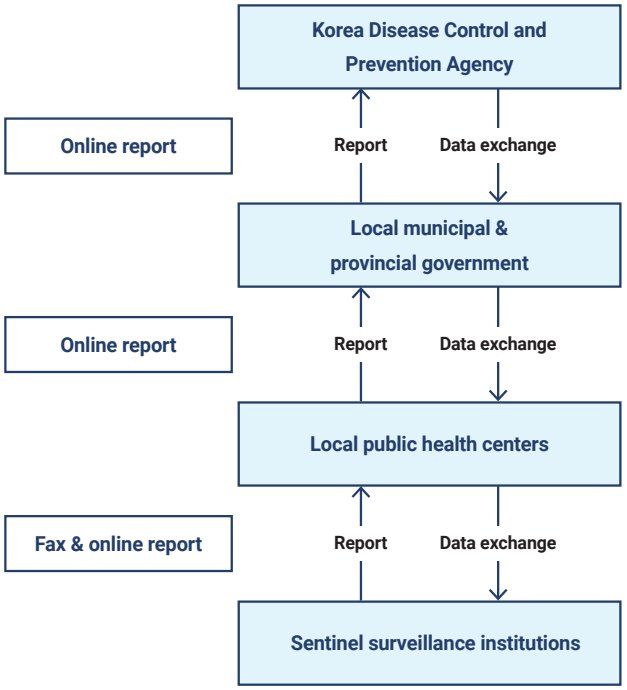

Figure 1. Sexually transmitted infection (STI) reporting system.
Upon confirmation of a STI listed under the 7 legal communicable diseases, the sentinel surveillance system (in local health centers, medical institutions, public hospitals) must alert and report to the local public health center, local municipal & provincial government, and the Korea Disease Control and Prevention Agency through the web reporting system.

Reporting by Sex and Age Group

Among the total of 2,179 cases, girls accounted for 1,499 cases (68.79%), which was approximately 2.2 times higher than the number in boys, who accounted for 680 cases (31.21%) (Figure 4). Among the 680 cases reported in boys, there were 36 cases (5.29%) of genital herpes, 344 cases (50.59%) of gonorrhea, 110 cases (16.18%) of condyloma acuminata, 190 cases (27.94%) of chlamydial infections, and 0 cases (0.0%) of chancroid. Among the 1,499 cases reported

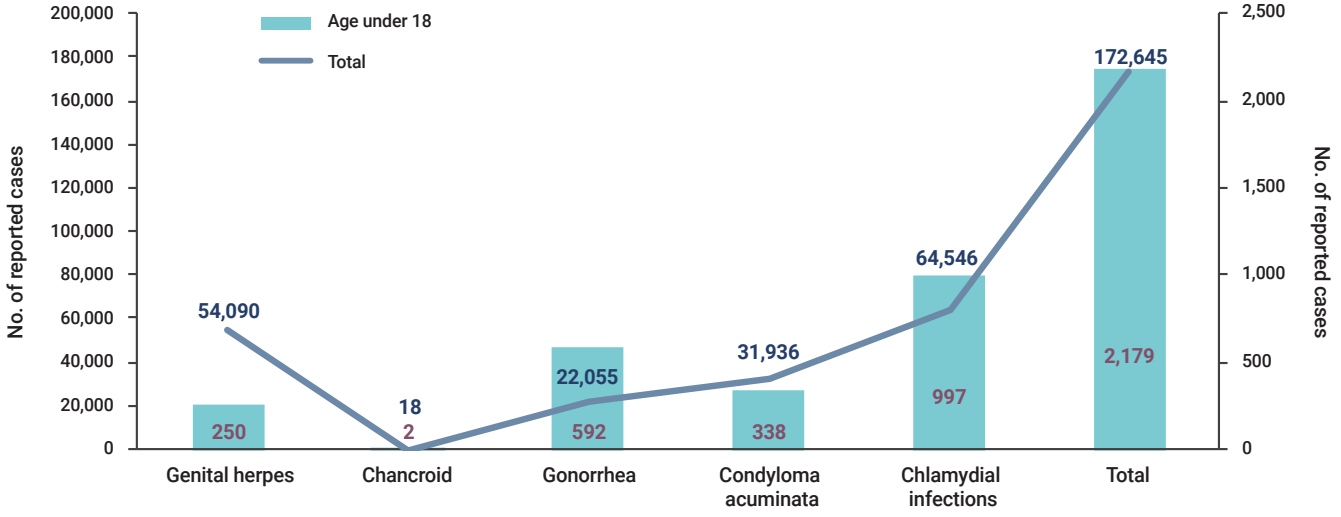

Figure 2. The number of reported cases of sexually transmitted infections (STIs) involving children below the age of 18 years.
In the last 10 years (2010–2019); the number of reports of STIs in children has been increasing. The incidence of chlamydial infections was the highest, while that of chancroid was the lowest.

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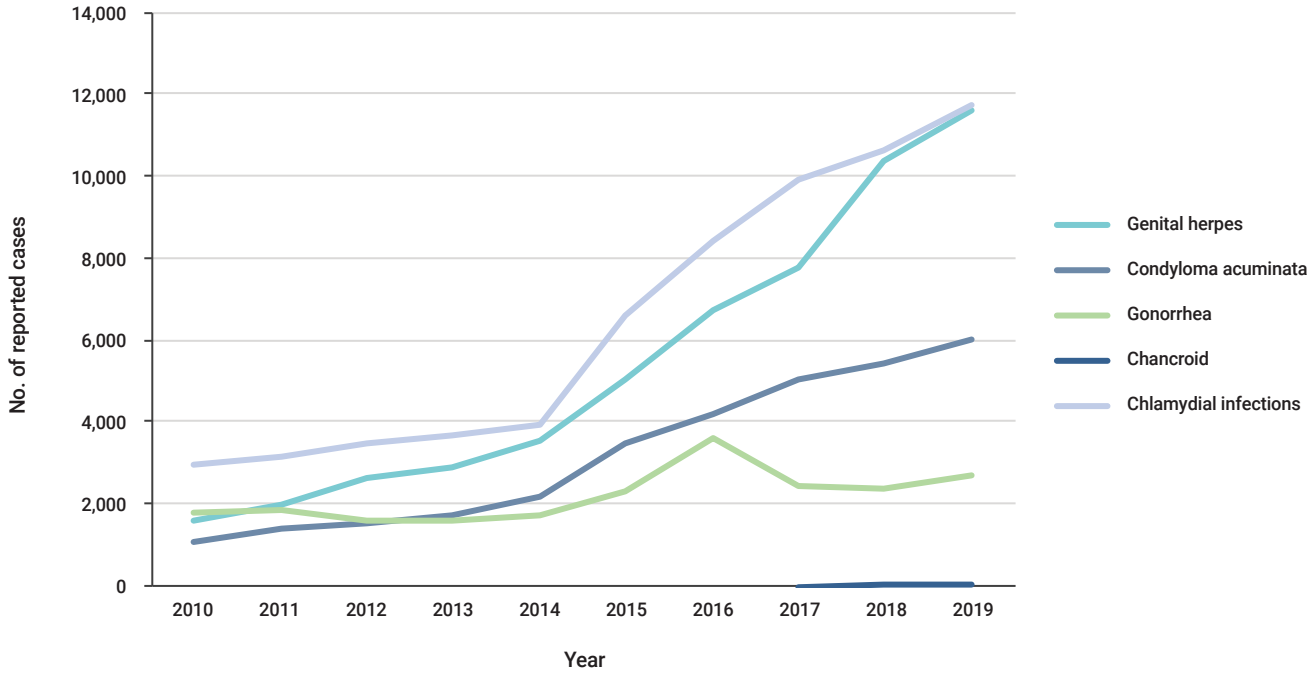

Figure 3. The number of reported cases of sexually transmitted infections (STIs) in children in Korea, by type of STIs.
The most commonly reported STIs in children in Korea were as follows: chlamydial infections, gonorrhea, genital herpes, condyloma acuminata, and chancroid.

in girls, there were 214 cases (14.28%) of genital herpes, 248 cases (16.54%) of gonorrhea, 228 cases (15.21%) of condyloma acuminata, 807 cases (53.84%) of chlamydial infections, and 2 cases (0.13%) of chancroid. Thus, it is evident that the most commonly reported STIs in boys and girls were gonorrhea and chlamydial infections, respectively. In cases reported by age group, reports of chlamydial infections were highest in all age groups at 997 cases (45.75%), followed by gonorrhea (592 cases, 27.17%), condyloma acuminata (338 cases, 15.51%), genital herpes (250 cases, 11.47%), and chancroid (2 cases, 0.09%) (Figure 5).

Discussion

An analysis of the reported data revealed a total of 172,645 cases of STIs over 10 years (2010–2019), of which 2,179 cases (1.26%) were in children below the age of 18 years. An analysis of the 2,179 cases of STIs in children revealed that there were approximately 2.2 times more cases in girls (1,499 cases, 68.79%) than in boys (680 cases, 31.21%). The most commonly reported STIs were chlamydial infections (997 cases, 45.75%), gonorrhea (592 cases, 27.17%), condyloma acuminata (338 cases, 15.51%), genital herpes (250 cases, 11.47%), and chancroid (2 cases, 0.09%). Chlamydial infections, genital herpes, and gonorrhea were common among adolescents aged between 14 to 17 years. Condyloma acuminata, in particular, were consistently reported in children below the age of 14 years.

The limitations of this study are as follows. Since the analyzed data were only cases reported from the 590 designated surveillance sites, it was difficult to identify cases in other institutions. Furthermore, previous reports of syphilis potentially caused by sexual abuse were excluded, as reports were documented under mandatory surveillance only until 2019. Finally, although a child is defined as an individual below the age of 18 years under the Child Welfare Act, the age listed in local government guidelines for reporting STIs has been adjusted to children below the age of 10 years to reflect the trend among younger individuals to engage in sexual activity. Thus, the number of reported cases might actually be higher than those in the analyzed data. In terms of the guidelines for STIs treatment, the World Health Organization and other nations have listed reporting standards involving specific STIs in which sexual abuse is highly suspected [7]. Such STIs listed in the United States include trichomonas, genital herpes, and condyloma acuminata [8], while in Canada, the list includes gonorrhea and trichomonas in children under 6 years of age, with an obligation to report chlamydial infections as a suspected case of sexual abuse [9].

However, the Korean STI treatment guidelines published in 2016 don't have enough information about the sexual abuse

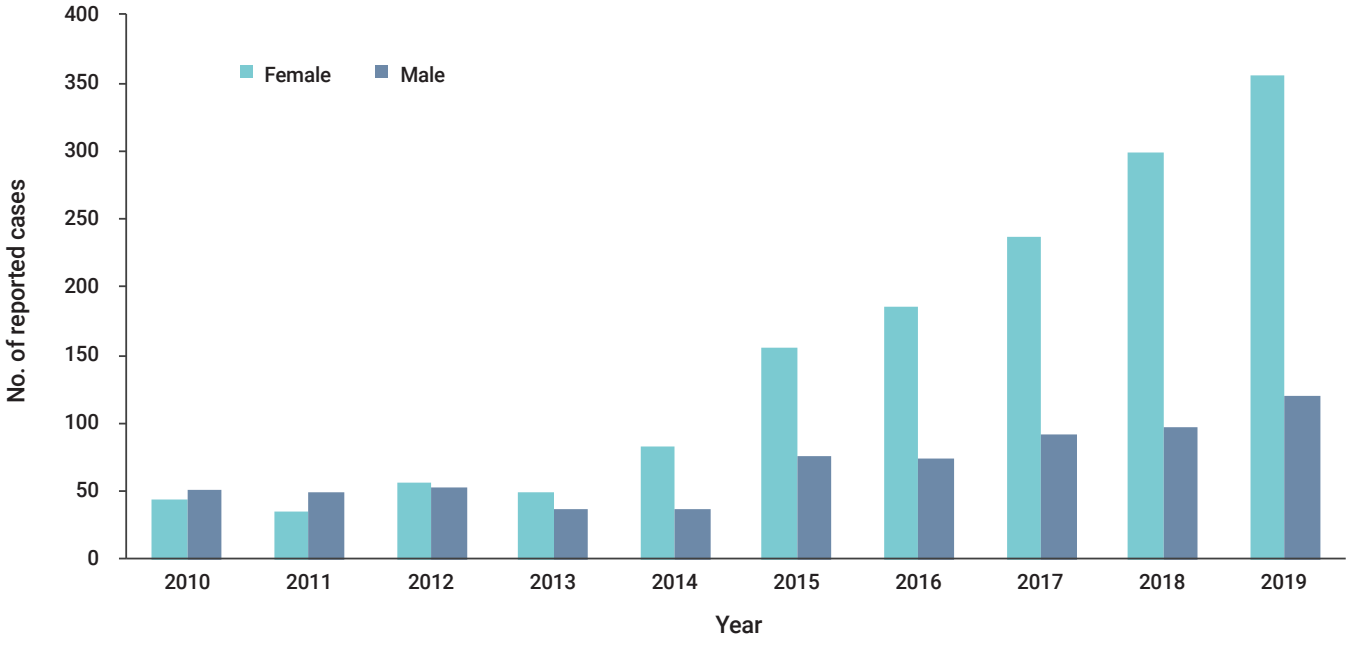

Figure 4. The number of reported cases of sexually transmitted infections in children in Korea, by sex.
Although there were more cases reported in boys until 2010/2011, the number of cases reported in girls has significantly increased since 2012.

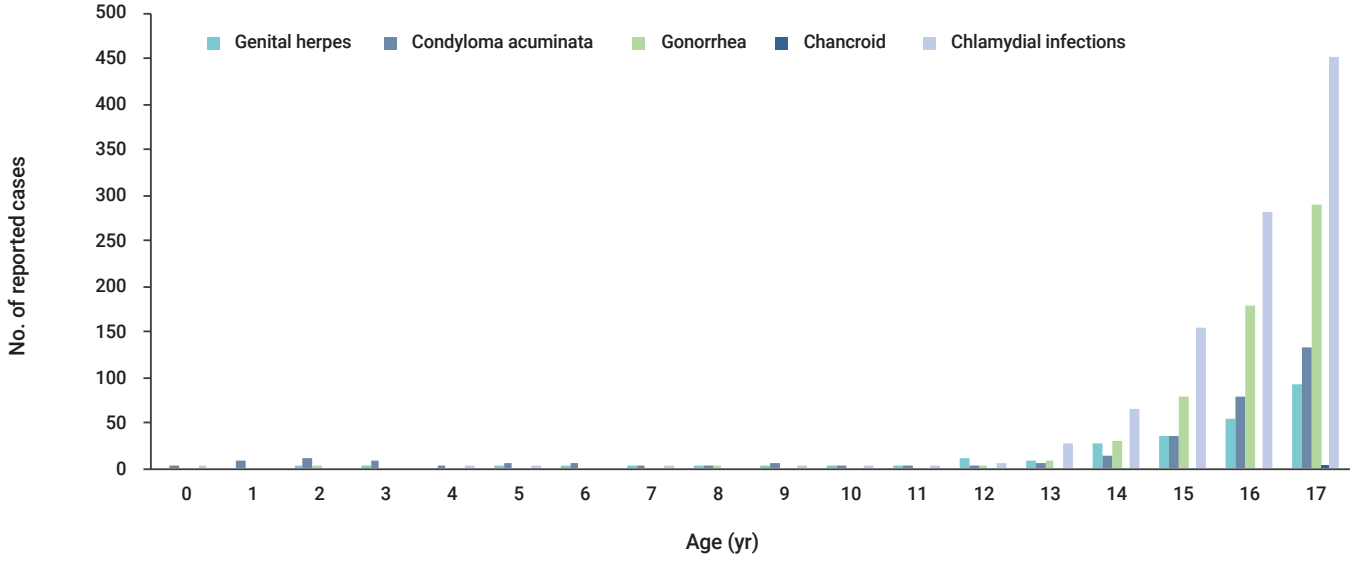

Figure 5. Number of reported cases of sexually transmitted infections (STIs) in children in Korea, by age.
The highest incidence was observed in children aged 17 years or older. In all age groups, the most commonly reported STIs were genital herpes, gonorrhea, and condyloma acuminata.

of children [10]. According to the 2020 STIs management guidelines, confirmed cases of STIs are to be reported to local police, local child protection services, and the '112' phone line, while no additional measure or examinations are conducted for suspected cases with visible clinical symptoms. Condyloma acuminata, which have been regularly reported in adolescents, are growths that occur on the external genitals from HPV infections and can be prevented with HPV vaccines. Although HPV vaccines are included in the mandatory vaccination program in Korea, they are limited to girls aged 11 to 12 years. However, in countries such as the United States, Canada, England, and Australia, the

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HPV vaccine is also considered mandatory for boys in the same age group.

Legal and institutional arrangements for the protection of children from sexual abuse must be made to foster a safe and healthy environment for the proper physical and emotional development of children. There is a need to establish specific management protocols in local governments and associated organizations for the recovery or management of STIs in children. Furthermore, for cases of STIs in which sexual abuse is highly suspected, there is a need to establish guidelines for reporting by responsible local government personnel and the response following the reports. Boys should also be considered in the mandatory HPV vaccination program to prevent HPV infections. Finally, to reduce the incidence of STIs in specific age and sex groups, special attention should be paid to evidence-based promotion and education.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Availability of Data
All data come from the studies included in references.

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Original Article

Perceptions of the COVID-19 vaccine and willingness to receive vaccination among health workers in Nigeria

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ABSTRACT

Objectives: The study aimed to examine health workers' perceptions of the coronavirus disease 2019 (COVID-19) vaccine in Nigeria and their willingness to receive the vaccine when it becomes available.

Methods: This multi-center cross-sectional study used non-probability convenience sampling to enroll 1,470 hospital workers aged 18 and above from 4 specialized hospitals. A structured and validated self-administered questionnaire was used for data collection. Data entry and analysis were conducted using IBM SPSS ver. 22.0.

Results: The mean age of respondents was 40 ± 6 years. Only 53.5% of the health workers had positive perceptions of the COVID-19 vaccine, and only slightly more than half (55.5%) were willing to receive vaccination. Predictors of willingness to receive the COVID-19 vaccine included having a positive perception of the vaccine (adjusted odds ratio [AOR], 4.55; 95% confidence interval [CI], 3.50–5.69), perceiving a risk of contracting COVID-19 (AOR, 1.50; 95% CI, 1.25–3.98), having received tertiary education (AOR, 3.50; 95% CI, 1.40–6.86), and being a clinical health worker (AOR, 1.25; 95% CI, 1.01–1.68).

Conclusion: Perceptions of the COVID-19 vaccine and willingness to receive the vaccine were sub-optimal among this group. Educational interventions to improve health workers' perceptions and attitudes toward the COVID-19 vaccine are needed.

Keywords: COVID-19; COVID-19 vaccine; Health workers; Nigeria; Perception; Willingness

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Introduction

The coronavirus disease 2019 (COVID-19) outbreak, which originated in Wuhan, China, in December 2019, has gradually spread to over 215 countries [1]. It was declared a pandemic by the World Health Organization in March 2020 [2]. Since the onset of the COVID-19 pandemic, more than 79 million cases and over 1.7 million deaths have been recorded globally as of December 29, 2020 [3].

The COVID-19 pandemic has had a devastating effect on many countries' economies, health systems, education systems, and infrastructure [4–6]. The disease presently has no cure, and disease management is mainly supportive. Regular hand washing, use of facemasks, social distancing, and cough etiquette are vigorously recommended to limit community transmission of the virus.

Researchers across the world have been working assiduously to develop vaccines against the highly contagious virus. Approximately 60 COVID-19 candidate vaccines are undergoing clinical evaluations, and another 172 COVID-19 candidate vaccines are at the preclinical evaluation stage as of December 29, 2020 [7]. It is believed that some of these vaccines will be ready for use by early 2021. However, there are widespread skepticism and divergent views regarding the legitimacy of various COVID-19 vaccines among people across the globe.

The effectiveness of vaccination programs and the global objective of eradicating the pandemic require optimal acceptance of the vaccine across all countries. The success of any vaccination program is largely dependent on how well the vaccines are accepted among the population and the willingness of people to be vaccinated. Vaccine hesitancy—a continuum that encompasses delay, reluctance, or refusal to receive a vaccine despite its availability [8]—has been found to be a major obstacle to vaccination among the general population and among health workers, and widely held perceptions of the safety of vaccines may contribute significantly to this phenomenon. COVID-19 vaccination programs, which are already ongoing in some countries, may face any of the aforementioned challenges, especially due to the novelty of the disease, perceived controversies related to its origin, and the fast-tracked development of vaccines. In tropical countries like Nigeria, some people still outrightly deny the existence of the disease due to the misconception that the virus does not thrive in hot climates. Beliefs such as this may pose additional barriers to vaccine acceptance. Health workers perceptions and willingness to receive vaccination have been documented as essential for improving vaccination rates among patients and the general population. Health workers play a key role in changing patients' behaviors and are among the first people to understand the magnitude of the problem and are in the right position to recommend vaccination [9,10]. Thus, this study aimed to examine perceptions of the COVID-19 vaccine among health workers in Nigeria and their willingness to receive the vaccine when it becomes available. It is believed that this study will help to identify potential barriers to the success of a COVID-19 vaccination program and inform subsequent planning and implementation of such a program.

Materials and Methods

Study Area

The study was conducted in October 2020 across 4 specialized hospitals located in southern Nigeria. The hospitals were the University of Medical Sciences Teaching Hospital Complex, Mother and Child Hospital (both located in Ondo State in Southwest Nigeria), University of Benin Teaching Hospital (in Edo State in South-South Nigeria), and the Delta State University Teaching Hospital (in Oghara, Delta State, located in South-South Nigeria). All the hospitals included in the study were specialized health facilities that offered a wide range of preventive and curative health services.

Study Design and Participants

The survey adopted a health facility-based, cross-sectional study design. We used non-probability convenience sampling to enroll 1,470 hospital workers aged 18 and above from 4 specialized hospitals included in the study. The study participants included both clinical and non-clinical health workers who were fully employed and willing to participate. We excluded trainees on attachment in the hospital and any non-consenting individuals.

Data Collection Instrument

A structured and validated self-administered questionnaire was used for data collection. The questionnaire was designed to meet the objective of the study and went through several drafts and reviews. We pretested the final draft of the questionnaire with 30 health workers at another health facility and made necessary modifications afterwards. The final questionnaire used in the study had 3 sections. The first section was related to the participants' socio-demographic characteristics such as age, sex, education level, occupation in the medical field, marital status, and religion. The second section assessed their perceived risk of contracting COVID-19, and the third section assessed perceptions of the COVID-19 vaccine and respondents' willingness to receive a potential COVID-19 vaccine. Perceptions about the COVID-19 vaccine were evaluated using 10 items that were combined into

a single composite variable for analysis. The items were a mix of directly-worded and reverse-worded questions. Each item was assigned a score on a 5-point Likert scale (strongly disagree, 1; disagree, 2; undecided, 3; agree, 4; and strongly agree, 5) to capture the full range of opinions. Some of the items were reverse-coded so that higher values indicated positive perceptions of the COVID-19 vaccine. A higher score indicated that the participant had positive perceptions of the COVID-19 vaccine. The total score was determined by adding the points from all 10 items, with a maximum possible score of 50 points. The mean score was 34 points, which was used as the cutoff for classifying the participants [11]. The participants were considered to have positive perceptions of the COVID-19 vaccine if their scores were ≥34 points, while participants whose scores were <34 points were considered to have negative perceptions of the vaccine. Participants' willingness to receive the COVID-19 vaccine and their perceived risk of contracting COVID-19 were each assessed using 1-item questions with 'yes' or 'no' responses.

Data Analysis and Scale Assessment

Data entry and analysis were conducted using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). Frequency and percentage distributions were used to indicate socio-demographic variables. Perceptions of the COVID-19 vaccine and willingness to receive the vaccine were presented as bar graphs. In addition, associations between socio-demographic variables, perceptions of the vaccine, and willingness to receive the COVID-19 vaccine were examined using the chi-square test. To determine the reliability of the questionnaire, Cronbach's α reliability coefficient was used. The 10-item scale had high reliability, with a Cronbach's α of 0.836. Multivariate logistic regression analysis was used to determine adjusted odds ratios (AORs) and 95% confidence intervals (CIs) in order to identify the predictors of participants' willingness to receive the vaccine. The outcome variable for the multivariate analyses was willingness to receive the COVID-19 vaccine, which was classified as a dichotomous variable ('yes' or 'no'). The independent variables (age, marital status, occupation within the medical field, work experience, etc.) were recategorized into dichotomous variables for bivariate and multivariate analyses. Variables with p-values <0.3 at the bivariate level were entered into the multivariable analysis [12]. The level of significance for each test was set at $p < 0.05$.

Results

A total of 1,470 health workers were involved in the study. As shown in Table 1, approximately 38.2% of the participants were between 31 and 40 years old, with a mean age of 40±6 years. The majority (64.3%) were male, 61.5% were married, and 88.2% had a tertiary education. A majority of the respondents (65.2%) had fewer than 10 years of work experience (Table 1).

Overall, 53.5% of the health workers had positive perceptions of the COVID-19 vaccine, while 46.5% had negative perceptions of the vaccine (Figure 1). After analyzing some of the specific items from the questionnaire, more than 80% of the health workers agreed that the vaccine would prevent the spread of infection to patients and other health workers; however, 45% felt that they might not be able to afford to obtain the vaccine. Approximately 2/3 (66.7%) of the participants had reservations regarding the vaccine, and 43% felt that the

Table 1. Socio-demographic characteristics of the study participants (n=1,470)

Variable	Frequency (n, %)
Age (y)	
18–30	510 (34.7)
31–40	561 (38.2)
41–50	289 (19.7)
>50	110 (7.4)
Sex	
Male	945 (64.3)
Female	525 (35.7)
Marital status	
Single	534 (36.3)
Married	904 (61.5)
Divorced	15 (1.0)
Widowed	17 (1.2)
Education	
No formal education	6 (0.4)
Primary	32 (2.2)
Secondary	135 (9.2)
Tertiary	1,297 (88.2)
Religion	
Christianity	1,397 (95.0)
Islam	61 (4.1)
Traditional religion	12 (0.8)
Work experience (y)	
≤9	958 (65.2)
≥10	512 (34.8)
Occupation within medical field	
Doctor	319 (21.7)
Nurse	450 (30.6)
Medical lab scientist/technician	85 (5.8)
Pharmacist/physiotherapist	112 (7.6)
Other health worker (administrator, health attendant, etc.)	504 (34.3)

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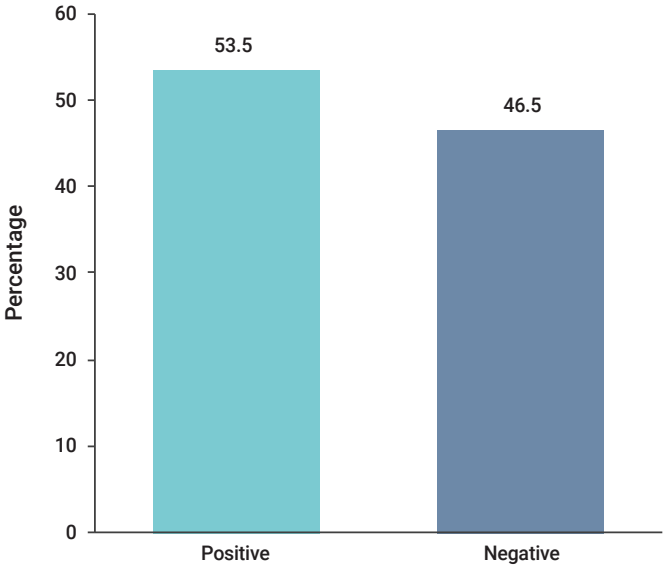

Figure 1. Perceptions of the coronavirus disease 2019 vaccine among health workers.

vaccine might not be safe (Figure 2), although a majority of the health workers (91.4%) perceived themselves to be at risk of contracting COVID-19. In total, only 55.5% of the health workers expressed willingness to receive the COVID-19 vaccine (Figure 3). Bivariate analysis to determine the factors associated with willingness to receive the COVID-19 vaccine revealed that health workers who had positive perceptions of the COVID-19 vaccine (72.3%) were more willing to receive COVID-19 vaccination than health workers with negative perceptions of the vaccine ($p < 0.001$). In addition, a high percentage (57.1%) of those who perceived themselves to be at risk of contracting COVID-19 were also willing to receive the vaccine ($p < 0.001$) (Table 2). Other factors significantly associated with willingness to receive the COVID-19 vaccine included education level ($p = 0.022$), years of work experience ($p = 0.016$), and one's occupation within the medical field ($p = 0.013$). However, age ($p = 0.052$), marital status ($p = 0.290$), religion ($p = 0.702$), and sex ($p = 0.301$) were not significantly associated with willingness

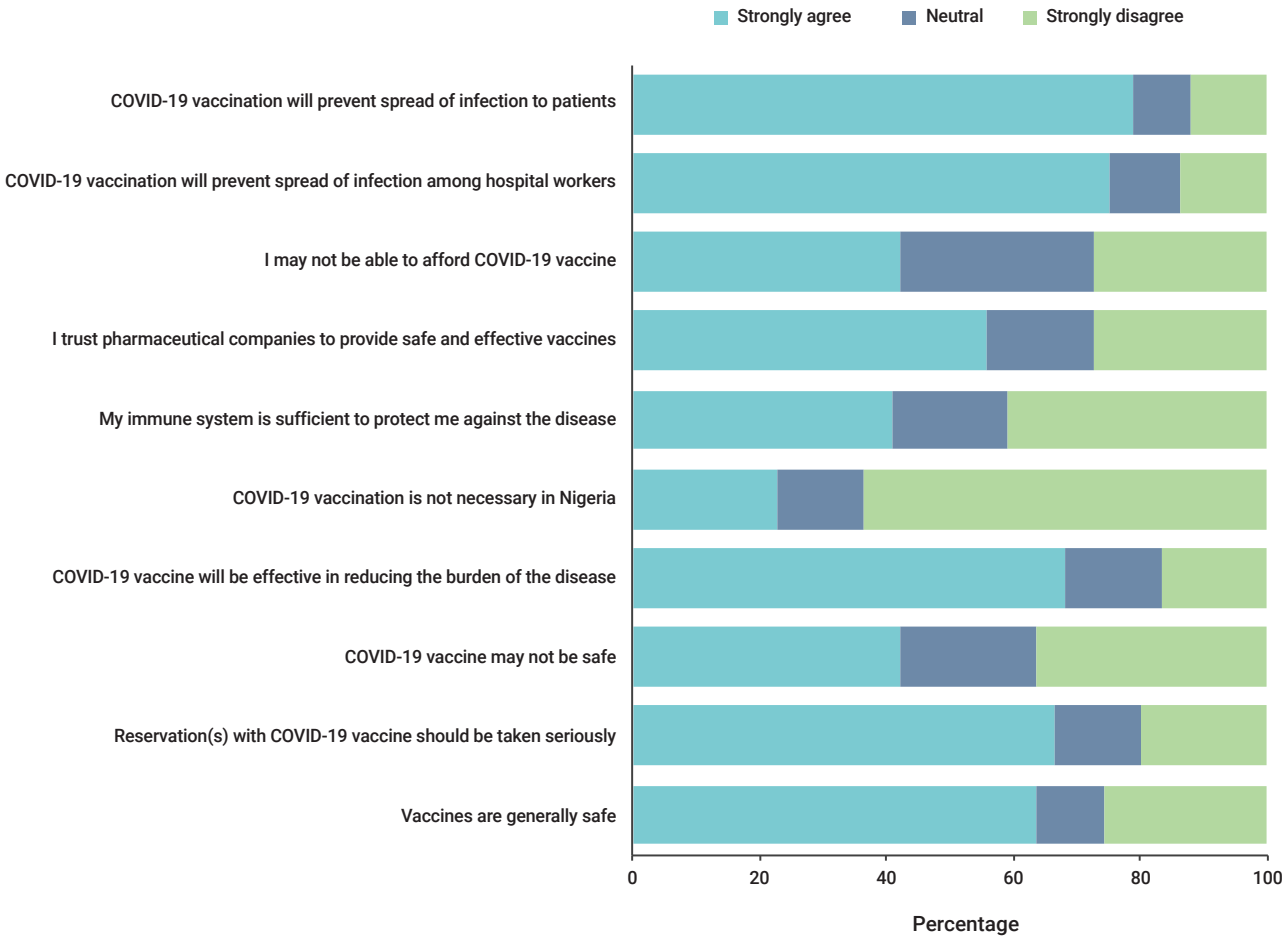

Figure 2. Distribution of health workers' responses to the 10-item scale on perceptions of the coronavirus disease 2019 (COVID-19) vaccine.

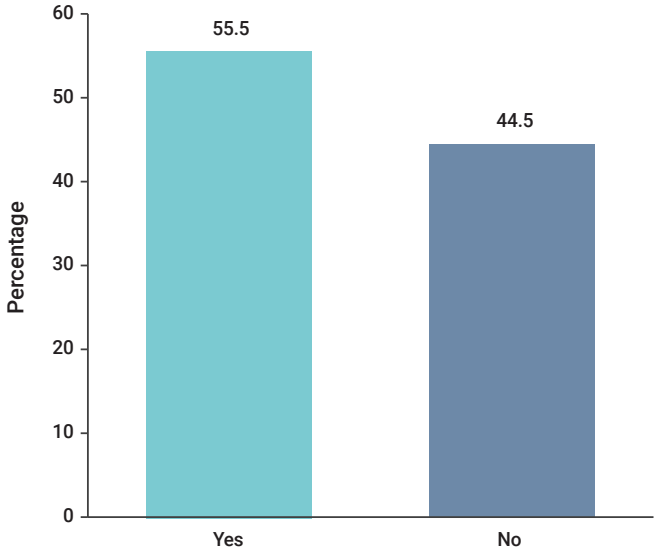

Figure 3. Willingness to receive the coronavirus disease 2019 (COVID-19) vaccine among health workers.

to receive the COVID-19 vaccine (Table 2).

Multivariate logistic regression analysis was used to determine the predictors of willingness to receive the COVID-19 vaccine (Table 3). Based on the analysis, predictors included having positive perceptions of the COVID-19 vaccine (AOR, 4.55; 95% CI, 3.50–5.69), perceiving a risk of COVID-19 infection (AOR, 1.50; 95% CI, 1.25–3.98), and being a clinical health worker (AOR, 1.25; 95% CI, 1.01–1.68). Having a tertiary education (AOR, 3.50; 95% CI, 1.40–6.86) and 10 or more years of work experience (AOR, 1.25; 95% CI, 1.11–3.93) were also predictors of willingness to receive the vaccine.

Discussion

Our study assessed perceptions of the COVID-19 vaccine among health workers and their willingness to receive the vaccine. In this study, we found that slightly more than half (53.5%) of the health workers had positive perceptions of the COVID-19 vaccine. This finding is quite revealing, as it is often assumed that the attitudes of health workers toward vaccination will be positive due to their knowledge and training. This, however, was not the case in this study, which gives insight into the need to address this challenge which could be a major barrier to widespread acceptance of the vaccine among health workers. It has been found that perceptions of vaccines among health workers and their perceived risk of infection influence vaccination decisions [13]. The study also found that approximately 4 in 10 health workers believed that they might not be able to afford the vaccine. This finding is significant since prior studies have documented the cost of vaccines as a primary reason health workers hesitate to receive them [10].

Notably, more than 2/3 of the health workers had reservations about receiving the vaccine even though only 43% of the participants specifically expressed safety concerns about the vaccine itself. Widespread conspiracy theories associated with the pandemic and a psychological need to understand various events surrounding the pandemic are possible explanations for this finding [14]. This finding is significant since psychosocial factors such as perceptions, emotions, trust in vaccines, and trust in vaccine providers have been found to contribute to vaccine hesitancy and refusal [15,16] and may have played a role in vaccine acceptance among these health workers.

In this study, we also found that only slightly more than half (55.5%) of the health workers were willing to receive the COVID-19 vaccine. This finding is surprising but explainable, as it has been found that public perceptions of the risks and benefits of vaccination constitute major obstacles to vaccine acceptance [17]. Health workers, as part of the general population, are also prone to subjective judgments that impact their behaviors and vaccination decisions, which may be the case in this study despite their medical knowledge. The acceptance rate in our study is similar to the 53.5% acceptance rate among United States residents [18], but lower than the 86% acceptance rate reported by Williams et al. [19]. The higher acceptance rate reported by Williams et al. [19] may be due to their study participants' high perceived susceptibility to COVID-19 infection since the participants in their study all had chronic respiratory illnesses. The proportion of those willing to receive the COVID-19 vaccine in our study fell short of the minimum rate of 75% required to reach herd immunity and stop the spread of the coronavirus epidemic [20]. This is alarming since our study was conducted among health workers who were expected to have a higher likelihood of being willing to receive the vaccine than the general population because of their medical knowledge. Willingness to receive the COVID-19 vaccine among our respondents was significantly associated with their perceptions of the COVID-19 vaccine, how many years of work experience they had, and their perceived risk of contracting COVID-19, which is a similar finding to previous studies [13,18,21–23]. Education level was also significantly associated with the participants' willingness to receive the COVID-19 vaccine in this study, which is consistent with the findings of similar studies on the COVID-19 vaccine [18,24,25]. Perceptions about vaccines and their safety are important factors that have been found to affect public uptake of vaccines [18,21]. These factors may be useful for educational interventions designed to

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Table 2. Factors associated with willingness to receive the COVID-19 vaccine

Variable	Willingness to receive the vaccine (*n* = 1,470)		Statistical indices	
	Yes	No	χ^2	*p*
Perceptions about the COVID-19 vaccine			193.340	< 0.001
Positive (*n* = 787)	569 (72.3)	218 (27.7)		
Negative (*n* = 683)	247 (36.2)	436 (63.8)		
Perceived risk of contracting COVID-19			16.924	< 0.001
Yes (*n* = 1,344)	768 (57.1)	576 (42.9)		
No (*n* = 126)	48 (38.1)	78 (61.9)		
Age (y)			3.786	0.052
18–40 (*n* = 1,071)	611 (57.0)	460 (43.0)		
≥ 41 (*n* = 399)	205 (51.4)	194 (48.6)		
Sex			0.881	0.301
Male (*n* = 525)	300 (57.1)	225 (42.9)		
Female (*n* = 945)	516 (54.6)	429 (45.4)		
Marital status			1.120	0.290
Not married (*n* = 566)	324 (57.2)	242 (42.8)		
Married (*n* = 904)	492 (54.4)	412 (45.6)		
Education level			5.224	0.022
Secondary education and below (*n* = 173)	82 (47.4)	91 (52.6)		
Tertiary education (*n* = 1,297)	734 (56.6)	563 (43.4)		
Religion			0.709	0.702
Christianity (*n* = 1,397)	773 (55.3)	624 (44.7)		
Islam (*n* = 61)	35 (57.4)	26 (42.6)		
Traditional religion (*n* = 12)	8 (66.7)	4 (33.3)		
Work experience (y)			1.142	0.016
≤ 9 (*n* = 958)	521 (54.4)	437 (45.6)		
≥ 10 (*n* = 512)	312 (60.9)	200 (39.1)		
Occupation within the medical field			6.195	0.013
Clinical health workers (*n* = 966)	526 (54.5)	440 (45.5)		
Non-clinical workers (*n* = 504)	240 (47.6)	264 (52.4)		

Data are presented as *n* (%).
COVID-19, coronavirus disease 2019.

improve health workers' perceptions and attitudes about the COVID-19 vaccine.

In our study, perceptions of the COVID-19 vaccine and one's perceived risk of contracting COVID-19 were strong predictors of vaccine acceptance, which is consistent with a similar study from Saudi Arabia [26]. Likewise, having a high education level was also a significant predictor of vaccine acceptance. Education and knowledge about vaccination have been found to help build trust and confidence about vaccination and may explain this finding [23]. The study also found that the occupations of health workers within the medical field and their length of work experience were predictors of willingness to receive the COVID-19 vaccine.

This study's strength is that it gives new insight into the perceptions of health workers regarding the COVID-19 vaccine in Nigeria, health workers' willingness to receive the vaccine, and possible factors that may influence acceptance of the vaccine. Another strength is the large sample size and multi-center design. However, the study has some limitations. The data were cross-sectional and therefore limited when it came to inferring causal relationships between variables. Some respondents may also have given responses to some questions in the questionnaire that were widely socially accepted at the time but which may change by the time the vaccine becomes available. This was minimized, however, by explaining and reassuring participants about the study's purpose.

In conclusion, our findings suggest that willingness to receive COVID-19 vaccination was sub-optimal among this group of health workers and was associated with

Table 3. Predictors of willingness to receive COVID-19 vaccination among health workers

Category of variables	AOR (95% CI)	p[a)]
Perceptions about the COVID-19 vaccine		
Negative (Ref)	1	
Positive	4.55 (3.50–5.69)	**< 0.001**
Perceived risk for COVID-19		
≤ No (Ref)	1	
≥ Yes	1.50 (1.25– 3.98)	**0.002**
Occupation within the medical field		
Non-clinical (Ref)	1	
Clinical health workers	1.25 (1.01–1.68)	**0.005**
Education level		
Secondary and below (Ref)	1	
Tertiary	3.50 (1.40–6.86)	**0.034**
Sex		
Female (Ref)	1	
Male	0.92 (0.60–2.68)	0.512
Marital status		
Not married (Ref)	1	
Married	1.02 (0.60–2.48)	0.563
Work experience (y)		
≤ 9 (Ref)	1	
≥ 10	1.25 (1.11–3.93)	**0.042**
Age group (y)		
18–40 (Ref)	1	
≥ 41	0.89 (0.64–1.26)	0.527

COVID-19, coronavirus disease 2019; AOR, adjusted odds ratio; CI, confidence interval.
[a)]Significant p-value in bold letters.

perceptions of the vaccine, the perceived risk of contracting COVID-19, education level, occupation within the medical field, and work experience. Vaccination of health workers is essential for protecting them against infectious diseases, and, considering their vital role in public health as major stakeholders in the fight against the COVID-19 pandemic and other major infectious diseases, improving vaccine acceptance among this group when it becomes available is critical. In addition, clear, well-articulated policies related to the COVID-19 vaccine are needed to combat the challenges that may arise from negative perceptions of the vaccine, concerns about affordability, and other reasons health workers cite for not obtaining vaccines.

Notes

Ethics Approval

Ethical approval was obtained from the ethics and research committees of the various health institutions where the study was conducted; the University of Medical Sciences Teaching Hospital Complex, Ondo City and University of Benin Teaching Hospital, Benin City. Written informed consent was obtained from each participant. The study protocol number was ADM/E22/A/VOL.VII/1483093.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets that were used for the analysis and preparation of this manuscript are available upon request. Interested persons can contact (femidele@gmail.com) or (oluseyiadejumo02017@gmail.com).

Authors' Contributions

Conceptualization: OAA, OAO; Methodology: all authors; Data curation: OAA, OAO; Investigation: OAA, CRM, ROO, OCO, KCO, SSO, OAJ, OML, ACE, MIN, AS, AOT, OSA, EOA, JOO; Formal analysis: OAO; Project administration: OAA; Resources: CRM, ROO, OCO, KCO, SSO, OAJ, OML, ACE, MIN, AS, AOT, OSA, EOA, JOO; Validation: OAA, CRM, ROO, OCO, KCO, SSO; Writing–original draft: OAO; Writing-review & editing: all authors.

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Original Article

Behavioral therapy and pharmacotherapy for relapse prevention in abstinent smokers: a rapid review and meta-analysis for the Korea Preventive Service Task Force

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ABSTRACT

Objectives: This study aimed to assess the effectiveness of relapse prevention interventions involving behavioral and pharmacological treatment among abstinent smokers.
Methods: This rapid review was conducted using MEDLINE, Cochrane CENTRAL, CINAHL, Embase, KMbase, and KoreaMed to identify studies published until June 20, 2020. The participants were abstinent smokers who quit smoking on their own, due to pregnancy, hospitalization, or by participating in a smoking cessation program. We found a systematic review that fit the objective of this study and included 81 randomized controlled trials (RCTs). Studies that did not present information on smoking cessation status, had no control group, or used reward-based interventions were excluded. Random effect and fixed effect meta-analyses were used to estimate the relative risk (RR) and 95% confidence interval (CI). In subgroup analyses, differences between subgroups were verified based on the participant setting, characteristics, intervention type, and intensity.
Results: Following screening, 44 RCTs were included in the meta-analysis. The review reported no differences in the success rate of relapse prevention between the behavioral interventions. Pharmacotherapy interventions showed higher success rates (RR, 1.15; 95% CI, 1.05–1.26; I^2 = 40.71%), depending on prior abstinence duration and the drug type.
Conclusion: The results indicated that pharmacotherapy has a significant effect on preventing relapse among abstinent smokers.

Keywords: Behavior therapy; Drug therapy; Randomized controlled trial; Rapid review; Relapse prevention; Smoking cessation

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Introduction

Smoking is one of the major global causes of morbidity and mortality, with about half of smokers dying from smoking-related diseases [1]. Research on the health effects of smoking began in the early 1960s, and in 1964, general surgeons in the United States released a research report [2]; since then, many epidemiological studies have examined the harmful effects of tobacco. According to the World Health Organization, more than 8 million people per year die due to tobacco-related addiction [3]; among these, 7 million deaths can be directly attributed to tobacco. Smoking increases the risk of chronic diseases, such as chronic obstructive pulmonary disease, hypertension, cardiovascular diseases, and susceptibility to cancer [4,5]. The health effects of smoking contribute to the burden of disease nationally and globally, especially in developing countries [6].

According to Statistics Korea, since 2010, the percentage of smokers who have attempted to quit smoking for more than 24 hours in the last year has been steadily increasing, reaching 52.7% in 2018 [7]. According to the findings of the European Network for Smoking and Tobacco Prevention, the relapse rate of smokers who quit smoking unaided tends to increase over time. A study reported complete abstinence rates among abstinent smokers of 19% at 4 weeks after quitting, 10% at 6 months, and 5% at 1 year [8]. Many smokers attempt to quit smoking with a desire to improve their health; however, they are unsuccessful due to severe nicotine withdrawal symptoms [9]. Nicotine dependence has been found to be a strong predictor of the success of smoking cessation [10]. Therefore, the process of abstinence requires multiple attempts, instead of a single trial [11], and it may occur after different durations of cessation attempts [12].

In this study, relapse refers to the phenomenon of recurrence of smoking amidst the process of attempting to quit smoking. During the smoking cessation process, behavioral changes are observed in people who try to quit smoking, which gradually leads to relapse after a period of abstinence [8]. Several interventions can help smokers continue on their path of smoking cessation. Behavioral therapies, such as cognitive-behavioral therapy, and pharmacological approaches are relapse interventions that help abstainers continue on their path of smoking cessation [13]. However, the success rate of abstinence decreases steadily over time due to relapses [14]. In addition, randomized controlled trials (RCTs) have reported mixed findings concerning the efficacy and long-term success of relapse prevention for smoking cessation [15].

In this study, we aimed to conduct an updated rapid review and meta-analysis of these RCT studies to examine the effectiveness of relapse prevention interventions in behavioral and pharmacological treatment among abstinent smokers who successfully quit smoking. This review provides updated evidence, including additional studies from another recent review. This study aims to provide sufficient evidence to recommend appropriate relapse prevention interventions for smoking cessation to the Korea Preventive Service Task Force (KPSTF).

Materials and Methods

A rapid review of behavioral therapy and pharmacotherapy for relapse prevention was conducted using the KPSTF's rapid review method to examine available evidence within a limited timeline [16]. The study protocol was approved by the KPSTF.

Search Strategy

We searched the following electronic international databases: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Additionally, domestic databases included KoreaMed and KMbase. The search terms included "relapse prevention," "recurrence," "smoking cessation," "smoke," "tobacco," and other relevant terms. As per the process of a rapid review, a systematic review (SR) or meta-analysis of the RCTs was explored initially. If we found an SR that could answer the key questions and aligned well with our inclusion and exclusion criteria, then we selected the most recent published SR fitting those criteria. Additional search strategies employed are provided in the supplementary files (Methods S1). There was no restriction on the publication year, and the most recent search date was June 19, 2020. The studies selected for this review were published in Korean and English.

Inclusion and Exclusion Criteria (PICO)

Studies conducting randomized controlled clinical trials were included in this review, while those with a follow-up period of less than 6 months were excluded.

The participants of the included studies were abstinent smokers, who voluntarily quit smoking (unassisted abstainers) or who quit smoking due to pregnancy, hospitalization, or by participating in a smoking cessation program (assisted abstainers). Abstinent smokers were defined as individuals who did not smoke at all within at least 24 hours. Participants who did not provide smoking cessation status at entry, who served in the military, or who did not report success at quitting smoking within 24 hours before entry were excluded.

Regarding the intervention, RCTs employing behavioral support and extended use of smoking cessation medication intended to prevent relapse were included. Among the included

studies, pharmacological intervention studies for smoking cessation used placebos for the control groups, while behavioral intervention studies for smoking cessation used no intervention, regular care, or minimal interventions for the control groups. Intervention studies with reward-based incentives were excluded.

Outcome Measure

The primary outcome was the prolonged or point abstinence rate at 6 months or more of follow-up from RCTs. For trials that reported multiple follow-up studies, we chose the longest follow-up duration for the primary outcome. Biochemical tests involving the exhaled carbon monoxide level or cotinine level in saliva or urine and self-report were employed to verify continuing abstinence. The secondary outcome was the prolonged or point abstinence rate at less than 6 months of follow-up when that was reported.

Data Collection and Processing

While selecting the studies for the rapid review, 2 reviewers identified potentially eligible studies for inclusion. First, the titles were screened, followed by the selection of the abstract and the full text of the articles for the review. SRs were screened by checking the inclusion and exclusion criteria before selecting relevant studies. Two reviewers cross-checked independently, and a third reviewer checked the selected articles and all of them reached a consensus. In order to prevent bias, the findings of all studies were carefully reviewed, and any duplicated research was excluded (Figure 1).

After finding the final SR for our study, 2 reviewers cross-checked the included RCTs to verify that they matched the inclusion and exclusion criteria. After selecting the studies, the following data from each RCT were identified: year of publication, author, intervention type, country, setting, number of participants, and abstinence verification method.

Quality Assessment

A Measurement Tool to Assess Systematic Reviews (AMSTAR) helps develop and evaluate SRs; moreover, it helps users focus on their methodological quality [17]. It comprises 11 items with 4 types of responses: "yes," "no," "can't answer," or "not applicable." The instrument incorporates the study design, characteristics, and data extraction, literature search including the gray literature, a combination of study results, publication bias, and conflict of interest. AMSTAR quality scores range from 0 to 11, where scores of 0 to 3 indicate low quality, 4 to 7 moderate quality, and 8 to 11 high quality. Finally, 5 SRs were selected; of which 2 that scored a higher rating and a recent Cochrane review published in 2019 were finally selected.

The study of Livingstone-Banks et al. [14], which was published in the Cochrane Library in October 2019 and aimed to assess relapse prevention interventions among recent quitters who relapsed to smoking, was used for this analysis. Studies until May 2019 using randomized or quasi-RCTs with a minimum of 6 months of follow-up from the quitting date were systematically reviewed.

Statistical Analysis

In the meta-analysis, statistical heterogeneity was tested by a graphical representation of study data through the forest plots and the Higgins I^2 test statistic. The Higgins I^2 test statistic indicates the proportion of variation between the sample estimates; an I^2 value $\geq 50\%$ indicates significant heterogeneity [18]. The Mantel-Haenszel method, which applies a fixed-effect model, is suitable when the number of studies is small. The DerSimonian and Laird method, which uses a random-effects model, has been used for a long time and measures overall effect estimates more accurately even with larger heterogeneity [19]. Considering the characteristics of studies and the statistical tests, a fixed-effects model was used when $I^2 < 50\%$ and a random-effects model was used when $I^2 > 50\%$.

Publication bias was tested using a funnel plot and the Egger test, which tests the linear relationship between the effect estimate and the standard error [20]. In order to identify significant effects of relapse prevention programs based on behavioral therapy and pharmacotherapy, differences between subgroups were verified according to participants' recruitment setting and characteristics, publication year and country, the type and intensity of intervention, the verification method of abstinence, publication bias, and reported conflict of interest, as analyzed using the Cochrane Q test. The risk of bias was analyzed using the Cochrane Collaboration's recommended tool to check the quality of the included studies. All analyses were performed using Stata/MP ver. 16.1 (StataCorp., College Station, TX, USA).

Results

Search Results

A total of 44 RCTs met the inclusion and exclusion criteria of the present study. Overall, 5,838 SRs were retrieved from 4 international databases; 4,630 of these were retained after removing duplicate studies by matching the title with the author. A total of 128 relevant studies were selected by screening the title and abstract, and 1 SR was eventually chosen. For the rapid review process, among the 81 RCTs in the selected SR, 44 RCTs were finally included in the meta-analysis. Figure 1 depicts the literature flow, and an attached

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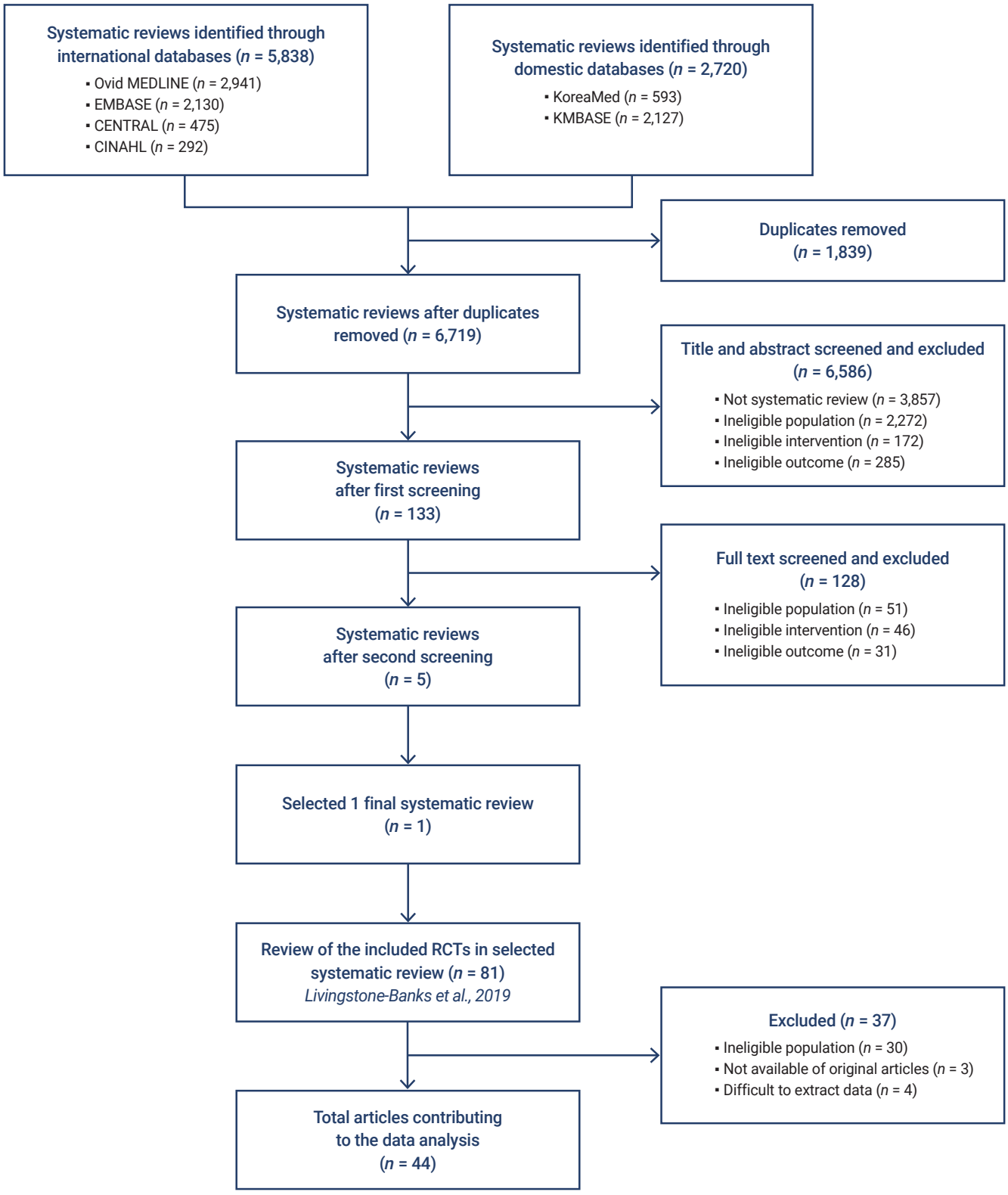

Figure 1. Flow diagram of the selection of eligible studies for the systematic review and meta-analysis.
CENTRAL, Cochrane Central Register of Controlled Trial; CINAHL, Cumulative Index to Nursing and Allied Health Literature; RCTs, randomized controlled trials.

supplementary file provides detailed information about the included studies (Table S1).

Effects of the Behavioral Therapy Intervention

Out of the 44 RCTs, 36 with relapse prevention interventions involving behavioral therapy were included; with 4 RCTs evaluating the effects of multiple behavioral therapy interventions. The 38 behavioral interventions resulted in no significant difference in the smoking cessation success rate for the intervention group over 6 months compared to the control group (relative risk [RR], 1.02; 95% confidence interval [CI], 0.98–1.07; I^2 = 21.81%) (Table 1, Figure 2). The funnel plot and Egger test were used to identify publication bias among studies of behavioral therapy. No publication bias was observed after visually evaluating the funnel plot or according to the Egger test (p = 0.18), as shown in Figure S1.

Of the 36 RCTs with 38 intervention groups for the secondary outcome, 12 RCTs reported outcomes at less than 6 months. The success rate of smoking cessation of the intervention group was not significantly higher than that of the control group (RR, 1.04; 95% CI, 0.98–1.10; I^2 = 23.77%). Furthermore, no publication bias was detected (p = 0.29) using the Egger test.

Effects of Pharmacotherapy Interventions

There were 10 RCTs on relapse prevention interventions based on pharmacotherapy, with 3 RCTs evaluating the effect of multiple interventions. Seventeen pharmacotherapy intervention groups showed significant effects on the success rate of smoking cessation compared to the control groups (RR, 1.15; 95% CI, 1.05–1.26; I^2 = 40.71%) (Table 2, Figure 3). There was no publication bias in the funnel plot (Figure S1) or in the Egger test (p = 0.46).

Among the 10 RCTs with 17 intervention groups, 7 (12 intervention groups) reported outcomes at less than 6 months as a secondary outcome. The success rate in the intervention group was significantly higher than in the control group (RR, 1.13; 95% CI, 1.02–1.25, I^2 = 57.44%). The Egger test detected no publication bias (p = 0.23).

Risk of Bias

A risk of bias assessment was performed on selected documents using the Cochrane Risk of Bias tool [21]. Incomplete outcome data (attrition bias), blinding of outcome assessment (detection bias), blinding participants and personnel (performance bias), allocation concealment (selection bias), and random sequence generation (selection bias) were evaluated using 3 grades: low, high, and unclear risk of bias. Of the studies evaluating

Table 1. Behavioral interventions for relapse prevention in abstinent individuals and subgroup analyses

Subgroup	Population (intervention-arm)	RR (95% CI)	I^2	p
Overall effect	13,494 (38)	1.02 (0.98–1.07)	21.81	-
Setting				0.43
Hospital/clinic	2,608 (6)	0.97 (0.87–1.09)	60.36	
Community	7,015 (17)	1.02 (0.96–1.09)	20.96	
Premature clinic	3,871 (15)	1.06 (0.99–1.15)	0	
Characteristics of participants				0.09
Unassisted abstainers	2,763 (7)	0.92 (0.84–1.01)	3.59	
Assisted abstainers	5,541 (11)	1.05 (0.97–1.13)	25.63	
Pregnant and postpartum women	4,122 (16)	1.07 (1.00–1.15)	0	
Hospitalized	1,068 (4)	1.02 (0.85–1.22)	68.51	
Type of intervention				0.89
Direct counseling	649 (3)	1.00 (0.86–1.67)	31.14	
Indirect counseling	2,022 (4)	0.98 (0.86–1.12)	0	
Self-help materials	3,898 (8)	1.03 (0.95–1.11)	47.80	
Multiple interventions	6,925 (23)	1.04 (0.97–1.10)	21.81	
Intensity of intervention				0.81
High	4,070 (15)	1.01 (0.93–1.11)	31.62	
Low	9,424 (23)	1.03 (0.93–1.11)	40.26	
Duration of prior abstinence				0.67
Less than 4 wk	6,458 (16)	1.03 (0.96–1.09)	41.72	
Unclear	5,912 (14)	1.05 (0.96–1.14)	25.48	
More than 4 wk	1,124 (8)	0.99 (0.90–1.09)	50.14	

RR, relative risk; CI, confidence interval; I^2, Higgins I^2 test statistic.

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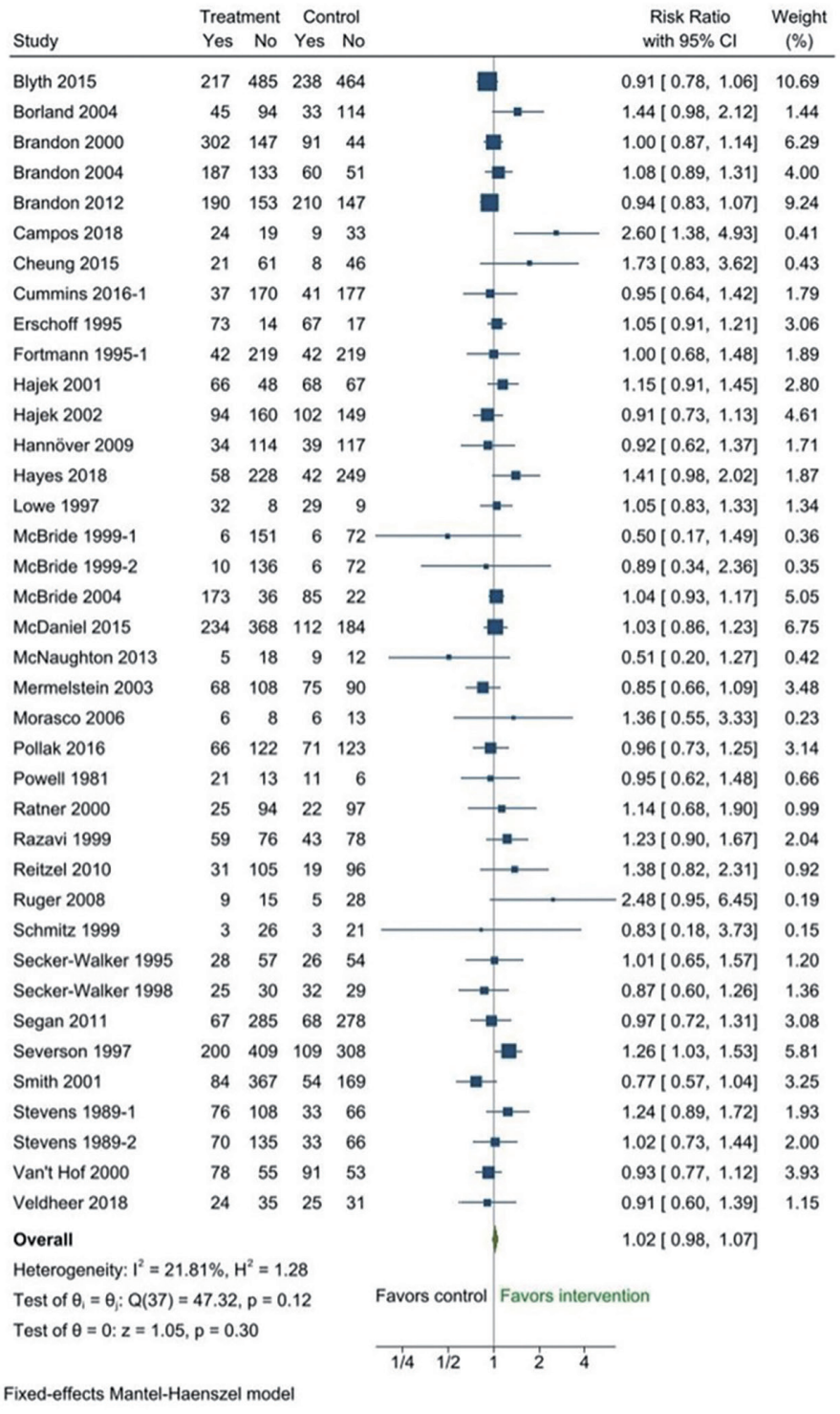

Figure 2. Summary of study findings of behavioral relapse prevention interventions.
CI, confidence interval; I^2, Higgins I^2 test statistic.

behavioral therapy, 1 study was evaluated as having a high risk of bias in random sequence generation, 5 studies in allocation concealment, 2 in blinding participants and personal, and 4 in blinding of outcome assessment. Regarding incomplete outcome data, 9 studies with behavioral interventions were unclear and 1 study reporting a pharmacotherapy intervention had a high risk of bias (Figure S2).

Table 2. Pharmacotherapy interventions for relapse prevention in abstinent individuals and subgroup analyses

Subgroup	Population (intervention-arm)	RR (95% CI)	I^2	*p*
Overall effect	4,051 (17)	1.15 (1.05–1.26)	40.71	-
Setting				0.26
Hospital/clinic	1,948 (4)	1.21 (1.06–1.37)	0	
Community	2,103 (13)	1.09 (0.96–1.24)	42.94	
Characteristics of participants				0.14
Unassisted abstainers	2,016 (12)	1.04 (0.91–1.19)	0.17	
Assisted abstainers	1,473 (3)	1.25 (1.09–1.42)	66.42	
Hospitalized	562 (2)	1.26 (0.89–1.79)	0	
Type of intervention				0.047
NRT	1,575 (7)	1.19 (0.99–1.44)	27.10	
NRT + bupropion	161 (2)	0.83 (0.64–1.07)	0	
Varenicline	1,297 (2)	1.23 (1.08–1.41)	82.28	
Bupropion	1,018 (6)	1.05 (0.88–1.26)	26.16	
Duration of prior abstinence				0.001
Less than 4 wk	2,752 (7)	1.23 (1.10–1.38)	12.74	
Unclear	1,010 (7)	1.11 (0.89–1.38)	0	
More than 4 wk	289 (3)	0.86 (0.75–0.99)	0	
Combination of intervention				0.47
Combined (behavioral + pharmacotherapy)	517 (2)	1.34 (0.87–2.05)	0	
Only pharmacotherapy	3,534 (15)	1.14 (1.04–1.25)	45.42	

RR, relative risk; CI, confidence interval; I^2, Higgins I^2 test statistic; NRT, nicotine replacement therapy.

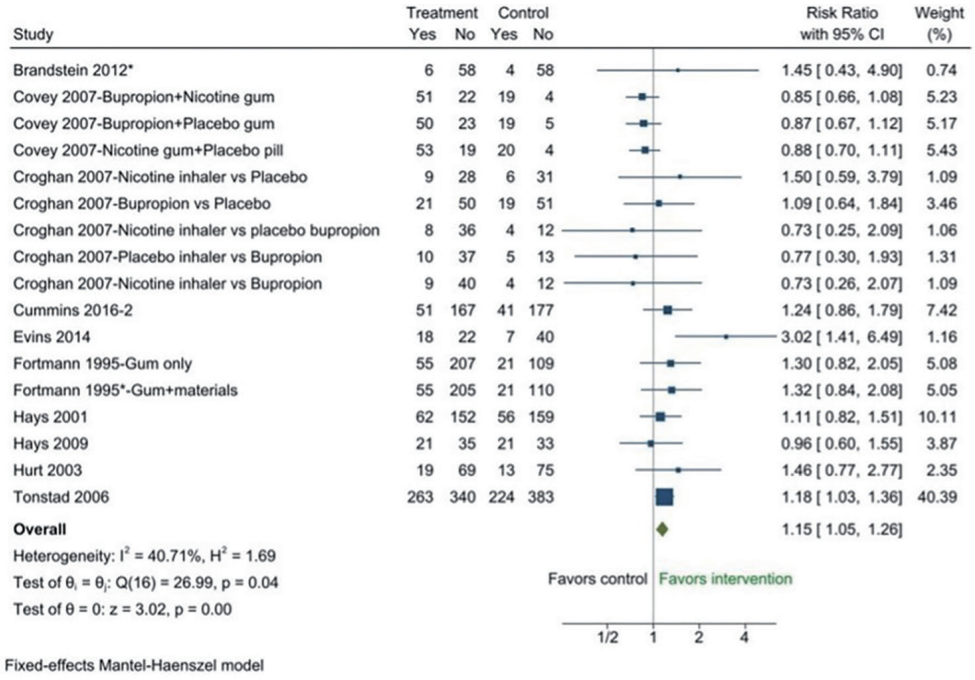

Figure 3. Summary of study findings of pharmacotherapy relapse prevention interventions for abstainers.
CI, confidence interval; I^2, Higgins I^2 test statistic.

Subgroup Analysis

Subgroup analyses were conducted to assess significant factors associated with the efficacy of relapse prevention interventions. Participants were divided into groups based on their characteristics: participants' recruitment setting, whether they enrolled in the smoking cessation program, were

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pregnant or hospitalized, the country of study, publication year, intervention type of behavioral therapy (counseling, self-help materials, or booklets), the intensity of the intervention, prior abstinence, verification method of abstinence, publication bias, and reports of conflicts of interest. There were no statistically significant differences among the subgroups in the behavioral intervention studies.

For the pharmacotherapy interventions, subgroup analyses were conducted among the following groups based on participants' recruitment setting, the characteristics of participants, whether they enrolled patients in the smoking cessation program or hospitalized inpatients, type of country, publication year, the intensity of the intervention, prior abstinence, verification method of abstinence, publication bias, reports of conflicts of interest, and drug type in pharmacotherapy (nicotine replacement therapy [NRT], bupropion, or varenicline). The success rate of smoking cessation varied depending on the type of drug ($p = 0.047$); while interventions with varenicline showed a significantly higher success rate, other modes of intervention that used different drugs did not show significant differences. Therefore, we excluded studies with varenicline, and no significant results were confirmed (RR, 0.97; 95% CI, 0.97–1.23). In addition, the success rate of smoking cessation varied depending on the duration of prior abstinence ($p = 0.001$); specifically, the success rate of smoking cessation was significantly higher when the baseline abstinence period was less than 4 weeks.

Discussion

We investigated the effectiveness of the relapse prevention program for abstinent smokers based on behavioral therapy or pharmacotherapy using a rapid review to develop a recommendation. Evidence from 44 RCTs reported that relapse prevention programs using pharmacotherapy increased the success rate of smoking cessation compared to control groups who used placebos. However, we could not find any difference in the success rate of smoking cessation between the intervention groups incorporating behavioral therapy and usual care. In this study, a meta-analysis was conducted by selecting the latest review about interventions for relapse prevention. Although several studies were excluded based on the exclusion criteria, the results from the included SR by Livingstone-Banks et al. [14] were consistent with those of this study. Our selected SR reported that the evidence does not support the use of behavioral interventions for assisted abstainers (RR, 0.98; 95% CI, 0.87–1.11) which is consistent with all previous studies. With pharmacotherapy, extended treatment helps in abstinence, but bupropion was not helpful and not enough evidence was available on NRT. Since we narrowed the scope of inclusion and exclusion criteria compared to the previous SR, we could conclude that the results were consistent.

In this review, a significant effect of existing behavioral interventions for relapse prevention among smoking abstainers was not detected. This indicates that the behavioral interventions provided no worthwhile benefit in preventing relapse in abstainers. However, a review of behavioral interventions of relapse prevention for abstainers by Agboola et al. [22] detected more positive results than those found in the present study. Although there are some discrepancies between prior reviews and this study, the differences in conclusions are not attributable to the included studies and are instead due to decisions related to subgroups and outcomes.

Furthermore, the results for some pharmacotherapies were more encouraging. Our study result reported that the extended use of smoking cessation drugs aided 15% of abstainers in maintaining successful smoking cessation, after 6 months of follow-up. The effect of pharmacological interventions was also observed at a shorter follow-up period, and was more prominent in abstainers at less than 4 weeks since quitting smoking. This might be a period when abstainers suffer from withdrawal symptoms. Some large and well-conducted studies illustrated the beneficial effects of varenicline in preventing relapse. However, studies on NRT or bupropion did not detect an effect on relapse prevention for abstainers. Varenicline is the most frequently prescribed medication for smoking cessation (87.9%) in the smoking cessation support services provided by the National Health Insurance Service [23]. This review provides evidence that pharmacological interventions, especially varenicline prescriptions, help abstinent smokers to continue their path of not smoking for over 6 months.

There are several limitations of this review. Firstly, the type and intensity of the behavioral therapy interventions in each study were highly variable; therefore, these conclusions about behavior therapy cannot be considered conclusive. Future studies should include RCTs with a single type of behavioral therapy intervention to further explore our conclusions about the effects of behavioral therapy on relapse prevention. Some studies applied a single intervention, but there were also complex interventions that applied 2 or more approaches. Accordingly, various subgroup analyses were performed. However, no significant effective specific behavioral therapy could be identified. Further research is required to provide more substantial results.

We intended to conduct a rapid SR that included RCTs conducted in Korea by searching Korean databases, but we could not find and include RCTs using Korean participants; thus, it was not possible to confirm any of these findings of relapse prevention within the Korean context. These findings

are meaningful and extracted from Korean databases; however, they indicate the need for an RCT on relapse prevention among the Korean population.

In terms of the limitations of pharmacotherapy, the subgroup analyses confirmed that the effect of pharmacotherapy depends on the drug type; however, it cannot be claimed that varenicline is the only successful drug for relapse prevention. To overcome this limitation, a subgroup analysis was conducted excluding those with varenicline, but no significant results were found. In addition, a combined program (behavioral and pharmacotherapy treatment) was reported to be more effective in smoking cessation than a single independent treatment [8]. However, in this review, no significant effects were revealed through various subgroup analyses. Moreover, it cannot be asserted that combined programs are not effective in preventing relapse, because only a small number of studies used combined programs and those studies used NRT.

Conclusion

In summary, this study confirmed that pharmacotherapy interventions improved the success rate of smoking cessation for abstainers through an analysis of 44 RCTs focusing on relapse prevention programs. To encourage and recommend effective relapse prevention programs, a sufficient number of studies with large populations and long-term follow-up assessments should be conducted using each drug for smoking cessation or combined interventions.

Supplementary Material

Methods S1. Search strategies; Table S1. Characteristics of the included studies on relapse prevention; Figure S1. Funnel plot of the studies; Figure S2. Results of risk of bias among the included studies. Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0017.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
All data generated or analyzed during this study are included in this published article. For other data, these may be requested through the corresponding author.

Authors' Contributions
Conceptualization: all authors; Data curation: NL, ESL; Formal analysis: NL, ESL; Investigation: all authors; Methodology: all authors; Project administration: BC; Resources: all authors; Software: all authors; Supervision: BC; Validation: all authors; Visualization: all author; Writing–original draft: NL, ESL; Writing–review & editing: all authors.

Additional Contributions
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Original Article

Validity and reliability of the Health-Related Quality of Life Instrument with 8 Items (HINT-8) in Korean breast cancer patients

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ABSTRACT

Objectives: This study evaluated the validity and reliability of the Health-Related Quality of Life Instrument with 8 Items (HINT-8) in postoperative breast cancer patients in South Korea.
Methods: The study included 300 breast cancer patients visiting a tertiary hospital. We measured health-related quality of life (HRQoL) using the HINT-8, the 5-level EQ-5D version (EQ-5D-5L), and the Functional Assessment of Cancer Therapy-Breast (FACT-B). Discriminatory ability, known-group validity, and convergent validity were assessed. Reliability was evaluated with the Cohen kappa, weighted kappa, and intraclass correlation coefficient (ICC).
Results: The EQ-5D-5L indexes ($p < 0.001$) and EQ visual analogue scale (VAS) scores ($p < 0.001$) were significantly higher in subjects with no problems in each item of the HINT-8 than in those with problems. The FACT-B total scores were also higher in subjects without problems on the HINT-8. Older age, lower education level, and comorbidities were associated with a lower HINT-8 index. The HINT-8 index was correlated with the EQ-5D-5L index and the EQ VAS, with correlation coefficients of 0.671 ($p < 0.001$) and 0.577 ($p < 0.001$), respectively. The correlation coefficients between the HINT-8 and the FACT-B ranged from 0.390 to 0.714. The ICC was 0.690 (95% confidence interval, 0.580–0.780).
Conclusion: The HINT-8 showed appropriate validity for capturing HRQoL in postoperative breast cancer patients.

Keywords: Breast neoplasms; Quality of life; Reproducibility of results

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Introduction

Breast cancer has high incidence and mortality rates, ranking first and fifth in incidence and

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mortality in world cancer statistics in 2020 [1]. In Korea, breast cancer was the type of cancer with the highest incidence in women in 2016, followed by thyroid cancer [2]. While the age-standardized incidence rate increased from 24.5 (per 100,000 people) in 1999 to 62.5 in 2016, the 5-year observed survival also showed an increasing tendency between 2012 and 2016 [2,3]. Accordingly, assessing health-related quality of life (HRQoL) is critical for capturing patients' experiences, in addition to traditional epidemiological measures such as mortality and survival rates.

There are 2 types of HRQoL measures: generic and disease-specific. Disease-specific instruments, such as the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), focus on issues related to a specific illness, whereas generic instruments assess overall health status in a wide range of populations, including healthy individuals [4]. Generic preference-based measures, such as the EQ-5D or the Short Form 6D, are widely used as a trial end-point and to generate utility estimates for economic evaluations [5,6]. However, the broad application of these generic instruments has been criticized due to cultural differences [7]. In light of this criticism, the Health-Related Quality of Life Instrument with 8 Items (HINT-8) was developed to fit the Korean context [8,9].

The psychometric properties of the HINT-8, a generic preference-based instrument, have been studied in the Korean general population [9]. In addition, its value set (a set of preference weights) was developed for use in the Korean population [10]. The HINT-8 can be used to estimate utility weights using this value set in economic evaluations. The Korea National Health and Nutrition Examination Survey (KNHANES), a national surveillance program assessing participants' health and nutritional status, has adopted the HINT-8 to evaluate quality of life since 2019. However, no study has yet investigated the validity and reliability of the HINT-8 in disease-specific populations, such as individuals with cancer. The psychometric properties of the HINT-8 in disease-specific populations should be studied to expand its use for decision-making in the healthcare sector. Therefore, we evaluated the validity and reliability of the HINT-8 in postoperative breast cancer patients in Korea.

Materials and Methods

Subjects and Study Setting

We recruited a consecutive series of 300 breast cancer patients in the ambulatory or inpatient care setting of a tertiary hospital in Seoul, South Korea between April and June in 2018. The target population was women (aged ≥ 30 y) who underwent surgery as a primary treatment for breast cancer. We only included female patients due to the substantial differences between male and female breast cancer, including the rare incidence of this condition in men [3]. Considering differences in patients' characteristics according to the postoperative duration, we categorized the population into 3 groups: group 1 (2–4 days after surgery, $n=50$), group 2 (within 5 years after surgery, $n=150$), and group 3 (more than 5 years after surgery, $n=100$). After obtaining written informed consent from each patient, a paper-based survey was conducted by a trained interviewer in the survey. After 1 to 4 weeks, 100 consecutive participants from the first survey were followed up through a telephone-based survey administered by the same interviewer. Considering fluctuations in HRQoL status during the immediate perioperative period [11], subjects in group 1 (2–4 days after surgery) were excluded from the retest for reliability assessment. The institutional review board of Asan Medical Center approved the study (No. 2018-0026).

Data Collection and HRQoL Assessment

Primary background information about demographics (age, education level, marital status, monthly household income, outpatient visit, hospitalization, and self-rated health) and clinical characteristics (duration of disease, surgery type, current treatment, and comorbidities) was collected from all participating subjects. The HINT-8, as the generic HRQoL instrument of interest, and other widely used instruments including the 5-level EQ-5D version (EQ-5D-5L) and the Functional Assessment of Cancer Therapy-Breast (FACT-B) were used in the initial and follow-up surveys [12,13].

The HINT-8 consists of 8 items (climbing stairs, pain, vitality, working, depression, memory, sleep, and happiness) and 4 levels (no problems, mild, moderate, and severe problems) representing 65,536 health states [8,9], which is a far higher number of states than the 3,125 states gathered by the EQ-5D-5L [14]. The HINT-8 scores range from 0.132 (worst possible health state, 44444444) to 1.000 (best possible health state, 11111111), and the index can be derived from the previously developed value set [10]. The EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) [14]. To derive a utility index from the descriptive system of the EQ-5D-5L, we used the tariff developed in Korea [15,16]. The EQ-5D-5L utility scores using the Korean tariff range from −0.066

(worst possible health state, 55555) to 1 (best possible health state, 11111), with a higher score indicating better health status. In addition to the EQ-5D-5L descriptive system, participants' overall current health status was assessed with the EQ visual analogue scale (EQ VAS) [14]. The EQ VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The Korean version 4 of FACT-B, a disease-specific instrument, was also used to confirm the validity of the HINT-8 in the population of Korean breast cancer patients [13,17]. The FACT-B consists of 5 subscales: physical well-being (PWB; score range, 0–28), social/family well-being (SWB; score range, 0–28), emotional well-being (EWB; score range, 0–24), functional well-being (FWB; score range, 0–28), and the breast cancer subscale (BCS; score range, 0–40). The FACT-B trial outcome index (TOI; score range, 0–96), FACT-General (FACT-G) total score (score range, 0–108), and FACT-B total score (score range, 0–148) are derived as follows: (1) FACT-B TOI = PWB score+FWB score+BCS score; (2) FACT-G total score = PWB score+SWB score+EWB score+FWB score; and (3) FACT-B total score = PWB score+SWB score+EWB score+FWB score+BCS score. In the FACT-B, a higher score represents better quality of life.

Statistical Analyses

The distribution of responses in each level of the different instruments was calculated, and the ceiling effect of the HINT-8 was examined in comparison with the EQ-5D-5L. To determine the discriminatory ability of the HINT-8, the mean scores of the different measures (EQ-5D-5L index, EQ VAS, and FACT-B total) were compared according to the presence of problems (without problems vs. with problems). The group with problems included participants with mild, moderate, or severe problems, whereas those who reported no problems were included in the group without problems. Regarding discriminative validity, it was assumed that the group reporting problems in the HINT-8 had a poor health state in other HRQoL instruments. To demonstrate the known-group validity of the HINT-8, the HINT-8 index score was evaluated according to sociodemographic and clinical features. We hypothesized that the HINT-8 index would be lower in older and less educated groups [18]. We also evaluated the EQ-5D-5L index scores between relevant groups, and then calculated the relative efficiency (RE) to compare the efficiency of 2 generic instruments to capture relevant differences in breast cancer patients [19]. The RE was defined as the ratio of the squared *t* statistics ($t^2_{HINT\text{-}8}/t^2_{EQ\text{-}5D\text{-}5L}$) or the ratio of ANOVA F statistics ($F_{HINT\text{-}8}/F_{EQ\text{-}5D\text{-}5L}$).

To evaluate convergent validity, the associations of the HINT-8 with the EQ-5D-5L and FACT-B were examined. It was assumed that a specific item of the HINT-8 would correlate more strongly with conceptually relevant categories of the other instruments (i.e., EQ-5D-5L dimensions and FACT-B subscales) than with unrelated ones. The Cohen kappa, weighted kappa coefficient, and intraclass correlation coefficient (ICC) were calculated to identify the reliability of the HINT-8, including individual items and the utility index [20]. A p-value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Subject Characteristics

The ages of subjects in the baseline and follow-up tests were 54.4 ± 9.1 and 54.4 ± 8.6 years, respectively (Table 1). Regarding the education level, the largest proportion (46.0%) of participants in the first survey had a university degree or higher, whereas the largest group in the follow-up survey (45.0%) had a secondary education level. The proportion of married participants was 79.7% and 79.0%, respectively. The average monthly household income (Korean won, KRW) was slightly higher in the baseline population than in the retest population (5,080,000 ± 5,160,000 vs. 4,920,000 ± 5,570,000 KRW). The duration of disease after diagnosis was 4.2 ± 4.0 years in the first paper-based survey and 4.8 ± 3.7 years in the second telephone-based survey. Patients who underwent partial mastectomy accounted for the largest proportion of participants in the baseline and follow-up groups (69.7% and 72.0%, respectively). In both rounds of tests, the proportion of patients undergoing current treatment was similar (46.3% vs. 49.0%). The proportions of participants with any comorbidities were 36.7% and 41.0% in the baseline and follow-up tests, respectively.

Distribution of Responses to HRQoL Instruments

The response distribution of individual HINT-8 items is shown in Figure 1A. In the HINT-8, more than 90% of the responses to the items of climbing stairs, pain, working, depression, and memory corresponded to levels 1 and 2 in the first survey, whereas the proportion of responses of levels 1 to 3 was over 90% for the vitality, sleep, and happiness items. The HINT-8 indexes were similar in the first and second surveys (0.801 ± 0.095 vs. 0.813 ± 0.091). The average EQ-5D-5L index was slightly higher than the HINT-8 indexes in both the test and retest results (0.850 ± 0.117 vs. 0.881 ± 0.115). In terms of descriptive responses to the EQ-5D-5L, 89.2% to 94.4% of participants responded with levels

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Table 1. General and clinical characteristics

Characteristic	Baseline (*n* = 300)	Follow-up (*n* = 100)
Age (y)	54.4 ± 9.1	54.4 ± 8.6
30–49	93 (31.0)	28 (28.0)
50–59	119 (39.7)	42 (42.0)
≥ 60	88 (29.3)	30 (30.0)
Level of education		
Less than intermediate school	46 (15.3)	19 (19.0)
Secondary school	116 (38.7)	45 (45.0)
University degree or higher	138 (46.0)	36 (36.0)
Marital status		
Married	239 (79.7)	79 (79.0)
Others	61 (20.3)	21 (21.0)
Monthly household income (₩10,000)	508 ± 516	492 ± 557
Q1 (*n* = 85)	124 ± 64	115 ± 66
Q2 (*n* = 75)	327 ± 65	312 ± 56
Q3 (*n* = 72)	555 ± 60	519 ± 65
Q4 (*n* = 68)	1,136 ± 740	1,091 ± 891
Outpatient visit in the past 2 weeks		
Yes	92 (30.7)	35 (35.0)
No	208 (69.3)	65 (65.0)
Hospitalization in the past 1 year		
Yes	71 (23.7)	22 (22.0)
No	229 (76.3)	78 (78.0)
Self-rated health		
Very good/good	100 (33.3)	33 (33.0)
Moderate/poor/very poor	200 (66.7)	67 (67.0)
Postoperative duration	4.2 ± 4.0	4.8 ± 3.7
2–5 day (*n* = 50)	50 (16.7)	0
< 5 y (*n* = 150)	150 (50.0)	60 (60.0)
≥ 5 y (*n* = 100)	100 (33.3)	40 (40.0)
Surgery		
Total mastectomy	60 (20.0)	17 (17.0)
Partial mastectomy	209 (69.7)	72 (72.0)
Reconstruction	31 (10.3)	11 (11.0)
Current treatment		
Yes	139 (46.3)	49 (49.0)
No	161 (53.7)	51 (51.0)
Comorbidity		
Yes	110 (36.7)	41 (41.0)
No	190 (63.3)	59 (59.0)

Data are presented as mean ± standard deviation or *n* (%).
₩, Korean won.

1 and 2, except in the domain of self-care in the first round, and 88.0% to 95.0% in the second round of tests (Figure 1B); 92.0% and 91.0% of respondents reported no problems (level = 1) for the item of self-care. The mean ± standard deviation (SD) of the total score of the FACT-B was 104.76 ± 20.73 and the TOI was 68.16 ± 13.66 in the baseline test (Figure 1C).

In the EQ-5D-5L, 21.0% of respondents reported the best possible health state (11111), whereas only 2.3% reported the best health state (11111111) in the HINT-8 (Table S1). The EQ VAS score of subjects who reported the best possible health state in the HINT-8 was 4.63 points higher than that of subjects with the corresponding state in the EQ-5D-5L. The respondents reporting the best possible health state in the HINT-8 showed higher FACT-B scores than those with a perfect health state in the EQ-5D-5L. The FACT-B total scores differed by 6.03 between subjects who reported a perfect health status in the 2 HRQoL instruments (i.e., HINT-8 and EQ-5D-5L).

Validity and Reliability

The results of discriminatory ability testing showed that subjects who reported no problems on the HINT-8 had higher scores in the EQ-5D-5L and EQ VAS than those with problems, and the differences were significant ($p < 0.001$) (Table 2). The discriminatory ability of the HINT-8 was also demonstrated in the FACT-B measures, and the differences were mostly significant, except in the memory and sleep items of the HINT-8 (Figure S1). The results of the test for determining the differences between groups to evaluate known-group validity are presented in Figure 2 (HINT-8) and Figure S2 (EQ-5D-5L). The results were consistent with the hypotheses for the HINT-8: older patients and less educated patients had significantly lower HINT-8 indexes than those in other groups. The current treatment group had a slightly lower HINT-8 index than the others (0.794 vs. 0.804), although the difference was not statistically significant ($p = 0.755$). There was a trend toward lower HINT-8 index scores in subjects with comorbidities than in subjects without any comorbidity, but this trend did not reach statistical significance (0.779 vs. 0.811, $p = 0.059$). In terms of EQ-5D-5L, while the results were consistent with our hypotheses for age groups (age 30–49 y, 0.848; age 50–59 y, 0.842; age ≥ 60 y, 0.827; $p = 0.493$) and comorbidities (yes, 0.813; no, 0.855; $p < 0.001$), there were no significant differences according to education level and marital status, income, and current treatment. The HINT-8 showed better known-group validity than the EQ-5D-5L. The RE statistic was more than 1, denoting better efficiency, for the following characteristics: age groups (RE = 4.63), level of education (RE = 7.20), monthly household income (RE = 2.47), self-rated health (RE = 1.59), and current treatment (RE = 8.09). However, the RE values were lower for marital status (RE = 0.69), hospitalization (RE = 0.94), duration of disease (RE = 0.11), and comorbidities (RE = 0.96), implying poor efficiency of the HINT-8 compared to the EQ-5D-5L. The RE measures of several characteristics indicated

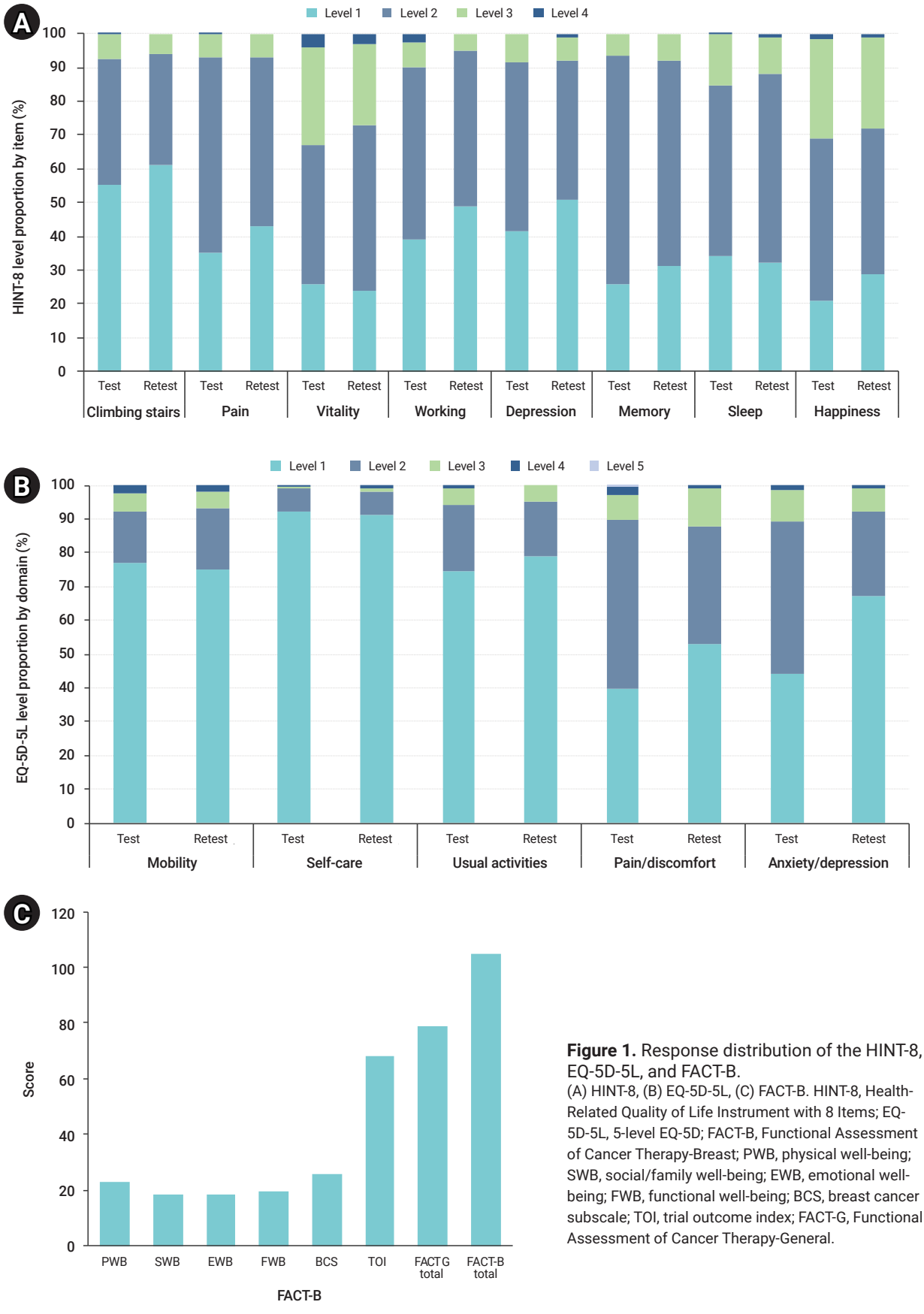

Figure 1. Response distribution of the HINT-8, EQ-5D-5L, and FACT-B.
(A) HINT-8, (B) EQ-5D-5L, (C) FACT-B. HINT-8, Health-Related Quality of Life Instrument with 8 Items; EQ-5D-5L, 5-level EQ-5D; FACT-B, Functional Assessment of Cancer Therapy-Breast; PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; BCS, breast cancer subscale; TOI, trial outcome index; FACT-G, Functional Assessment of Cancer Therapy-General.

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Table 2. Comparison of the EQ-5D-5L index, the EQ VAS, and the FACT-B total score according to the presence of problems in the HINT-8

HINT-8 item	Level[a)]	*n*	EQ-5D-5L index	EQ VAS	FACT-B total
Climbing stairs	1	162	0.878 ± 0.094**	82.29 ± 12.74**	27.71 ± 5.00**
	2 or 3 or 4	138	0.794 ± 0.130	74.86 ± 17.49	23.30 ± 6.29
Pain	1	104	0.901 ± 0.098**	84.01 ± 11.04**	28.14 ± 4.86**
	2 or 3 or 4	196	0.807 ± 0.117	76.14 ± 16.86	24.38 ± 6.20
Vitality	1	78	0.891 ± 0.114**	84.68 ± 13.05**	27.36 ± 5.54*
	2 or 3 or 4	222	0.821 ± 0.116	76.83 ± 15.85	25.09 ± 6.10
Working	1	121	0.891 ± 0.088**	83.84 ± 11.59**	27.97 ± 4.87**
	2 or 3 or 4	179	0.805 ± 0.125	75.51 ± 16.93	24.14 ± 6.26
Depression	1	117	0.899 ± 0.094**	85.12 ± 11.08**	28.02 ± 4.90**
	2 or 3 or 4	183	0.802 ± 0.119	74.87 ± 16.65	24.19 ± 6.23
Memory	1	81	0.887 ± 0.097**	83.28 ± 12.60**	27.70 ± 4.74**
	2 or 3 or 4	219	0.822 ± 0.122	77.24 ± 16.21	24.94 ± 6.30
Sleep	1	101	0.877 ± 0.098**	83.55 ± 10.95**	26.94 ± 5.36*
	2 or 3 or 4	199	0.821 ± 0.125	76.49 ± 16.94	25.05 ± 6.27
Happiness	1	60	0.899 ± 0.105**	88.18 ± 9.10**	27.83 ± 5.26*
	2 or 3 or 4	240	0.825 ± 0.118	76.54 ± 15.95	25.15 ± 6.11

Data are presented as mean ± standard deviation.
EQ-5D-5L, 5-level EQ-5D; EQ VAS, EQ visual analogue scale; FACT-B, Functional Assessment of Cancer Therapy-Breast; HINT-8, Health-Related Quality of Life Instrument with 8 Items.
[a)]Without problems: level 1, no problems; with problems: level 2, mild; level 3, moderate; level 4, severe problems.
*$p < 0.05$, **$p < 0.001$.

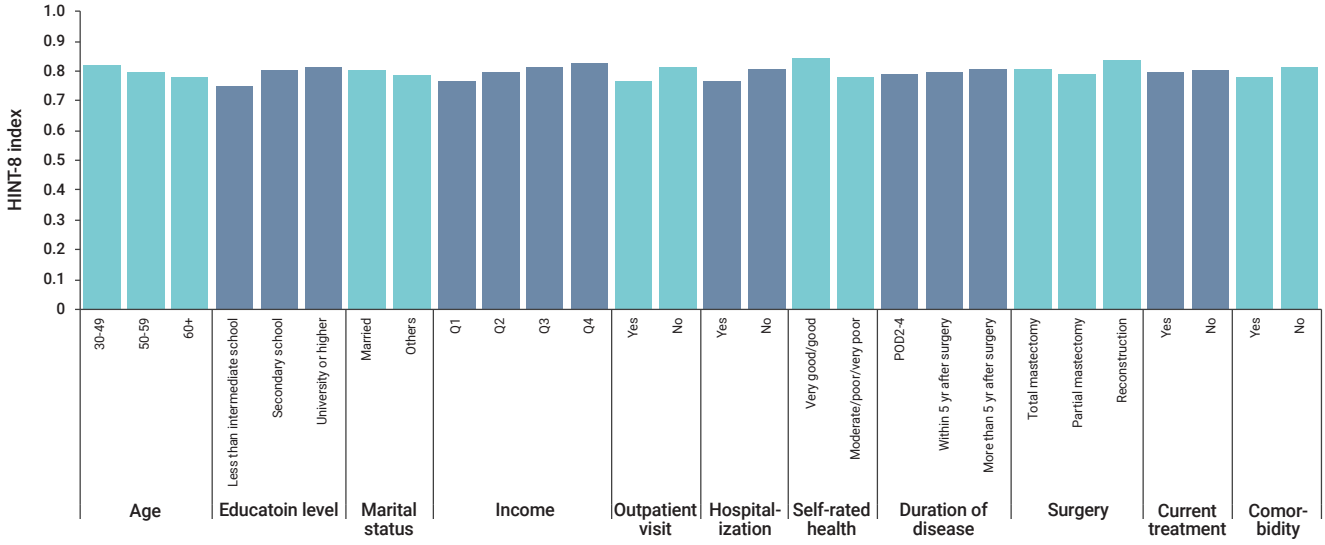

Figure 2. Mean scores of HINT-8 indexes according to general and clinical characteristics.
All *p*-values less than 0.05 except marital status (p=0.760), duration of disease (p=0.471), current treatment (p=0.755), and comorbidities (p=0.059). HINT-8, Health-Related Quality of Life Instrument with 8 Items; Q, quartile; POD, postoperative day.

similar efficiency (outpatient visit, RE = 1.21; surgery, RE = 1.05). The results of the correlation analysis between the HINT-8 and the other instruments are presented in Tables 3 and 4. The climbing stairs item showed an almost strong correlation with the mobility domain of the EQ-5D-5L ($r = 0.493$, $p < 0.001$). The working item of the HINT-8 showed moderate to strong correlations with the dimensions of mobility, usual activities, and pain/discomfort. There was a strong correlation between the depression item of the HINT-8 and the anxiety/depression domain of the EQ-5D-

Table 3. Correlation coefficients between the HINT-8 and the EQ-5D-5L

HINT-8	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	EQ-5D-5L index	EQ VAS
Climbing stairs	0.493**	0.165*	0.321**	0.365**	0.241**	−0.440**	−0.227**
Pain	0.407**	0.135*	0.373**	0.600**	0.290**	−0.553**	−0.310**
Vitality	0.311**	0.104	0.249**	0.290**	0.331**	−0.377**	−0.373**
Working	0.454**	0.108	0.419**	0.429**	0.338**	−0.505**	−0.338**
Depression	0.264**	0.162*	0.255**	0.224**	0.727**	−0.453**	−0.378**
Memory	0.206**	0.035	0.166*	0.318**	0.198**	−0.303**	−0.191**
Sleep	0.182*	0.175*	0.257**	0.263**	0.301**	−0.307**	−0.283**
Happiness	0.246**	0.071	0.229**	0.243**	0.511**	−0.376**	−0.461**
HINT-8 index	−0.473**	−0.158**	−0.435**	−0.581**	−0.561**	*0.671***	*0.577***

All coefficients were derived by Spearman correlation analysis except for those of the HINT-8 index with the EQ-5D-5L index and the EQ VAS (Pearson correlation). Pearson correlation coefficients are in italics.
HINT-8, Health-Related Quality of Life Instrument with 8 Items; EQ-5D-5L, 5-level EQ-5D; EQ VAS, EQ visual analogue scale.
*$p < 0.05$, **$p < 0.001$.

Table 4. Correlation coefficients between the HINT-8 and the FACT-B

HINT-8	PWB	SWB	EWB	FWB	BCS	TOI	FACT-G total	FACT-B total
Climbing stairs	−0.367**	−0.148*	−0.207**	−0.287**	−0.374**	−0.402**	−0.303**	−0.347**
Pain	−0.582**	−0.202**	−0.253**	−0.375**	−0.368**	−0.501**	−0.413**	−0.439**
Vitality	−0.469**	−0.211**	−0.330**	−0.358**	−0.230**	−0.407**	−0.406**	−0.397**
Working	−0.566**	−0.219**	−0.272**	−0.414**	−0.357**	−0.519**	−0.431**	−0.456**
Depression	−0.387**	−0.300**	−0.589**	−0.477**	−0.379**	−0.506**	−0.524**	−0.532**
Memory	−0.301**	−0.213**	−0.143*	−0.240**	−0.237**	−0.295**	−0.271**	−0.290**
Sleep	−0.351**	−0.114*	−0.211**	−0.439**	−0.244**	−0.424**	−0.322**	−0.336**
Happiness	−0.357**	−0.445**	−0.474**	−0.545**	−0.350**	−0.512**	−0.570**	−0.566**
HINT-8 index	*0.714***	*0.390***	*0.535***	*0.621***	*0.568***	*0.767***	*0.698***	*0.731***

All coefficients were derived by Spearman correlation analysis except for those of the HINT-8 index with all FACT-B subscale and summary scores (Pearson correlation). Pearson correlation coefficients are in italics.
HINT-8, Health-Related Quality of Life Instrument with 8 Items; FACT-B, Functional Assessment of Cancer Therapy-Breast; PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; BCS, breast cancer subscale; TOI, trial outcome index; FACT-G, Functional Assessment of Cancer Therapy-General.
*$p < 0.05$, **$p < 0.001$.

5L indexes (r = 0.727, $p < 0.001$). The happiness item in the HINT-8 was strongly correlated with the anxiety/depression domain of the EQ-5D-5L (r = 0.511, $p < 0.001$). The HINT-8 index was moderately correlated with individual domains of the EQ-5D-5L (from −0.581 to −0.435) except the self-care domain (r = −0.158). The correlation coefficients of the HINT-8 index with EQ-5D-5L and EQ VAS were 0.671 and 0.577, respectively. The pain and working items in the HINT-8 had a strong relationship with the PWB subscale of the FACT-B (−0.582 and −0.566, respectively). The depression item of the HINT-8 had a strong correlation with the EWB subscale, as well as the FACT-G, FACT-B total score, and TOI. The happiness item of the HINT-8 was strongly correlated with the FWB subscale, in addition to the FACT-G, FACT-B total score, and TOI. In general, there were strong correlations between the HINT-8 indexes and FACT-B subscales and other aggregated scores (i.e., TOI, FACT-G total, and FACT-B total), whereas there was a relatively moderate correlation (r = 0.390) between the HINT-8 index and SWB.

Agreement between surveys ranged from 43.0% to 70.0% (Table 5). The Cohen kappa coefficients of individual items in the HINT-8 ranged from 0.134 to 0.436 and the weighted kappa ranged from 0.249 to 0.513, indicating fair agreement except for the vitality item. The ICC of the HINT-8 index was 0.690 (95% confidence interval [CI], 0.580–0.780).

Discussion

This study compared the psychometric properties of the HINT-8, a newly developed general HRQoL instrument targeting the Korean population, with widely used generic and disease-specific HRQoL instruments. The comparative analysis between subjects with no problems and those with problems on the HINT-8 showed significant differences in

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Table 5. Test-retest reliability of the HINT-8

HINT-8	Kappa (95% CI)	Weighted kappa (95% CI)	Agreement rate (%)
Climbing stairs	0.396 (0.235–0.557)	0.469 (0.316–0.622)	66
Pain	0.428 (0.273–0.584)	0.467 (0.320–0.615)	68
Vitality	0.134 (–0.010–0.277)	0.249 (0.112–0.386)	43
Working	0.428 (0.280–0.577)	0.440 (0.304–0.575)	67
Depression	0.436 (0.281–0.591)	0.513 (0.374–0.652)	68
Memory	0.416 (0.238–0.593)	0.464 (0.293–0.635)	70
Sleep	0.418 (0.257–0.579)	0.499 (0.355–0.644)	66
Happiness	0.390 (0.241–0.539)	0.444 (0.294–0.593)	60
HINT-8 index	0.690 (0.580–0.780)[a]	-	-

HINT-8, Health-Related Quality of Life Instrument with 8 Items; CI, confidence interval.
[a]Intraclass correlation coefficient (95% CI).

the EQ-5D-5L index, EQ VAS, and FACT-B total score; groups reporting no problems had higher scores than the others. The results are interpreted as showing that the response levels of the HINT-8 meaningfully distinguish between the levels of specific health states. The results of known-group validity were consistent with those of a previous validity study of the EQ-5D-3L with respect to age and education level [5,21]. The hypotheses related to the known-group validity of the HINT-8 were mostly verified; younger, more highly educated subjects and patients with a longer disease duration showed a better HRQoL status. However, the differences between patients according to the duration of disease were not significant ($p = 0.471$). This non-significant difference was also observed in clinical features such as current treatment and comorbidities. The lack of statistical significance may be related to the small sample sizes of individual subgroups, which occurred because of resource restrictions and efforts to recruit a wide spectrum of patients with different HRQoL statuses based on previous studies [22–26]. Considering the RE statistics between the HINT-8 and the EQ-5D-5L, the HINT-8 showed better or similar known-group validity for most characteristics (RE statistics, range: 0.69–8.09), with the only exception being the duration of disease (RE = 0.11).

The comparison between the HINT-8 and the EQ-5D-5L showed strong correlations between the 2 relevant areas such as pain and depression (r = 0.600 and r = 0.727, respectively). Moreover, the correlation between the utility indexes of the 2 generic instruments (i.e., HINT-8 and EQ-5D-5L) was also strong (r = 0.671). The correlation coefficients between the HINT-8 index and the FACT-B (FACT-B subscales and total score) were 0.390–0.731 in current study. In previous studies, the correlations between the EQ-5D-3L index and FACT-B were strongest in SWB and weakest in FACT-B total scores, with ranges of 0.11–0.56 reported by Lee et al. [27] and 0.199–0.557 by Kim et al. [5], respectively. The HINT-8 showed a good correlation with the EQ-5D-5L in general. In addition, correlations of the HINT-8 with the FACT-B were better than the EQ-5D-3L. The results support the feasibility of using the HINT-8 instead of the EQ-5D-5L, a currently widely used tool in decision-making such as economic evaluations in patients with breast cancer.

The reliability of the categorical variables of the HINT-8 was acceptable, with weighted kappa coefficients of 0.249–0.513; using the cutoff points proposed by Landis and Koch [28], these values are interpreted as indicating fair or moderate agreement [29,30]. The overall Cohen kappa values derived from this study were lower than those of a previous study in the general population (0.565–0.799) [10]. The ICC of the HINT-8 index between the test and the retest (0.690; 95% CI, 0.580–0.780) was also to some extent lower than the outcomes derived from the HINT-20 and the HINT-8 (0.813 and 0.853, respectively) [10,20]. These inconclusive results regarding reliability may be attributed to differences in the survey administration methods between the baseline and the follow-up survey. A similar pattern was reported in the prior study of the EQ-5D-5L that used different survey administration methods; the kappa values of individual domains of the EQ-5D-5L ranged from 0.206 to 0.446 and the ICC was 0.626 [30]. Although the telephone interview method has been reported as equivalent to patient-completed surveys, variations in the agreement between individual domain scores were reported by Chatterji et al. [31].

A strength of the HINT-8 is the inclusion of a greater number of health states (65,536 health states) than those included in commonly used generic tools such as EQ-5D-3L and EQ-5D-5L [9,10]. Compared with the EQ-5D-5L, the HINT-8 showed good properties related to the ceiling effect.

Only 2.3% of participants reported a perfect health state in the HINT-8, whereas the corresponding proportion was 21.0% in the EQ-5D-5L. In addition, the EQ VAS score of the group with the full health state measured by the HINT-8 was higher than in the EQ-5D-5L (EQ VAS 93.00 vs. 88.37, respectively). These results indicate that the HINT-8 may be a more elaborate tool representing diverse health states that is superior for capturing changes in HRQoL among relatively healthy individuals. Considering the proper level of validity and better results in certain aspects including more informative health states, the HINT-8 is a usable tool to evaluate HRQoL in patients with breast cancer.

Despite the overall good psychometric properties of the HINT-8, this study has several limitations. First, the results should be generalized with caution because all subjects were recruited consecutively in either the ambulatory or inpatient units of a single tertiary hospital. Second, patients were enrolled into 3 subgroups according to the duration of disease (group 1, 2–4 days after surgery; group 2, within 5 years after surgery; group 3, more than 5 years after surgery) with predesignated numbers of samples in each subgroup. Resource restrictions and the variety of patients with clinical conditions affecting HRQoL resulted in small sizes in the different groups. Lastly, the use of different survey methods in the baseline and the follow-up tests may have affected the reliability of the results. The first test consisted of a paper-based survey administered in the hospital setting, including outpatient clinics and inpatient wards, whereas the follow-up survey was conducted through personal mobile devices. The use of mobile devices implies that participants were in a variety of locations at the time of the second survey, which might have affected the reliability of the test. The use of the same survey mode may improve the reliability of the instruments in future studies. Furthermore, future studies are needed both to assess the impact of different survey methods and to investigate tactics for minimizing the effects resulting from the use of different survey methods.

In conclusion, our study showed the HINT-8 is applicable to Korean women recovering from breast cancer surgery as a measurement of HRQoL. In particular, the HINT-8 showed better properties than the EQ-5D-5L in certain aspects such as known-group validity. Considering the inconclusive findings regarding reliability, its reliability should be more investigated in further research.

Supplementary Material

Table S1: Analysis of ceiling effects; Figure S1: Difference of FACT-B score between groups reporting with problems and without problems for each HINT-8 item; Figure S2: Mean scores of EQ-5D indexes according to general and clinical characteristics. Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0005.

Notes

Ethics Approval

The institutional review board of Asan Medical Center approved the study (No. 2018-0026). The written informed consent was obtained from all subjects prior to participating in the study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

All data generated or analyzed during this study are included in this published article and its supplementary information files. For other data, these may be requested through the corresponding author.

Authors' Contributions

Conceptualization: MWJ, HJL, JWL; Data curation: JK, SHA, BHS, JWL, SBL; Formal Analysis: JK; Funding acquisition: MWJ; Investigation: all authors; Methodology: MWJ, HJL, JWL; Project administration: JK, HJL; Supervision: MWJ; Writing–original draft: JK; Writing–review & editing: all authors.

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Brief Report

COVID-19 vaccine safety monitoring in the Republic of Korea: February 26, 2021 to April 30, 2021

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ABSTRACT

Objectives: On February 26, 2021, coronavirus disease 2019 (COVID-19) vaccination was started for high-priority groups based on the recommendation of the Advisory Committee on Immunization Practices with 2 available COVID-19 vaccines (AstraZeneca and Pfizer-BioNTech) in Korea. This report provides a summary of adverse events following COVID-19 vaccination as of April 30, 2021.

Methods: Adverse events following immunization are notifiable by medical doctors to the Korea Immunization Management System (KIMS) under the national surveillance system. We analyzed all adverse events reports following COVID-19 vaccination to the KIMS from February 26 to April 30, 2021.

Results: In total, 16,196 adverse events following 3,586,814 administered doses of COVID-19 vaccines were reported in approximately 2 months (February 26 to April 30, 2021). Of these, 15,658 (96.7%) were non-serious adverse events, and 538 (3.3%) were serious adverse events, including 73 (0.5%) deaths. The majority of adverse events (n=13,063, 80.7%) were observed in women, and the most frequently reported adverse events were myalgia (52.2%), fever (44.9%), and headache (34.9%). Of the 73 deaths following the COVID-19 vaccination, none were related to the vaccines.

Conclusion: By April 30, 3.6 million doses of the COVID 19 vaccine had been given in Korea, and the overwhelming majority of reports were for non-serious events. The Korea Disease Control and Prevention Agency continues to monitor the safety of COVID-19 vaccination.

Keywords: Adverse event; COVID-19; Safety; Vaccines

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Introduction

Coronavirus disease 2019 (COVID-19) is a serious pandemic that has spread globally since it was first reported in Wuhan, China, in December 2019. As of May 1, 2021 in Korea, more than

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114,000 people had confirmed infections and 1,831 had died of COVID-19 [1]. Globally, countries have implemented various control measures such as the use of masks, physical distancing, testing of exposed or symptomatic patients, or isolating infected individuals and their contacts to prevent the transmission of COVID-19. However, vaccines are needed to reduce the morbidity and mortality associated with COVID-19, and achieving herd immunity through vaccination is a key strategy to prevent the spread of the virus [2,3].

In 2020, various COVID-19 vaccines were developed based on different mechanisms of triggering an immune response. Currently, new mRNA vaccines, viral vector vaccines, and synthetic antigen vaccines have been developed and distributed worldwide for vaccination. Vaccination is one of the most effective ways to prevent the spread of infectious diseases; however, since vaccines are biological products, they might cause adverse events [4]. As reported in the clinical trials of the COVID-19 vaccines, adverse events following vaccination include pain, redness, and rashes at the site of injection and systemic reactions such as fever, myalgia, and headache. Anaphylaxis, although rare, was also reported [5–7].

The Korea Immunization Management System (KIMS) integrates and manages the records of registration for vaccination and reported adverse events, and also manages vaccine distribution in Korea. The Ministry of Food and Drug Safety approved the AstraZeneca vaccine on February 10, 2021 and the Pfizer-BioNTech vaccine on March 5, 2021. Shortly thereafter, the Advisory Committee on Immunization Practices recommended priority vaccination for healthcare personnel and vulnerable groups, including residents in nursing facilities and long-term care facilities.

In Korea, medical doctors are required to report any adverse events following immunization (AEFIs) in accordance with the Infectious Diseases Control and Prevention Act [8]. This study collected and analyzed the data of adverse events after COVID-19 vaccination through the KIMS to identify the epidemiological characteristics of AEFIs and unexpected health problems.

Materials and Methods

Adverse events after COVID-19 vaccination are monitored through the national passive monitoring system. AEFIs are primarily reported to local public health centers by medical doctors using the KIMS, a web-based reporting system. Serious events include intensive care unit admission, reports of death, adverse events of special interest, persistent or significant disabilities or incapacities, congenital anomaly/birth defects, and life-threatening adverse events.

A total of 16,196 adverse events following vaccination with the AstraZeneca and Pfizer-BioNTech vaccines were reported to the KIMS from February 26 to April 30, 2021; these adverse events were analyzed in this study. The AEFIs were examined by sex, age group, type of AEFIs, and type of vaccine. In addition, symptoms were analyzed including both non-serious and serious AEFIs. The chi-square test and SAS ver. 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analysis.

Results

In total, 3,586,814 doses of COVID-19 vaccines were administered, and 16,196 adverse events were reported between February 26 and April 30, 2021. Of these, 15,658 (96.7%) were general adverse events, and 538 (3.3%) were serious adverse events. The report rates gradually decreased from 1.8% in the first week of vaccination to 0.3% in the eighth week (Figure 1).

The rate of adverse events was 0.6% in women and 0.2% in men. The number of vaccinations was 2,279,364 (63.5%) in women, which were 1.7 times higher than that in men. The number of reported adverse events was also approximately 3 times higher in women than in men. The rate was highest in the age group of 18 to 29 years old at 2.9%, and the rate decreased as recipients' age increased (Table 1).

A total of 15,658 (96.7%) non-serious adverse events, including myalgia, fever, and headache, were reported, and 538 (3.3%) serious adverse events, including death and suspected anaphylaxis, were observed. Of all the adverse events, 13,968 were reported after AstraZeneca vaccines; 383 of these were serious adverse events including death and suspected anaphylaxis. The rate of adverse events after AstraZeneca vaccination was 7.7 per 1,000 doses, and the rate of serious adverse events, including death, was 0.2 per 1,000 doses. A total of 2,228 adverse events were reported after Pfizer-BioNTech vaccines, with 155 serious adverse events including deaths. The rate of adverse events after Pfizer-BioNTech vaccines was 1.3 per 1,000 doses, and the rate of serious adverse events, including death, was 0.09 per 1,000 doses.

Overall, the most frequently reported adverse events were myalgia (8,450, 52.2%), fever (7,274, 44.9%), and headache (5,660, 34.9%). The most frequently reported adverse events following vaccination with AstraZeneca vaccines included myalgia (7,780, 55.7%) followed by fever (6,878, 49.2%), and headache (5,185, 37.1%). The most frequently reported adverse events following vaccination with Pfizer-BioNTech vaccines were myalgia (670, 30.1%), dizziness (523, 23.5%), and headache (475, 21.3%), in decreasing order (Figure 2).

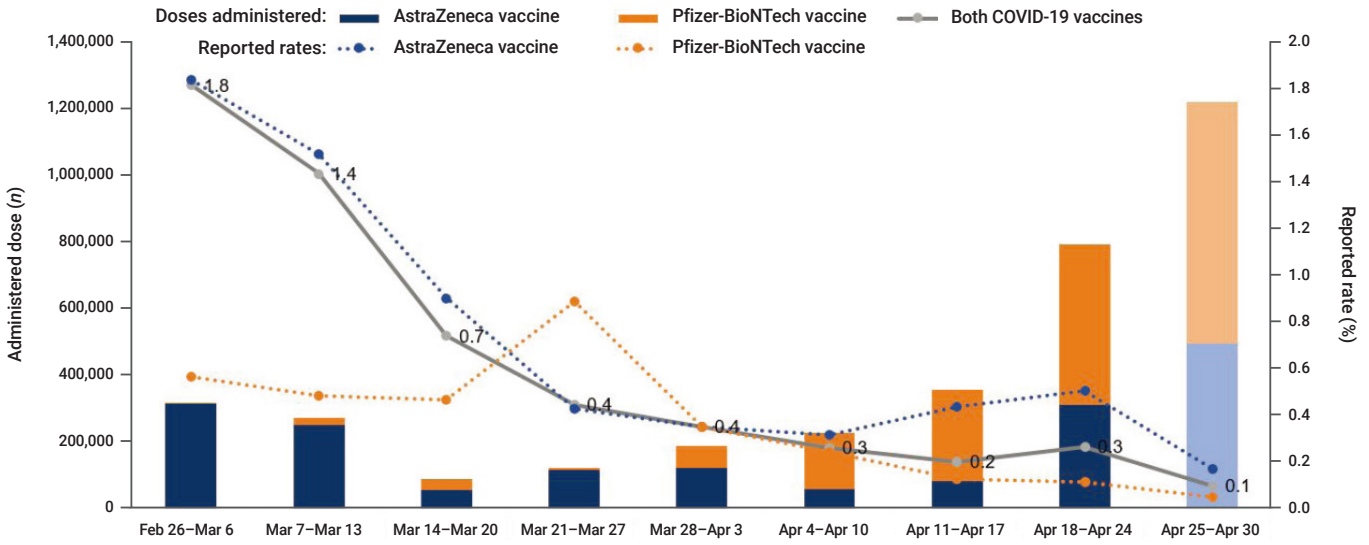

Figure 1. Doses administered and the reported rates of adverse events per week, February 26 to April 30, 2021. We added the first 2 days of vaccination campaign (February 26–February 27, 2021) to the first week. Similarly, the very last week of this paper included only 6 days (April 25–30, 2021). As the last week of this paper will be a slight undercount as more data may be reported in the coming days, the very right bar is indicated in a light color. COVID-19, coronavirus disease 2019.

Table 1. Reports of adverse events following COVID-19 vaccination, by recipients' sex, age group, and type of vaccine: Republic of Korea, February 26, 2021 to April 30, 2021 (as of May 1, 2021)

Variable	Vaccination doses (*n* = 3,586,814)	Adverse events reported[a] (%) (*n* = 16,196)				*p*-value[d]
		Non-serious adverse events[b] (*n* = 15,658)	Serious adverse events[c]			
			Death (*n* = 73)	Anaphylaxis (*n* = 173)	Others (*n* = 292)	
Sex						< 0.001
Male	1,307,450 (36.5)	2,968 (19.0)	38 (52.1)	30 (17.3)	97 (33.2)	
Female	2,279,364 (63.5)	12,690 (81.0)	35 (47.9)	143 (82.7)	195 (66.8)	
Age (y)						< 0.001
18–29	180,115 (5.0)	5,198 (33.2)	1 (1.4)	35 (20.2)	33 (11.3)	
30–49	698,354 (19.5)	5,583 (35.7)	1 (1.4)	88 (50.9)	75 (25.7)	
50–74	939,634 (26.2)	3,499 (22.3)	15 (20.5)	31 (17.9)	80 (27.4)	
≥ 75	1,768,711 (49.3)	1,378 (8.8)	56 (76.7)	19 (11.0)	104 (35.6)	
AstraZeneca vaccine						NA
1st dose	1,807,921 (50.4)	13,585 (86.8)	44 (60.3)	139 (80.3)	200 (68.5)	
2nd dose	186 (0.01)	0	0	0	0	
Pfizer-BioNTech						< 0.001
1st dose	1,550,412 (43.2)	1,471 (9.4)	28 (38.4)	33 (19.1)	87 (29.8)	
2nd dose	228,295 (6.4)	602 (3.8)	1 (1.4)	1 (0.6)	5 (1.7)	

NA, not available.
[a]Data were calculated using information and suspected adverse events after coronavirus disease 2019 (COVID-19) vaccination reported by medical facilities or doctors. The results do not suggest causality between the vaccines and adverse events. [b]Non-serious adverse events include the following: common symptoms such as redness at the site of injection, pain, swelling, myalgia, fever, headache, chills, and others. [c]Serious adverse events include the following: death, suspected anaphylaxis, major adverse events (adverse events of special interest, admission to the intensive care unit, life-threatening events, permanent disability/sequelae, and others). [d]Chi-square (Pearson or Fisher exact) test of proportion of serious/non-serious adverse events by groups.

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A total of 1,550,412 first doses and 228,295 second doses of Pfizer-BioNTech vaccines were administered until April 30, 2021. The adverse event rate was higher after the second dose than after the first dose (first dose vs. second dose: 0.1%, 95% confidence interval [CI], 0.10–0.11 and 0.3%, 95% CI, 0.25–0.29; respectively). Both COVID-19 vaccines showed higher adverse event rates among younger age groups (Figure 3).

In total, 173 events of suspected anaphylaxis were reported: 139 and 34 events after administration of AstraZeneca and Pfizer-BioNTech vaccines, respectively.

The age of the 73 subjects who died after vaccination ranged from 25 to 95 years (median, 82 years). Thirty-five (47.9%) of the deaths were in women, and most deaths occurred in elderly recipients or those with underlying medical conditions. In cases of deaths, provincial rapid investigation teams and the injury investigation committee thoroughly evaluated the causality between vaccination and death through epidemiological investigations using medical records, death certificates, and autopsy results. No associations between death and vaccination have been identified as of April 30, 2021.

Discussion

In Korea, 2 types of COVID-19 vaccines (AstraZeneca, Pfizer-BioNTech) are currently available, and as of April 30, 2021, a total of 3,586,814 doses were administered. The rate of adverse events as reported through the KIMS, the national passive monitoring system, was approximately 0.5%. During the first few months of the COVID-19 vaccination campaign in Korea, certain priority groups such as health

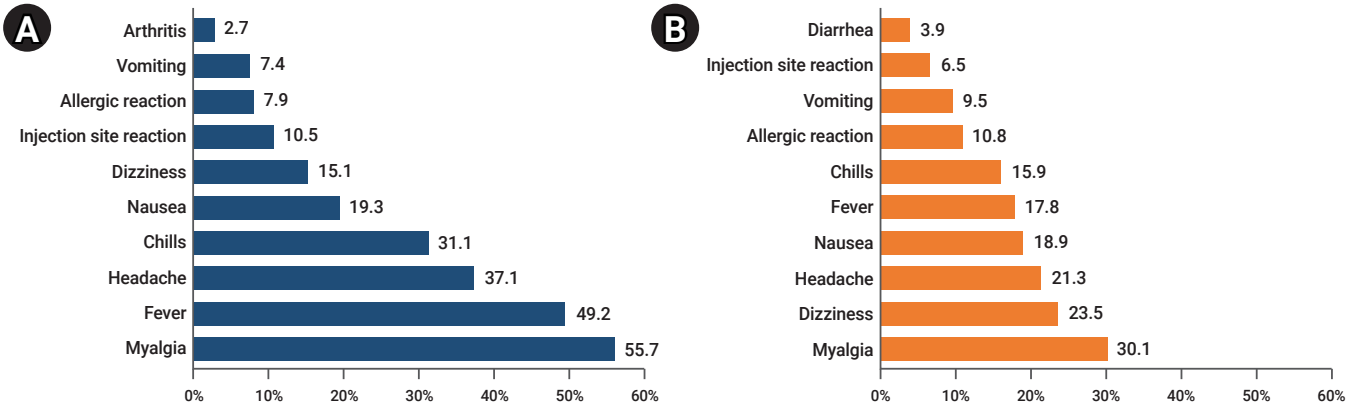

Figure 2. (A) Frequent symptoms and signs of adverse events following AstraZeneca coronavirus disease 2019 (COVID-19) vaccination. (B) Frequent symptoms and signs of adverse events following Pfizer-BioNTech COVID-19 vaccination.

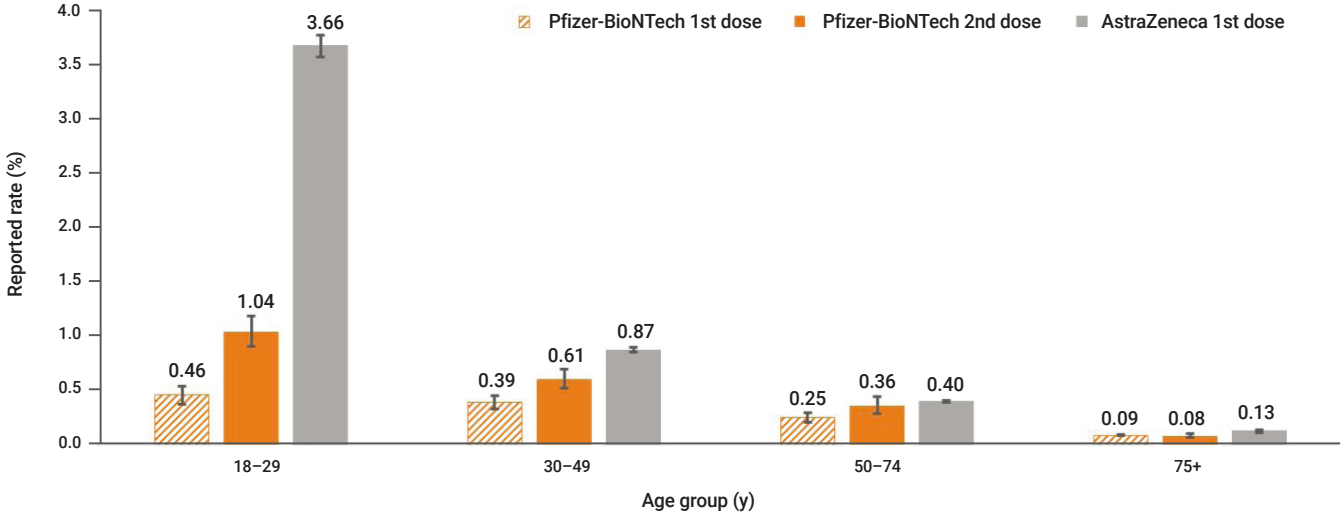

Figure 3. Reported adverse event rates following coronavirus disease 2019 (COVID-19) vaccination by age group.

care personnel and vulnerable people have been a focus for vaccination efforts. Therefore, it might be too early to evaluate adverse events after vaccination. However, as shown in clinical trials and data from other countries, most of the reported adverse events (97%) were non-serious events comprising local and systemic reactions, including myalgia, headache, fever, and pain at the injection site [5,6].

Most of the 73 deaths reported after COVID-19 vaccination occurred in the elderly or those with underlying diseases. AEFIs were more frequently reported after the second dose than after the first dose of the Pfizer-BioNTech vaccine. This is similar to the findings of the clinical trial [7]. However, no second-dose data for AstraZeneca vaccines are yet available due to the early stage of the vaccination campaigns.

There are some limitations of this study, as follows. First, the number of adverse events reported by medical doctors may be an underestimation, as only data of patients who visited medical institutions due to adverse events were included. Moreover, the number of reports may also increase due to the growing interest in adverse events with the introduction of new vaccines.

The Korea Disease Control and Prevention Agency is monitoring and investigating AEFIs to assess any unexpected health problems due to COVID-19 vaccinations. We note that all findings in this paper are from the first few preliminary months of the national vaccination program. It is important for healthcare providers to report AEFIs and participate in epidemiological investigations to support operational decisions around the vaccine roll-out.

Notes

Ethics Approval
Given the current activity was conducted and authorized by the public health authority; and the purpose was to disseminate information to the public, the current study was exempted by the ethical board review.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Availability of Data
The data used in this study is protected under the Personal Information Protection Act.

Authors' Contributions
Conceptualization: HO, YKL; Data curation: EKK, YL, EL, TEK; Formal analysis: IH, HO; Investigation: YL, TEK, EL, EKK, HO; Methodology: HO, IH, YKL; Validation: YKL; Writing–original draft: HO, YKL; Writing–review & editing: all authors.

Additional Contributions
We thank the relevant ministries, including the Ministry of Interior and Safety; cities and provinces, medical staffs in health centers, and medical facilities for their effort in responding to the vaccine safety monitoring.

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Brief Report

The laboratory test procedure to confirm rotavirus vaccine infection in severe complex immunodeficiency patients

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ABSTRACT

The rotavirus vaccine is a live vaccine, and there is a possibility of infection by the virus strain used in the vaccine. We investigated the process of determining whether an infection was caused by the vaccine strain in a severe complex immunodeficiency (SCID) patient with rotavirus infection. The patient was vaccinated with RotaTeq prior to being diagnosed with SCID. The testing process was conducted in the following order: confirming rotavirus infection, determining its genotype, and confirming the vaccine strain. Rotavirus infection was confirmed through enzyme immunoassay and VP6 gene detection. G1 and P[8] were identified by multiplex polymerase chain reaction for the genotype, and G3 was further identified using a single primer. By detecting the fingerprint gene (WC3) of RotaTeq, it was confirmed that the detected virus was the vaccine strain. Genotypes G1 and P[8] were identified, and the infection was suspected of having been caused by rotavirus G1P[8]. G1P[8] is the most commonly detected genotype worldwide and is not included in the recombinant strains used in vaccines. Therefore, the infection was confirmed to have been caused by the vaccine strain by analyzing the genetic relationship between VP4 and VP7. Rotavirus infection by the vaccine strain can be identified through genotyping and fingerprint gene detection. However, genetic linkage analysis will also help to identify vaccine strains.

Keywords: Infantile diarrhea; Laboratory test; Rotavirus infections; Rotavirus vaccines; Severe combined immunodeficiency

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Introduction

Rotavirus is a common cause of severe enteritis in newborns and infants worldwide. It can cause gastroenteritis with severe diarrhea and dehydration, leading to hospitalization and even death. Immunization with the rotavirus vaccine has been proven to reduce disease severity from rotavirus gastroenteritis [1–3]. Two types of rotavirus vaccines were developed

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in 2006 and have been introduced and used in Korea since 2007 [4]. The vaccines that are licensed and used in Korea are Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq (Merck Sharp & Dohme Corp., Kenilworth, NJ, USA). Although there are differences in the antigen composition between the 2 vaccines, both are live-attenuated vaccines for oral administration. Live vaccines have a risk of inducing disease, especially among immune-compromised individuals [5]. Many reports have shown that rotavirus vaccination is dangerous, particularly for children with severe combined immunodeficiency (SCID) [6,7]. The introduction of the rotavirus vaccine into the national immunization program (NIP) is under review in Korea, and after its inclusion, the incidence of vaccine-related diseases is expected to increase. Therefore, it is necessary to consider the pathogen characterization process for investigating vaccine-related infection cases. This study reviewed the process of examining a specimen from a SCID patient with confirmed rotavirus infection. In addition, we reviewed the laboratory analysis process to determine whether the vaccine-derived strain of rotavirus has infected a SCID patient.

Materials and Methods

A fecal sample was obtained from a 3-month-old male infant who presented to the Samsung Medical Center, Seoul. He was immunized with RotaTeq at 8 weeks of age and was diagnosed with SCID shortly thereafter. Subsequently, he had persistent diarrhea and was diagnosed with rotavirus infection through a rotavirus test. The patient's sample was tested at the Korea Disease Control and Prevention Agency to determine whether the rotavirus infection was due to vaccination or another source. The sample was pretreated for a laboratory test. The fecal sample was diluted to 10% (wt/vol) in phosphate-buffered saline (pH 7.2), vortexed for 1 minute, and centrifuged at 8,000 × *g* for 10 minutes. An antigen test (enzyme immunoassay, EIA) and a genetic test (VP6) were performed on the supernatant fluid after centrifugation to re-confirm the rotavirus infection. RIDASCREEN (R-biopharm AG, Darmstadt, Germany) was used for the EIA test. For the VP6 gene test, nucleic acid was extracted from the fecal sample using a QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany), and reverse-transcription polymerase chain reaction (RT-PCR) was performed [8].

The rotavirus genotype was confirmed using the RT-PCR genotyping method recommended by the World Health Organization (Table 1) [8–10]. The VP4 and VP7 genes were primarily amplified by RT-PCR using nucleic acids extracted from the sample. The second PCR (multiplex PCR) was performed using the primary PCR product as a template. Subsequently, the genotype was determined by confirming the correct amplicon size through an automatic electrophoresis device (Fragment Analyzer Systems; Agilent, Santa Clara, USA) and analysis software (PROSize

Table 1. Oligonucleotide sequences used in this study

Purpose	Target gene	Primer	Sequence (5'→3')	Position	Amplicon size (bp)	Reference
Screening	VP6	6BEG.303	AAYGTRTGTATGGATGARATG	303–323	824	[8]
		VP6-R	GTCCAATTCATNCCTGGTGG	1106–1126		
Genotyping	VP4	Con3	TGGCTTCGCTCATTTATAGACA	11–32	876	[9]
		Con2	ATTTCGGACCATTTATAACC	868–887		
		2T-1 (P[4])	CTATTGTTAGAGGTTAGAGTC	474–494	483	
		pUK (P[5])	GCCAGGTGTCGCATCAGAG	336–354	555	
		3T-1 (P[6])	TGTTGATTAGTTGGATTCAA	259–278	267	
		1T-1 (P[8])	TCTACTTGGATAACGTGC	339–356	345	
		4T-1 (P[9])	TGAGACATGCAATTGGAC	385–402	391	
	VP7	VP7-F	ATGTATGGTATTGAATATACCAC	51–71	881	
		VP7-R	AACTTGCCACCATTTTTTCC	914–932		
		aBT1 (G1)	CAAGTACTCAAATCAATGATGG	314–335	618	
		aCT2 (G2)	CAATGATATTAACACATTTTCTGTG	411–435	521	
		G3	ACGAACTCAACACGAGAGG	250–269	682	
		aDT4 (G4)	CGTTTCTGGTGAGGAGTTG	480–498	452	
		aAT8 (G8)	GTCACACCATTTGTAAATTCG	178–198	754	
		G9	CTTGATGTGACTAYAAATAC	757–776	179	
Vaccine strain detection	NSP3 (WC)	NSP3F-B	TGGCCGATACTAGAACTACAGA	288–308	555	[10]
		NSP3R-B	TGATTACATCAATGGAATTTAGC	842–820		

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3.0; Agilent). Secondary PCR was additionally performed using a single primer for each genotype to investigate the other genotypes unidentified by multiplex PCR. Primary PCR products were also cloned, and the nucleotide sequence was analyzed to confirm whether there was a co-infection involving various genotypes.

The fingerprint gene of RotaTeq, NSP3 (WC3), was detected to determine whether the virus from the patient was the vaccine strain [10]. The nucleotide sequences of VP7 and VP4 from vaccine-derived rotavirus strains were compared with the RotaTeq vaccine strain and human wild-type strains. Multiple sequence alignments were performed with Clustal W, and phylogenetic trees were constructed in MEGA 6.0 using the neighbor-joining tree method, with 1,000 bootstrap replicates based on the Kimura-2 model. The reference sequences used in the phylogenetic analysis were obtained from the GenBank database.

Results

Rotavirus infection was verified, as the sample was positive on EIA and VP6 genetic testing. The genotype was identified as G1P[8] by the RT-PCR genotyping method. Individual PCR testing was also performed for each genotype to identify the other genotypes (G2, G3, G4) present in the same amount in RotaTeq. As a result, G3 was also confirmed. Cloning was performed, but no additional genotypes were identified. Finally, it was confirmed that amplified NSP3 (WC3) was the gene introduced in the vaccine recombination process (Table 2). In addition, the phylogenetic trees constructed for the VP7 and VP4 genes of the RotaTeq vaccine strains (G1, P[8]) revealed that all strains clustered closely together (Figure 1).

Discussion

SCID is a genetic condition that results in lack of cellular and humoral immunity. Immunization with rotavirus vaccines (2-dose Rotarix or 3-dose RotaTeq) begins with the first dose, which is administered at 2 months. However, the immune system is usually tested after 4 months of age. Therefore, most SCID infants would have already received a live rotavirus vaccine prior to the diagnosis of SCID. In this case, the patient had been vaccinated with the rotavirus vaccine (RotaTeq) before being diagnosed with SCID and had persistent diarrhea, which is a symptom of rotavirus infection. There have been several reports of rotavirus infection in infants with SCID following vaccination with the RotaTeq live-attenuated vaccine [6,11]. In the United States, the incidence of rotavirus-related diarrhea decreased after the inclusion of rotavirus vaccination in the NIP and then increased again [12]. An analysis of the rotavirus epidemic after the introduction of the NIP confirmed that the vaccine strain was the cause of about 60% of infections [13]. When the rotavirus vaccine is introduced into the NIP, rotavirus-related diarrhea is generally reduced, but infections with the vaccine's rotavirus strain infection increase to some extent. Children with immune deficiencies such as SCID are at a high risk of vaccine-associated infections.

RotaTeq is a preventive vaccine against rotavirus infection caused by the G1, G2, G3, G4, and P[8] types and comprises 5 recombinant strains (G1P[5], G2P[5], G3P[5], G4P[5], and G6P[8]). Therefore, in this study, tests were conducted to confirm rotavirus infection, genotyping, and identification of the vaccine strains. The rotavirus genotypes detected in the patient were G1 and P[8], which are associated with the vaccine strain. The identification of other genotypes included in equal amounts in the vaccine was attempted, although G1 and P[8] were confirmed using RT-PCR genotyping. It was impossible to identify genotypes other than G1 and P[8] by cloning, but G3 was also confirmed through individual PCR for each genotype. Moreover, it was confirmed that the patient's infection was related to the rotavirus vaccination, as demonstrated by the amplification

Table 2. Testing process used for confirming infection due to the rotavirus vaccine strain in an infant with severe combined immunodeficiency

Step	Laboratory test		Final result
	Method	Result	
1	Antigen-captured EIA	Positive	Rotavirus infection
	VP6 RT-PCR	Positive	
2	RT-PCR genotyping	G1P[8]	Genotype used in RotaTeq
	VP7 RT-PCR (Single primer)	G3	
	Cloning of VP4 and VP7	NT	
3	NSP3 (WC3) RT-PCR	Positive	Vaccine strain

EIA, enzyme immunoassay; RT-PCR, reverse-transcription polymerase chain reaction; NT, not detected.

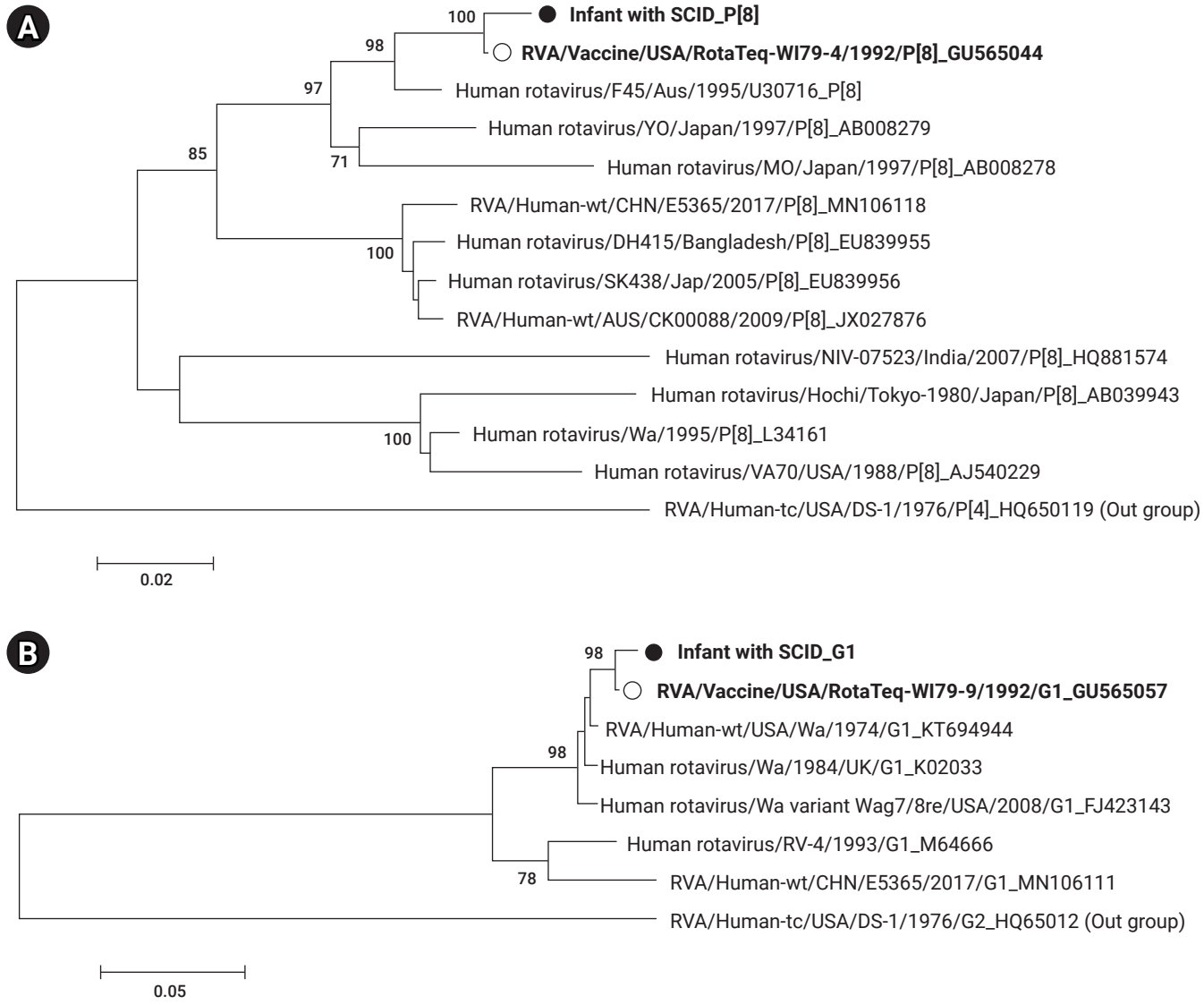

Figure 1. Phylogenetic trees based on the sequences of rotavirus VP4 (A) and VP7 (B) detected from an infant with severe complex immunodeficiency (SCID) (●) compared with (○) RotaTeq (G1 and P[8]). The number at each node indicates the level of bootstrap support (%) based on neighbor-joining analysis of 1,000 resampled datasets. Only values above 70% are displayed.

of the NSP3 (WC3) gene used in the RotaTeq vaccine for the recombination of vaccine strains.

G1 and P[8] were identified in the genotyping analysis, and rotavirus G1P[8] seemed to be detected. Although G3 was confirmed by PCR using a single primer, it was not possible to confirm the 5 kinds of recombinant strains (G1P[5], G2P[5], G3P[5], G4P[5], and G6P[8]) used in the vaccine. In particular, G1P[8] is the most commonly detected genotype globally, and it is not possible to distinguish whether it is transmitted from vaccines, infected people, or the environment. Some reports have described distinguishing the vaccine strain from the wild-type strain [10,14], and a rapid method using real-time RT-PCR has been recently developed [15]. In this study, the WC3 gene, a fingerprint gene of RotaTeq, was detected, and a thorough analysis of the VP4 and VP7 genes confirmed a close relationship with the vaccine strain. However, the G1P[8] type was not used directly in the RotaTeq vaccine. It was previously found that the patients shed G1P[8] among the 5 surface proteins (G1, G2, G3, G4, P[8]) when infected by the recombinant vaccine [5]. Therefore, based on these findings, the possibility that the detected virus was a wild-type strain could not be confirmed; instead, the detected virus was confirmed to be the vaccine strain.

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Conclusion

This study confirmed that the rotavirus infection in SCID patients was related to the vaccine strain by identifying the genotype (G1, G3, P[8]) and detecting the bovine gene (WC3) used in the vaccine strain (RotaTeq). However, it is difficult to identify all the genotypes used in the vaccine immediately, and genetic linkage analysis may be helpful to determine whether there is another wild-strain infection.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
All relevant data are within the manuscript.

Authors' Contributions
Conceptualization: DYL; Supervision: DYL; Methodology: SRC; Investigation: SRC; Writing–original draft: SJC; Writing–review & editing: WC, MGH; All authors read and approved the final manuscript.

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