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Aims & Scope

Osong Public Health and Research Perspectives (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health.
PHRP publishes original articles, review articles, short communications, commentaries, editorials, and letters to the editor, 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

Original Articles

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Editorial

Can we reach a 70% level of herd immunity to return to normality?

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The global second wave of the coronavirus disease 2019 (COVID-19) pandemic peaked in mid-January 2021, and the spread of COVID-19 then increased again starting in March, cumulatively causing approximately 136 million cases and about 3 million deaths. This third wave of the pandemic has been continuing to spread throughout Europe and Southwest Asia. During and after the second wave of the pandemic, immunizations in Israel, the United Kingdom (UK), and the United States of America significantly reduced deaths and incident cases [1,2]. In Israel, where 58.9% of the population received more than 10 million vaccinations using the Pfizer vaccine—allowing the population to reach the level of herd immunity in a specific group—the mortality rate was markedly reduced. On the one hand, this example provides a good model of a vaccination campaign, but on the other hand, imported South African variants have led to reinfections, and there is a cautious outlook regarding the possibility that the number of infections will increase due to fatigue with non-pharmaceutical interventions (NPIs) in the young [3]. In the United States of America, more than 189 million doses have been given, with 2-dose vaccinations covering over 74 million individuals, or 22.3% of the total population. However, since NPIs have been lifted in some states, cases seem to be on the rise once more. Owing to the incidence of unusual blood clot events, the Janssen COVID-19 vaccine was recently withdrawn for urgent use, but it still may be a successful and effective 1-shot vaccine. In the UK, about 48% of the population has been vaccinated at least once, and the number of cases and deaths has decreased. However, a recent report described deep vein thrombosis with thrombocytopenia linked to the AstraZeneca (AZ) COVID-19 vaccine. When the intensive care unit (ICU) hospitalization rate was compared between individuals who received the AZ vaccine and a group without vaccination, the AZ vaccine group showed lesser favorable outcomes than the unvaccinated group with a low rate circulation of coronavirus (2 cases per 10,000); therefore, the AZ vaccine is currently not recommended for those under 30. Still, it seems to be a promising vaccine [4]. Chile has vaccinated 12 million people, and 39% of the population has been vaccinated more than once, but the incidence of cases and deaths remains high, unlike in other countries. Altogether, the uncertainty in the vaccine supply around the world, the hesitation about vaccination due to severe side effects, and the decrease in vaccine efficacy due to the spread of mutant strains mean that it may be difficult to return to normal daily life this year in USA [5,6].

What countermeasures can be taken by our country (the Republic of Korea) in this situation? First of all, we must rapidly increase the vaccination rate. Out of Korea's 79 million contracts for

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vaccines, approximately 1.57 million are being secured and vaccination is being promoted, resulting in a vaccination rate of 2% of the population [2]. The high-risk group, consisting of people over 65 years old, was assigned to receive vaccinations first and foremost to reduce mortality and the incidence of severe COVID-19 cases. Although some hypersensitivity reactions have been reported, vaccine hesitancy is low, and vaccines must be imported on a continuous basis to meet the government's target immunization level of 70%. However, in contrast to what the original plan predicted, vaccine supply might be difficult to come by. As the need for vaccination will increase year after year due to the possibility of COVID-19 becoming an endemic disease, now is a critical time to ramp up CMO vaccine production and to create original domestic vaccines using new technologies.

Secondly, with a broader range of variants occurring in some countries, preparedness is more important than expected. B. 1.1.7 has been reported in 132 countries, B.1.351 in 82, and B.1.128.1 in 51. The B.1.351 and B1.1.28.1 variants increase transmissibility and severity, and decrease neutralizing activity. Reinfections have already been reported [7]. Furthermore, it has been reported that vaccines—especially the AZ vaccine—have limited efficacy in preventing infections with the B.1.1.7 variant. For B.1.351, it has been demonstrated that most of the vaccines, including the Moderna, Pfizer, and AZ vaccines, had a lower neutralizing antibody titer, and the AZ vaccine had no effect on mild cases, leaving an information gap regarding the effectiveness of the vaccine against asymptomatic infections. It was also reported to have a low neutralizing antibody titer against B1.1.28.1. Before the newer variants in Korea become the main epidemic or natural selection creates another new variant in Korea, the vaccination rate should be rapidly increased, and measures to prevent the transmission of variants should be strengthened by monitoring imported cases and quarantining people suspected to be infected. Of course, as the vaccination rate rises, so does the freedom to travel and the possibility of an influx of variants. Supporting both low- and middle-income countries in increasing vaccination rates can ensure that no country falls behind. The submission of a certification of a negative COVID-19 test by travelers should also prevent variants from being exported.

Thirdly, despite the above-mentioned quarantine and vaccination measures, which are effective in reducing severe cases and deaths, there is a gap in the prevention of asymptomatic infection and transmission, making it necessary to maintain social distance and wear a mask to block transmission. Whether or not herd immunity is achieved through vaccination, it will be difficult to return to the previous normal. Long-term countermeasures must be prepared quickly for the winter. As protection that focuses on the elderly in the winter, certain activities (such as visiting nursing homes, various gatherings, sports facilities, religious gatherings, and dining) will be not permitted for people over the age of 65 [6]. Distance working and education will be promoted more aggressively than in previous years. In addition, because there is a high likelihood that the number of severely ill patients will increase and there will be a shortage of ICU beds and workforce, as seen in 2020, measures to secure stable ICU nurses and beds in preparation for the double burden caused by the seasonal influenza epidemic should be supplemented.

Finally, R&D is a powerful tool to combat emerging reemerging diseases. People must be encouraged to conduct research, research funds must be raised, and the research environment must be improved. Eventually, COVID-19 control and eradication will be a battle between the development of vaccines, treatments, and diagnostics and stockpiling of supplies. There is a particularly pressing need to establish correlates of protection so that vaccine efficacy results obtained with pre-existing variants can be translated to newly emerging variants because it is impractical and time-consuming to repeat clinical trials with each new variant that may exhibit immune escape [8].

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The author has no conflicts of interest to declare.

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Original Article

COVID-19 transmission: a rapid systematic review of current knowledge

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ABSTRACT

Objectives: The objective of this study was to identify the potential and definite sources of transmission of coronavirus disease 2019 (COVID-19).
Methods: Due to time constraints and the acute nature of the pandemic, we searched only PubMed/MEDLINE from inception until January 28, 2021. We analyzed the level of evidence and risk of bias in each category and made suggestions accordingly.
Results: The virus was traced from its potential origin via possible ways of transmission to the last host. Symptomatic human-to-human transmission remains the driver of the epidemic, but asymptomatic transmission can potentially contribute in a substantial manner. Feces and fomites have both been found to contain viable virus; even though transmission through these routes has not been documented, their contribution cannot be ruled out. Finally, transmission from pregnant women to their children has been found to be low (up to 3%).
Conclusion: Even though robust outcomes cannot be easily assessed, medical personnel must maintain awareness of the main routes of transmission (via droplets and aerosols from even asymptomatic patients). This is the first attempt to systematically review the existing knowledge to produce a paper with a potentially significant clinical impact.

Keywords: Airborne particulate matter; COVID-19; Pathogen transmission

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Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic on March 11, 2020 by the World Health Organization; since then, the disease has spread to more than 129 million people and has claimed more than 2,8 milllion lives [1]. This novel coronavirus disease has proven, so far, to be both highly transmittable (unlike severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) and not too fatal (unlike Ebola) [2]. Numerous reports concerning vehicles of transmission have been published, implicating a vast spectrum of possible transmission routes, including fomites [3], asymptomatic transmission (through simple exhalation) [4], and body fluids and secretions. In this systematic review, the first in the current literature according to our knowledge, we analyzed all available data on the possible transmission routes of COVID-19.

Materials and Methods

Objective

This study was performed to identify potential and definite sources of transmission of COVID-19.

Types of Studies

Due to the acute nature of the pandemic, all types of studies were considered eligible for inclusion; therefore, cohort studies (prospective and retrospective), case reports (including 3 or fewer cases) and case series (more than 3 cases), comments, research letters, laboratory studies, reviews, and meta-analyses were included. We excluded studies that did not focus on transmission routes of the disease. Only studies in English, or studies with an abstract available in English, from which adequate data extraction could be performed, were included.

Search Methods

Due to time constraints and the acute nature of the pandemic, we decided to search only PubMed/MEDLINE from inception until January 28, 2021. The snowball procedure was performed in order to identify studies from the references of the included studies. The search was conducted using terms "COVID-19," "novel coronavirus," "SARS-CoV-2," "transmission," "transmissibility," and their synonyms using Boolean operators (OR, AND). Two authors (LT, PM) independently searched the database and disagreements were resolved through consensus with a third reviewer.

Selection of Studies

Two authors (LT, PM) independently assessed the titles and abstracts, and after the initial stage of exclusion of irrelevant studies, they retrieved the full texts for further assessment. A flow diagram (Figure 1) visually depicts the study selection process.

Data Extraction

Two authors (LT, PM) independently performed data extraction from the included studies based on a prespecified Excel sheet. The data extracted were relevant to the study characteristics (author, journal, year, country, type), the demographic characteristics

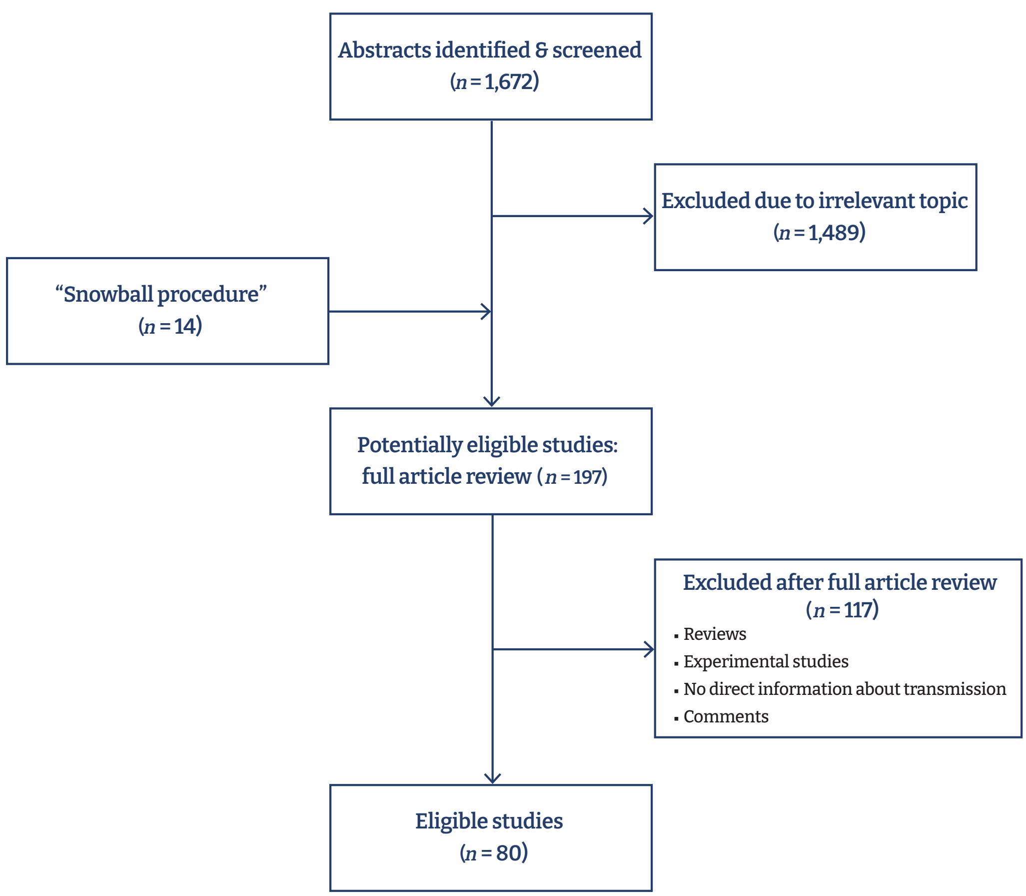

Figure 1. Flowchart of the study.

of patients (age, sex ratio, proposed route of transmission, comorbidities) and specific data related to the disease (positive samples, duration of positive samples, antibody titers). The last author (AF) reviewed the 2 Excel sheets and disagreements were resolved through consensus.

Risk of Bias Assessment

We assessed the risk of bias using the Newcastle-Ottawa scale [5] for cohort studies. Due to the lack of standardized tools for assessing case reports and case series, we used the Joanna Briggs checklist for case series [6] and the criteria established by Pierson [7] to evaluate case reports.

Results

The initial search yielded 1,672 results. After the exclusion of 1,489 studies due to irrelevant topics or a lack of information about the transmission of COVID-19, 197 studies underwent full-text review. The snowball procedure revealed 14 more references, and after the exclusion of 117 additional studies, 80 were finally included in the review (Figure 1). Thirteen were cohort studies [8–20] and the rest were case series, case reports, or studies with other designs. Table 1 presents the characteristics of the studies [3,4,8–62]. To summarize the findings, symptomatic human-to-human transmission remains the main vehicle that drives the epidemic, but asymptomatic transmission can potentially contribute in a substantial manner. Feces and fomites have both been found to contain viable virus; even though transmission through these routes has not been documented, their contribution cannot be ruled out. Finally, the transmission from pregnant women to their children has been found to be low (up to 3%). The risk of bias assessment revealed that 4 cohort studies were of low quality (<6 of 9 stars) according to the Newcastle-Ottawa scale, while most case series and case reports were of good overall quality (Tables S1–S3).

Discussion

The most important transmission route of a respiratory virus is the air, but a variety of vehicles are implicated in this mechanism. These vehicles are categorized according to their size: large droplets with a diameter of >20 μm, small particles with a diameter of <5 to 10 μm, and intermediate particles with sizes between 10 and 20 μm [63]. The above-mentioned categorization is of major clinical and epidemiological significance since (a) large droplets cannot follow inhalation streamlines and fall very quickly, following gravity, but can stay on surfaces and produce fomites; and (b) small particles usually evaporate and form residual particulates (aerosols) that can travel in the air, transmit the virus at greater distances, and (if their size is <5 μm) travel deep in the human respiratory tract [64]. Moreover, up-to-date data suggest that exhalations, sneezes, and coughs can produce turbulent gas that not only traps and carries larger droplets, but can significantly decrease their evaporation, thereby extending their lifetime by a factor by up to 1,000 times [65]. The above-mentioned data can—and perhaps should—alter global policies of social distancing and support more aggressive use of face masks among the general population.

Transmission from Animals to Humans: the Start of the Nightmare

A laboratory genomic analysis revealed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is 96% identical on the whole-genome level to a bat coronavirus CoVZXC21 (RaTG13), and there is a very high similarity (80% sequence identity) between this novel coronavirus and the SARS coronavirus (SARS-CoV-1) that was responsible for the earlier SARS pandemic in the recent past [21]. The study of Xu et al. [22] provides some insights into these issues. The authors found that the human angiotensin converting enzyme 2 (ACE-2) receptor is the gate of viral entry into the human body, while a simple nucleotide replacement (Arg426 with Asn426) increased the binding ability of the novel virus, which may explain its high transmissibility. Although the available data clearly suggest that bats are the reservoir of SARS-CoV-2 and that patient zero was linked to the Wuhan market, the fact that bats are not sold in this market suggests that there may be a possible intermediate host such as snakes, pangolins, or even turtles [66]. The quest to elucidate this major aspect of the pandemic is still ongoing.

Direct Contact as the Main Vehicle and Airborne Transmission as a Possible Alternative Symptomatic Transmission

SARS-CoV-2 is, mainly, a respiratory virus. Therefore, its main route of transmission is contact with droplets produced by a symptomatic patient by coughing, sneezing, or exhaling. We identified 35 studies published in the literature, most of them being case reports or case series, that provide enough evidence for human-to-human transmission through droplets or direct contact with symptomatic patients [3,4,12,13,17,19,23–48,67–70]. All these case series reported either familial clusters, clusters from common indoor places (meetings, buses, temples, hospitals, spas, restaurants), or crowded outdoor facilities (markets). These studies all suggest that transmission of SARS-CoV-2 between humans is relatively easy, as expected.

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Table 1. Study characteristics

Study	Type of study	Country	Type of transmission	Vehicle of transmission
Xu et al. [22]	Experimental	China	Bat to human	
Zhou et al. [21]	Experimental	China	Bat to human	
Zhang et al. [48]	Experimental	China, Wuhan	Multiple routes	Droplets, aerosol, feces, blood, serum
Dong et al. [55]	Case report	China, Wuhan, Renmin Hospital	Vertical	Amniotic fluid, placenta
Yu et al. [58]	Case series	China	Vertical	Amniotic fluid, placenta, close contact
Fan et al. [56]	Case report	China	Vertical	Amniotic fluid, placenta, close contact
Chen et al. [8]	Retrospective	China, Wuhan Zhongnan Hospital of Wuhan University	Vertical	Amniotic fluid, placenta
Li et al. [57]	Case report	China, Zhejiang Province	Vertical	Amniotic fluid, placenta
Chen et al. [9]	Retrospective	China, Hubei	Vertical	Amniotic fluid, placenta, close contact
Zeng et al. [18]	Retrospective	China, Wuhan Zhongnan Hospital of Wuhan University	Vertical	Amniotic fluid, placenta, close contact
Wang et al. [16]	Case report	China, The Affiliated Infectious Hospital of Soochow University	Vertical	Amniotic fluid, placenta
Zhu et al. [20]	Retrospective	China, Maternal and Child Health Hospital of Hubei Province	Vertical	Amniotic fluid, placenta
Xiao et al. [52]	Case series	China, Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, Guangdong Province	Fecal-oral	Feces
Ling et al. [14]	Retrospective	China, Shanghai Public Health Clinical Center	Fecal-oral	Feces
Zhang et al. [53]	Case series	China, Tianjiin	Fecal-oral	Feces
Xie et al. [60]	Case series	China, Union Hospital, Tongji Medical College, Wuhan	Ocular	Tears
Xia et al. [59]	Case series	China, Zhejiang, University School of Medicine First Affiliated Hospital, Hangzhou	Ocular	Tears
Sun et al. [62]	Case report	China, Eighth People's Hospital of Guangzhou Medical University	Urine	Urine
Cai et al. [23]	Case series	China, Wenzhou	Respiratory contact	Droplets, aerosol, fomites
Chan et al. [24]	Case series	China	Respiratory contact	Droplets, aerosol, fomites
Ghinai et al. [25]	Case report	USA, Illinois	Respiratory contact	Droplets, aerosol, fomites
He et al. [26]	Case series	China, Guangzhou Eighth People's Hospital	Respiratory contact	Droplets, aerosol, fomites
Holshue et al. [27]	Case report	USA, Washington	Unknown	Unknown
Huang et al. [28]	Case series	China	Respiratory contact	Droplets, aerosol, fomites
Kakimoto et al. [29]	Case series	Japan, Yokohama	Respiratory contact	Droplets, aerosol, fomites
Kimball et al. [30]	Case series	USA, Washington	Respiratory contact	Droplets, aerosol, fomites
Le et al. [31]	Case report	Vietnam	Respiratory contact	Droplets, aerosol, fomites
Li et al. [32]	Case series	China, Zhoushan	Respiratory contact	Droplets, aerosol, fomites
Li et al. [12]	Prospective	China, Wuhan	Respiratory contact	Droplets, aerosol, fomites
Li et al. [13]	Retrospective	China, Department of Thoracic Surgery Tongji Hospital	Respiratory contact	Droplets, aerosol, fomites
Lillie et al. [33]	Case series	UK	Respiratory contact	Droplets, aerosol, fomites
Liu et al. [34]	Case report	Taiwan	Respiratory contact	Droplets, aerosol, fomites
Luo et al. [35]	Case series	China, Huai'an No. 4 Hospital of Jiangsu Province	Respiratory contact	Droplets, aerosol, fomites
Phan et al. [36]	Case report	Vietnam	Respiratory contact	Droplets, aerosol, fomites
Pongpirul et al. [37]	Case report	Thailand	Respiratory contact	Droplets, aerosol, fomites
Qian et al. [38]	Case series	China, Zhejiang	Respiratory contact	Droplets, aerosol, fomites
Rothe et al. [39]	Case series	Germany	Respiratory contact	Droplets, aerosol, fomites
Shim et al. [40]	Case series	South Korea	Respiratory contact	Droplets, aerosol, fomites

(Continued to the next page)

Table 1. Continued

Study	Type of study	Country	Type of transmission	Vehicle of transmission
Tong et al. [41]	Case series	China, Zhoushan in Zhejiang Province	Respiratory contact	Droplets, aerosol, fomites
van Doremalen et al. [42]	Experimental	USA	Respiratory contact	Droplets, aerosol, fomites
Wang et al. [43]	Retrospective	China, Wuhan Zhongnan Hospital of Wuhan University	Respiratory contact	Droplets, aerosol, fomites
Wei et al. [17]	Retrospective	China	Respiratory contact	Droplets, aerosol, fomites
Xu et al. [44]	Case series	China, Guangzhou Women and Children's Medical Center	Respiratory contact	Droplets, aerosol, fomites
Yu et al. [45]	Case series	China, Wuhan	Respiratory contact	Droplets, aerosol, fomites
Yu et al. [46]	Case series	China, Shangai, Wuhan	Respiratory contact	Droplets, aerosol, fomites
Zhang et al. [47]	Case series	China	Respiratory contact	Droplets, aerosol, fomites
Zhong et al. [19]	Retrospective	China, Zhongnan Hospital, Wuhan	Respiratory contact	Droplets, aerosol, fomites
Bai et al. [4]	Case series	China, Anyang	Respiratory contact	Droplets, aerosol, fomites
Ong et al. [3]	Case series	Singapore	Respiratory contact	Droplets, aerosol, fomites
Li et al. [11]	Prospective	China	Sexual intercourse	Semen
Zhao et al. [49]	Case series	China	Respiratory contact	Droplets, aerosol, fomites
Sayampanathan et al. [15]	Retrospective	Singapore	Respiratory contact	Droplets, aerosol, fomites
Kawasuji et al. [10]	Retrospective	Japan	Respiratory contact	Droplets, aerosol, fomites
Lin et al. [54]	Case series	China	Respiratory contact	Droplets, aerosol, fomites
Chia et al. [50]	Case series	Singapore	Respiratory contact	Droplets, aerosol, fomites
Kasloff et al. [51]	Experimental	Canada	Respiratory contact	Droplets, aerosol, fomites
Kaya et al. [61]	Case series	Turkey	Ocular	Tears, conjunctival secretions

The real problem originates from disturbing data reported in experimental studies suggesting that the virus could remain vital for hours in the air and potentially spread through aerosols. For instance, a study reported that some viable virus particles were present for at least 3 hours in the air and in the form of aerosols [42]. Although conflicting data have been reported on virus transmissibility via aerosols, as well as virus longevity and infectibility in aerosols in real-world settings, these findings are alarming and may have important implications for measures taken by the general public. If this is the case, then a mask should always be used when entering a closed-door room.

Asymptomatic Transmission

Unlike SARS-CoV-1 [71], the novel SARS-CoV-2 has an important but likely devastating characteristic: the viral load of asymptomatic or presymptomatic patients is the same as that of symptomatic patients [49,72], although the former may not seem to be as contagious as the latter [15]. It is not known exactly when a presymptomatic patient becomes contagious, but an interval of 2 to 3 days before symptom onset has been suggested [10,26]. Sufficient reports in the literature have suggested asymptomatic transmission from patients who eventually developed symptoms (presymptomatic, with viral shedding during the incubation period) [46] or from patients who were totally asymptomatic, at rates even as high as 50% [4,73], even though most of authors could not definitively prove this assumption [74]. With an estimation that 20% of cases are totally asymptomatic and that the risk ratio of secondary attack from an asymptomatic versus symptomatic patient is 0.35 (95% confidence interval, 0.1–1.27), asymptomatic transmission is an important aspect of the current epidemic [75]. Some research has also reported a link between different mutations of the virus with the infectivity of asymptomatic patients [76].

Fomites

It is common knowledge that many contagious diseases can be transmitted through fomites, which are produced by droplets that settle on surfaces after following their trajectory through the air [22]. Some experimental studies have illustrated the presence of the virus on different surfaces after hours or even days in some cases: up to 72 hours for plastic and stainless steel, 8 hours for copper, no more than 24 hours for cardboard [42], and interestingly up to 24 hours on human skin (which makes hand hygiene extremely important) and nearly 8 hours on banknotes [77]. Of course, experimental data provide some insight, but not the same level of evidence as a clinical trial. Guo et al. [78] found that more than 50% of the objects situated in intensive care units and general wards were contaminated

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by the virus (computer mouse, 75%; bed rails, 43%), whereas the virus was present in other rooms where no patients had been transferred, possibly through staff shoes (half of which were found to be positive). Researchers have found extensive environmental contamination in clinical settings, from patients with only mild upper respiratory tract disease or even without any symptoms (87% of room sites including air outlet fans, table, chairs and bed rails) [3,50]. However, the finding of the utmost clinical significance is the viability of the virus in personal protective equipment, especially due to the global shortage that dictated the need for its reuse. The study by Kasloff et al. [51] provides insights on this important issue: the virus (even at low levels) remained viable for 7 days on nitrile gloves and for almost 21 days in N95 and N100 masks (titers decreased from 24 to 48 hours, stabilized from 48 hours to 4 days and then declined from day 7 to day 21). This clearly demonstrates the need for careful attention in the possible reuse of this equipment to avoid secondary transmission to medical staff. These studies present data from hospital wards and intensive care units (with high loads of virus) and probably do not reflect the transmission dynamics in other settings, and they do not provide any data about possible transmission from surfaces; nevertheless, they demonstrate the relatively high circulation of the virus in our surroundings and therefore the need for surface disinfecting policies [79]. According to a recent systematic review, in household settings, contamination of patients' surroundings was as high as 14%, with patients' utensils, electronic high-touch surfaces, beds, and floors representing the most frequently contaminated surfaces [80]. Finally, since fomite transmission is difficult to prove, some publications used mathematical models to demonstrate the contribution of fomites to the growth of the epidemic via transmission, underscoring the need for awareness of this important aspect of transmission [81].

Fecal Transmission

ACE-2 receptors are highly expressed in the small intestine [82] and clearly play a role in modulating intestinal inflammation [83]. SARS-CoV-2 utilizes the ACE-2 receptor as the main gate for entering the human body and recent data have suggested that the intestine could serve as a target organ for SARS-CoV-2 [52]. This may explain the gastrointestinal manifestations that are present in a small proportion of patients. There are sufficient data to prove the presence of viral genetic material in patients' stool [84], making the fecal-oral route a serious candidate for viral shedding. Moreover, viral clearance in stool seems to be even more prolonged than its clearance in nasopharyngeal swabs [14,84], and this fact suggests that patients (especially children) potentially transmit the virus via contaminated feces even after they have been discharged and recovered [48,53,54]. Virus shedding via stool is present even in patients without gastrointestinal symptoms, a fact with significant implications for pandemic control [85]. Despite the above-mentioned data, there are currently no reports of fecal-oral transmission of COVID-19, even though some researchers have reported recovering infectious virus from stool samples [86]. Nevertheless, sharing toilets with an infected person must be discouraged.

Pregnancy

The previous pandemic viruses, SARS and MERS, had high fatality rates in pregnant women, which raised theoretical concern regarding their possible risk in the COVID-19 pandemic [87]. We identified 10 studies that dealt with COVID-19 transmission during pregnancy or delivery [8,9,16,18,20,55–58,88]. Vertical transmission (through the placenta) and breastfeeding were investigated. All studies, except for 1, reported negative findings for COVID-19 in neonatal nasopharyngeal swabs, amniotic fluid, and placenta; however, some studies reported positive immunoglobulin M (IgM) and immunoglobulin G antibodies in neonates within hours of birth [18,55], suggesting either a damaged placenta (since IgM antibodies cannot pass through the normal placenta) or virus passage and secondary development of antibodies. It is also important to emphasize that since IgM antibodies develop 3 to 7 days after infection and blood was drawn 2 hours after birth, these antibodies could not have developed due to infection after birth. The infant with a positive throat swab may have acquired the virus due to close contact with the mother, since the authors did not report when the swab was taken and whether the neonate had contact with the mother [58]. Nevertheless, some data have been reported regarding newborns who, despite negative swabs and being separated from the mother without any contact immediately after delivery, developed symptoms suggesting COVID-19 after birth, but the level of evidence is very low for proving vertical transmission [56]. Kotlyar et al. [89] conducted a meta-analysis of 936 SARS-COV-2–tested neonates with COVID-19–positive mothers from 39 studies and identified maternal-to-fetal transmission of the virus in 3.2% of neonates in the third trimester. Regarding breast milk, a recent systematic review found that among 92 newborns whose mothers' milk was tested, only 4 tested positive for SARS-CoV-2 and 5 were reactive for IgM antibodies. Based on these results and taking into account the benefits of breastfeeding, the Centers for Disease Control and Prevention recommend that women with a suspected or confirmed infection with

COVID-19 have no indication to stop breastfeeding [90].

Other Potential Routes of Transmission

There are sparse data in the literature about possible transmission routes that cannot contribute to widespread infection, but nevertheless may have implications for everyday life, clinical practice, and the personal protective equipment required for several activities. A confirmed case had positive polymerase chain reaction (PCR) results for SARS-CoV-2 in tears and conjunctival secretions; this patient had conjunctivitis, and the results were negative for patients who did not have conjunctivitis [59]. Xie et al. [60] managed to find traces of SARS-CoV-2 on the ocular surface of patients who did not have any eye symptoms, suggesting that the virus could even spread from the normal conjunctiva, whereas other authors demonstrated that patients with oral swabs negative for SARS-CoV-2 could have positive swabs for the conjunctiva and tears [61]. Similarly, a case report described SARS-CoV-2 isolation in urine samples [62]. The presence of the virus in the blood was proven in 15% of patients in 1 study; although the median PCR cycle value was 35.1, suggesting a very low RNA concentration, this finding suggests the possibility of transmission through blood products [28]. Finally, recent reports reported isolating SARS-CoV-2 in the semen of patients in the acute phase, as well as in 8.7% of patients in the recovery phase [11]. A recent systematic review seems to agree with the above-mentioned results, finding a low but significant rate of patients with SARS-CoV-2–positive semen [91]. Medical personnel and the general population should be aware of these findings to minimize the already low probability of transmission through these routes.

Supplementary Materials

Table S1. Risk of bias for cohort studies; **Table S2.** Risk of bias for case series; **Table S3.** Risk of bias for case reports. Supplementary data is available at https://doi.org/10.24171/j.phrp.2021.12.2.02.

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 come from the studies included in references.

Authors' Contributions

Conceptualization: PM, LT; Data curation: PM, LT; Formal analysis: LT; Investigation: all authors; Methodology: LT, PM; Project administration: PM; Resources: all authors, Software: all authors; Supervision: PM; Validation: all authors; Visualization: all authors; Writing–original draft: PM; Writing–review & editing: all authors.

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Original Article

Global variation of COVID-19 mortality rates in the initial phase

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ABSTRACT

Objectives: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused devastation in over 200 countries. Italy, Spain, and the United States (US) were most severely affected by the first wave of the pandemic. The reasons why some countries were more strongly affected than others remain unknown. We identified the most-affected and less-affected countries and states and explored environmental, host, and infrastructure risk factors that may explain differences in the SARS-CoV-2 mortality burden.
Methods: We identified the top 10 countries/US states with the highest deaths per population until May 2020. For each of these 10 case countries/states, we identified 6 control countries/states with a similar population size and at least 3 times fewer deaths per population. We extracted data for 30 risk factors from publicly available, trusted sources. We compared case and control countries/states using the non-parametric Wilcoxon rank-sum test, and conducted a secondary cluster analysis to explore the relationship between the number of cases per population and the number of deaths per population using a scalable EM (expectation–maximization) clustering algorithm.
Results: Statistically significant differences were found in 16 of 30 investigated risk factors, the most important of which were temperature, neonatal and under-5 mortality rates, the percentage of under-5 deaths due to acute respiratory infections (ARIs) and diarrhea, and tuberculosis incidence ($p < 0.05$)
Conclusion: Countries with a higher burden of baseline pediatric mortality rates, higher pediatric mortality from preventable diseases like diarrhea and ARI, and higher tuberculosis incidence had lower rates of coronavirus disease 2019-associated mortality, supporting the hygiene hypothesis.

Keywords: Coronavirus; Environment; Mortality; Public health

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Introduction

By April 1, 2020, over 810,000 confirmed cases and 40,000 confirmed deaths were reported due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally [1]. In the initial stages of the pandemic of coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2, the incidence and mortality rates varied widely in different countries. Among the countries with the highest incidence and mortality rates due to COVID-19, certain populous countries such as the United States (US), Brazil, and Mexico were particularly affected [1]. The trajectories of COVID-19-specific mortality rates highlight the discrepancies of the COVID-19 impact worldwide. Within the US, New York City became the epicenter of the US and was particularly hard-hit early. In the first month following the confirmation of COVID-19, 130,689 cases were identified and the mortality rate was 244 deaths per million. In comparison, Pennsylvania, which has a comparable total population size to New York City, had 28,685 confirmed cases in the first month and a significantly lower mortality rate, at 59 deaths per million [1]. Similar discrepancies were noted across different countries such as Italy and France, which have comparable population sizes; however, Italy had 69,176 confirmed cases and 126 deaths per million by the end of the first month, as reported by the World Health Organization (WHO) [1], whereas France had 43,977 confirmed cases in the first month and a lower mortality rate, at 45 deaths per million, within the same period [1].

Based on variations at the state, regional, and national levels, as well as the beliefs of leaders, different policies and practices were implemented to contain the pandemic with varying success. The extent of the contribution of natural and environmental factors to variation in the COVID-19 incidence and mortality rates across different countries is unclear, as is the contribution of various policies implemented by countries and regions. Consequently, we estimated the mortality rates in the first month of the pandemic for all countries, as the total number of cases of COVID-19 is not yet known given gaps in testing for COVID-19 as reported by the WHO [1]. All countries were assessed in their first month of the pandemic, and factors associated with high morbidity and mortality were explored. This has implications because it can provide insights into what makes a society vulnerable to the rapid spread of COVID-19, with relevance for the future. In particular, identifying the risk factors that contributed to variation in mortality rates has important implications for the second and third waves of the pandemic. A careful case-control analysis of contributors (including environmental, natural, and policy differences) to the severity of disease and mortality in COVID-19 was conducted to shed light on discrepancies in the first wave of the pandemic globally.

Materials and Methods

Cases and controls were selected by matching countries with the highest COVID-19 mortality rates compared to those with the lowest. Matching was done based on the population size and WHO region (where possible). This study covered the period between March and May 2020 to represent the first wave of the COVID-19 pandemic. We shortlisted all countries that had at least 100 cases by March 31 (106 countries), as identified by Ritchie et al. [2]. We referred to the day when a country reported its 100th case as day X. For each country, we took the time of 1 month (30 days) after the day of the first 100 cases (day X). We referred to this as day Y, whereby Y = X + 30 days. All further data were obtained for day Y of each country, as identified by Ritchie et al. [3]. All countries were arranged in descending order by the total deaths/population in those 30 days, and the top 10 countries were selected. For countries with an area greater than 5,000,000 km^2, the unit of comparison was by state/province. These countries included Russia, Canada, the US, Brazil, and Australia. The top 10 countries in terms of COVID-19 deaths per population were selected for analysis as cases. To select controls, countries and US states were listed by decreasing order of population.

For each case, 6 controls were matched according to the closest population size. Controls were selected based on 3 criteria: (1) the control countries were closest in population size to the case country, (2) 2 controls were from the same WHO region and 4 from different WHO regions, and (3) the COVID-19 death rates per population of the controls were at least 3 times lower than that of the case (Table 1, Figure 1).

Data Sources, Collection Process, and Tool

Based on 3 different contributors (the environment, infrastructure, and host-related factors), potential risk factors that may determine the severity of COVID-19 burden in these 3 categories were shortlisted (Table 2). For each variable, reliable sources of publicly available information for all countries were utilized. Data were manually entered in Microsoft Excel and a tool was utilized to process the data. A complete list of sources is found in Table S1.

After piloting the data, 2 control countries (Taiwan and Hong Kong) had many missing variables due to the non-availability of data, and variables were treated as missing. For 23 out of 30 variables, comparable data were not found for states within the US (Table S1). Therefore, data available for the entire country were used instead. For infrastructure factors, data for public transportation were missing; given high intercity variability, only the top metropolitan city in the country was considered. Population size was

Table 1. List of case and control countries/states

Case country/state	Same WHO region controls		Different WHO region controls			
New Jersey	Tennessee	Indiana	Austria	United Arab Emirates	Hong Kong	Belarus
Connecticut	Oklahoma	Utah	Kuwait	Bosnia and Herzegovina	Moldova	Armenia
New York	Florida	Texas	Australia	Niger	Sri Lanka	Taiwan
Michigan	Washington	Arizona	Jordan	Sweden	Portugal	Kyrgyzstan
Louisiana	Alabama	Kentucky	Georgia	Slovakia	New Zealand	Croatia
Spain	Uzbekistan	Poland	Argentina	Iraq	Afghanistan	Algeria
Belgium	Czech Republic	Greece	Tunisia	Cuba	Dominican Republic	Rwanda
Italy	Turkey	Ukraine	South Africa	Colombia	South Korea	Kenya
Netherlands	Romania	Kazakhstan	Ecuador	Guatemala	Cambodia	Senegal
United Kingdom	Germany	Russia	Thailand	Egypt	Philippines	Vietnam

WHO, World Health Organization.

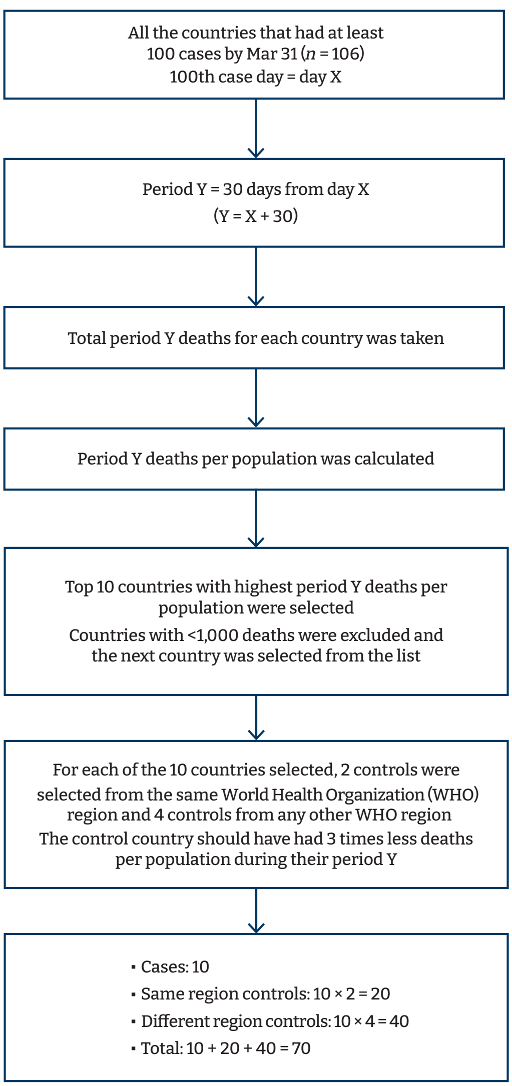

Figure 1. Algorithm used to select case and control countries/states.

used to ascertain the top metropolitan city, and the public transportation system of the selected cities was analyzed for further analysis.

Data Analysis

Temperatures in March and April were found separately, using the arithmetic mean to obtain the average temperature of March and April. Public transportation was divided into 4 categories: (1) none, (2) over-ground transport system only (buses/trams), (3) underground mass public transport only, and (4) over-ground and underground transport systems. Data analysis was carried out in Stata 15.1 (StataCorp., College Station, TX, USA), and Power BI (Microsoft Corp., Redmond, WA, USA) was used for the graphics. Due to the skewed distribution of variables, data were reported as median and interquartile range. The non-parametric Wilcoxon rank-sum test was used to compare factors between the 2 groups. The cluster analysis was performed using a scalable EM clustering algorithm, which iteratively refines an initial cluster model to fit the data and determines the probability that a data point exists in a cluster. The algorithm ends the process when the probabilistic model fits the data. The function used to determine the fit was the log-likelihood of the data given the model.

Ethical Approval

Ethical approval was not required, as all information was freely available in the public domain.

Results

Geographically, all cases were in the northern hemisphere; 5 were states within the US, whereas the other 5 were

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countries in Europe (Figure 2). Controls were located across 6 continents (Figure 2). The risk factors that were significantly different in cases versus control countries/states are given in Figures 3 and 4; of the 30 risk factors that were investigated, 16 were found to be significant. Host-related factors were also observed to contribute to the difference in mortality rates (Figures 5, 6). A secondary analysis was conducted to compare the number of cases and the number of deaths in period Y, and the results are shown in Figure 7. Italy and Spain had a much higher proportion of deaths per reported cases than the US. There were limited data for the case countries/states on

Table 2. Comparison of risk factors in case and control countries and states (significant factors only)

Risk factor	Control	Case	*p*
Environmental factor			
March temperature (°C)	12.3 (4.1–20.8)	5 (2.5–8.6)	0.035
April temperature (°C)	15.3 (9.6–21.6)	8.1 (7.6–11.7)	0.013
Average temperature (°C)	13.5 (6.8–20.6)	6.6 (5.5–10.2)	0.023
UV light index (J/m²)	3,230 (2,138–4,862)	1,662 (1,645–2,444)	0.008
Host factor			
Life expectancy at birth (y)	75.2 (71.5–77.6)	81.4 (81.2–82.8)	0.040
Under-5 mortality rate (/1,000 live births)	10 (6–22)	4 (3–4)	0.003
Neonatal mortality rate (/1,000 live births)	6 (3–12)	2 (2–2)	0.008
Tuberculosis incidence (/100,000 population)	26.5 (5.5–69.0)	4.6 (2.3–8.0)	0.004
% of under-5 deaths due to diarrhea	1.7 (0.4–5.4)	0.3 (0.2–0.4)	0.016
% of under-5 deaths due to acute respiratory infection	1.0 (5.3–15.1)	1.8 (1.4–2.4)	0.002
Presence of national BCG program	42 (70)	0	<0.001
Infrastructure factor			
Education index	0.69 (0.60–0.78)	0.81 (0.79–0.86)	0.012
Population density (people/km^2)	90 (57–136)	275 (205–378)	0.017
Human Development Index	0.77 (0.70–0.84)	0.92 (0.89–0.92)	0.003
% of GDP on healthcare	6.8 (5.3–8.2)	9.6 (8.9–10.1)	0.014
Population of age ≥ 65 (% of total population)	12 (5–16)	18 (16–19)	0.001

Data are presented as medians (interquartile range) or *n* (%).
IQR, interquartile range; UV, ultraviolet; BCG, Bacillus Calmette-Guérin; GDP, gross domestic product.

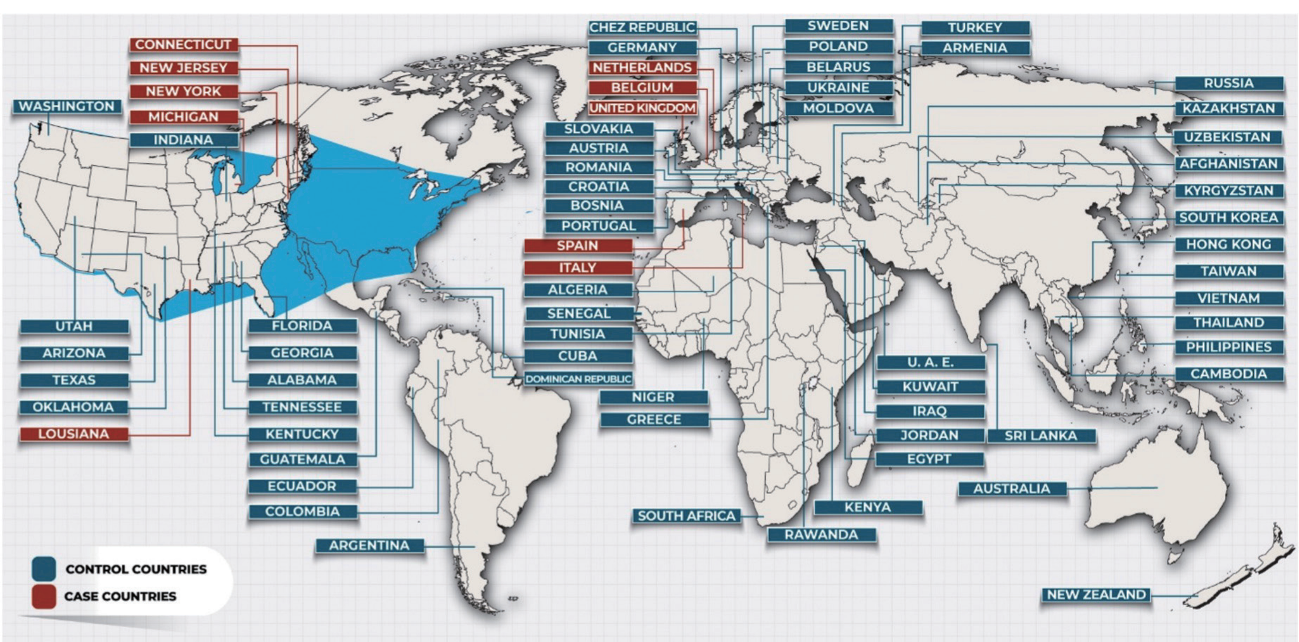

Figure 2. Map showing case and control countries/states.

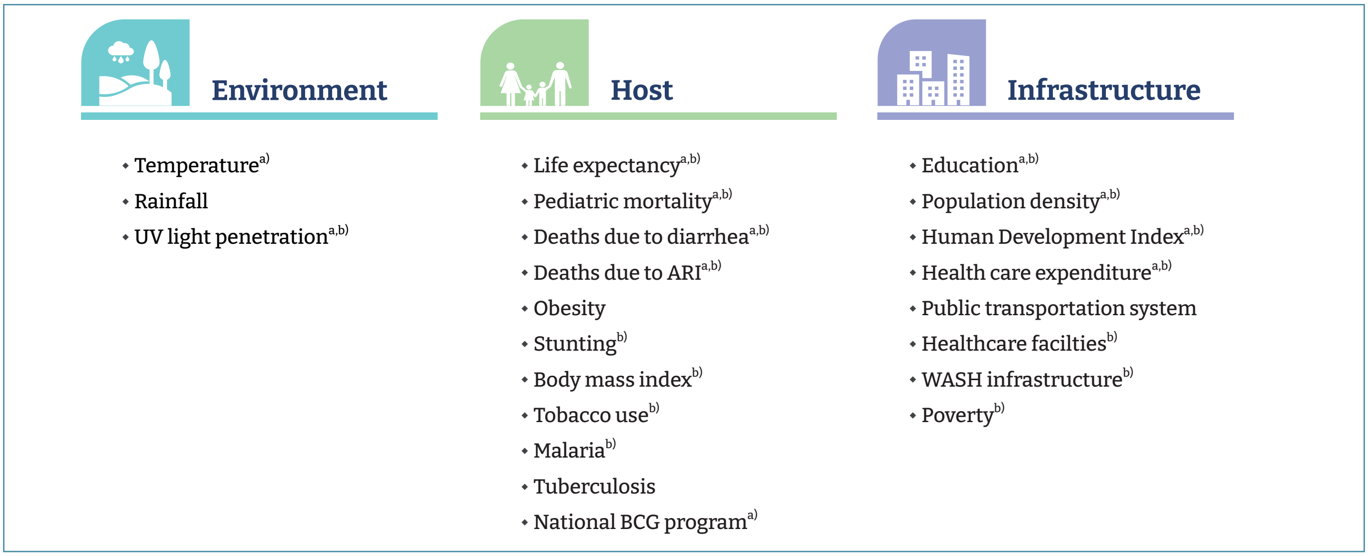

Figure 3. Three domains of risk factors studied.
[a)]Statistically significant differences noted between cases and controls. [b)]Individual State data was not available; therefore, data was taken for whole of United States. UV, ultraviolet; ARI, acute respiratory infection; BCG, Bacillus Calmette-Guérin; WASH, water, sanitation, and hygiene.

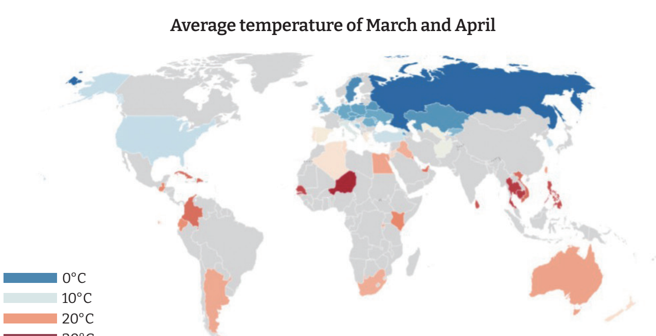

Figure 4. Map showing temperatures in included countries/states.

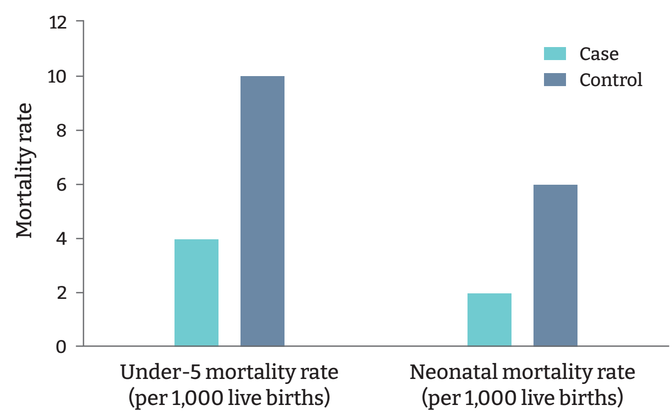

Figure 5. Comparison of pediatric mortality rates in case and control countries/states.

stunting, malaria incidence, and poverty.

Environmental Factors

The case countries/states recorded lower average temperatures in March and April (6.6°C) than the controls within that period (13.5°C, $p = 0.023$) (Table 2). The ultraviolet (UV) light index was lower in the case countries/states (1,662.0 J/m^2) than in the controls (3,229.5 J/m^2, $p = 0.008$) (Table 2).

Host-Related Factors

Among the host-related factors, pediatric and neonatal mortality rates, causes of under-5 deaths, adult life expectancy, and others were significantly different among the cases and controls. The neonatal mortality rate was 2 per 1,000 live births in the cases versus 6 per 1,000 live births in the controls ($p = 0.008$) (Table 2). The under-5 mortality rates were 4 and 10 per 1,000 live births in the cases and controls, respectively ($p = 0.003$) (Table 2, Figure 5). In the case countries/states, 0.3% of under-5

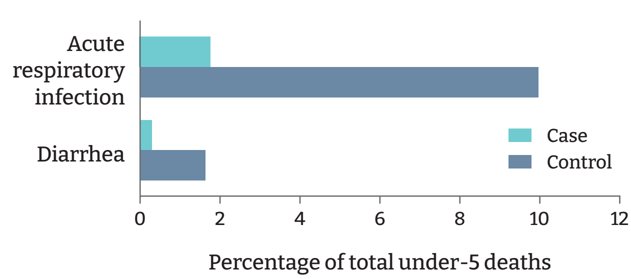

Figure 6. Comparison of top causes of under-5 deaths in case and control countries/states.

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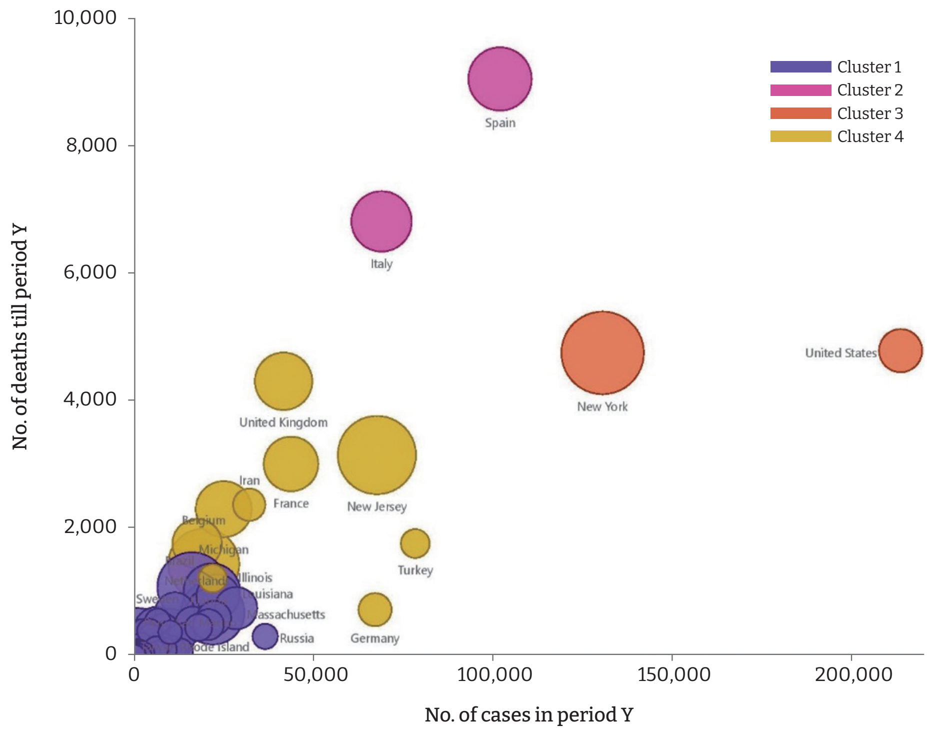

Figure 7. Comparison of number of deaths and number of cases in period Y in all included countries/states.

deaths were due to diarrhea, versus 1.7% in the controls ($p = 0.016$) (Table 2). Furthermore, 1.8% of all under-5 deaths in the case countries/states resulted from acute respiratory infections, versus 10.0% in the controls ($p = 0.002$) (Table 2, Figure 6). In the cases, the tuberculosis incidence was found to be 4.6 per 100,000 population, versus 26.5 in the controls ($p = 0.004$) (Table 2). National Bacillus Calmette-Guérin (BCG) vaccination programs were not present in the cases, whereas 42 control countries/states (70%) had these programs ($p < 0.001$) (Table 2).

Infrastructure

The education index was 0.81 in the case countries/states and 0.69 in the controls ($p = 0.012$), whereas the Human Development Index was 0.92 versus 0.77 in the case and control countries/states, respectively ($p = 0.003$) (Table 2). The case countries/states spent 2.87% of gross domestic product more than the control countries on healthcare, and this was a significant difference ($p = 0.014$). The population density was 3 times higher in the case countries/states than in the controls (275 vs. 90 people/km^2 of land area, $p = 0.017$) (Table 2).

Discussion

The analysis of our data showed many interesting results. The cases were all high-income countries in North America and Europe. There was a significant difference in living standards between the case and control countries, with the controls belonging to the low-income group (overall) with poorer healthcare and education and higher mortality from diarrhea and respiratory infections in childhood. Our findings suggest that countries with poorer economies and health systems did not experience worse outcomes in the early stage of the COVID-19 pandemic.

The baseline mortality due to acute respiratory infections was more than 5 times higher in the controls than in the cases. Our findings suggest that young children, including infants, who have a higher susceptibility and burden of other respiratory infections, may have milder COVID-19 due to the long-term boost of the innate immune response, known as trained immunity, as noted by Netea et al. [4]. The case countries all had lower incidence rates of tuberculosis, as well as no national BCG vaccination programs. An association of anti-tuberculosis antibodies with decreased severity of COVID-19 has been reported by Kovacic [5] and Miller et al. [6]. Countries with a long-standing BCG program had some degree of protection against COVID-19, corroborating the finding of Escobar et al. [7] that every 10% increase in the BCG index was associated with a 10.4% reduction in COVID-19 mortality. Taken together, the higher burden of tuberculosis and pediatric mortality in the control countries can be explained by the "hygiene hypothesis," which relates to the decreasing incidence of infections in Western countries, as identified by Stiemsma et al. [8].

Welliver [9] noted that temperature and the UV light index were significant indicators, whereby colder temperatures seemed to favor a high burden of COVID-19, similar to the associations of temperature with influenza and other respiratory viruses. However, further studies are needed to confirm this finding. Population density seems to have been a vital factor that differentiated the cases and controls. The case countries/states had more than 3 times the number of people living per square kilometer of land. This is a logical result, since crowding leads to higher rates of transmission of droplet infections. In countries with lower population densities, Corburn et al. [10] pointed out that most of the population lives in rural settings with automatic distancing, whereas heavily urbanized areas pose difficulties in implementing social distancing due to the living environment.

It is of note that several of our indicators, including obesity, stunting, and tobacco use, proved not to be statistically significant. We suspected that the case countries/states would primarily have cities with underground mass public transit available, but our findings were insignificant. Seventy percent (7 out of 10) of our case countries/states and 51.7% (31 out of 60) of our controls had underground mass public transit available, and this difference was not statistically significant. Tobacco use and obesity, which are risk factors for many diseases, were also not found to be significant between the case and control countries/states. Stunting, malaria incidence, and poverty index data were not available for many developed countries. As malaria and stunting are not major public health concerns in that part of the world, these parameters are not rigorously documented. Moreover, these countries have stronger economies and have not been assigned a poverty index number, so this variable was treated as missing data.

The Cases of Spain, Italy, and the United States

Our secondary analysis revealed that Italy and Spain had much higher proportions of deaths among COVID-19 cases than that of the US (Figure 7). One explanation is that the testing threshold for Spain and Italy was much higher, increasing the likelihood of high-risk patients testing positive. However, Roser et al. [11] reported that the COVID-19 positivity rates of Spain, Italy, and the USA were 3% to 5%, 5% to 10%, and 10% to 20%, respectively. Another explanation is that in Italy and Spain, a higher percentage of the population is over 65 years of age than in the US. A more detailed look at the individual country numbers indicated that 23% of the population of Italy is over 65 years of age, whereas the corresponding percentages in Spain and the US are 19% and 16%, respectively. This factor may have contributed to the high level of mortality in Italy, but other factors are also likely to have played a role. The contribution of population demographics to increased COVID-19 mortality has been explored by Kontis et al. [12], who showed a correlation with the elderly population across different countries. Another possible explanation posited by Islam et al. [13] is that the COVID-19 virus strains present in Europe were deadlier than the North American strains. A genome-wide association study of severe COVID-19 patients conducted by Severe Covid-19 GWAS Group et al. [14] identified a gene cluster on chromosome 3 as a risk locus for respiratory failure. The COVID-19 Host Genetics Initiative [15] reported that nearly 50% of individuals in South Asia are carriers of this suspicous region, while Zeberg and Paabo [16] identified that 16% of people in Europe are carriers. Although the specific genes contributing to the severity of COVID-19 remain elusive, other contributors, including socioeconomic changes and preexisitng conditions, may have contributed to the high disparities in the death toll.

Strengths

We systematically explored 30 variables related to the life sciences, including climate, population demographics, public health indices, and infrastructure. The study employed a holistic approach aiming to account for many risk factors. By using mortality per population as the principal measure of severity of the disease, 2 goals were achieved: first, the study eliminated patients with mild disease and therefore focused only on those who were a burden on the health system, and second, a fair comparison was made between countries with larger and smaller populations. The control countries were matched based on population size for all dependent variables. Lastly, all data were obtained from publicly available, verifiable sources.

Limitations

The study aimed to identify the top 10 countries and states that were worst affected by COVID-19 in the early stage of the pandemic. Many countries/states had a limited number of laboratory polymerase chain reaction testing kits and were unable to test a sufficient number of suspected individuals. The case and control countries/states were identified based on the COVID-19 mortality data from only March and April 2020; analyzing the spread of the virus in the following months may yield different results regarding the top 10 countries/states. For 23 of the 30 variables, data were not available for individual states of the USA and combined

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data of the USA were used, leaving no differences across the states. Furthermore, population-level data (not individual data) were employed, which may have caused this study to be affected by the ecological fallacy, which is an important bias in studies involving population-level data collection.

Conclusion

The death toll following the first wave of the COVID-19 pandemic was affected by all 3 types of determinants (environmental, host-related, and infrastucture-related). We investigated various factors that potentially contributed to the global discrepancy in mortality rates. Countries implemented various control measures such as suspending public transport and promoting physical isolation. Even as the national emergency responses varied across countries, significant impacts of key environmental, host-related, and infrastructure-related determinants were identified. Our results shine light on the epidemiological contributors to variation in COVID-19 mortality. Our findings may guide future researchers to investigate these parameters concerning COVID-19 and help deduce factors related to COVID-19 preparedness for the second and third waves of the pandemic. Actions to mitagate future global health threats require identifying deficiencies in the existing health systems, as well as improving coordination and implementation.

Supplementary Material

Table S1. All indicators except public transportation. Supplementary data is available at https://doi.org/10.24171/j.phrp.2021.12.2.03.

Notes

Ethics Approval

Ethical approval was not required, as all information was freely available in the public domain.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

Authors' Contributions

Conceptualization: SAA; Data curation: SHS, AS, AR, FS; Formal analysis: AR, FS; Investigation: AR, FS; Methodology: SHS, AS, MTY, SAA; Project administration: SAA; Software: AR, FS; Supervision: SAA; Validation: AR, FS, MTY, SAA; Visualization: MTY, SAA; Writing–original draft: SHS, AS, AR, FS; Writing–review & editing: SHS, AS, MTY, SAA.

Additional Contributions

The authors would like to acknowledge Gaurav Patel, MD for his contribution to the graphics of Figure 2.

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Original Article

Trends in recent waterborne and foodborne disease outbreaks in South Korea, 2015–2019

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ABSTRACT

Objectives: This study analyzed trends in foodborne and waterborne diseases in South Korea between 2015 and 2019.
Methods: The data consisted of information on outbreaks of waterborne and foodborne infectious diseases reported through the Korea Centers for Disease Control and Prevention (KCDC) system. We analyzed the trends and epidemiological aspects of outbreaks by month, place of occurrence, and causative pathogens in this observational study.
Results: The number of outbreaks has steadily increased over the last 5 years, but the number of cases per outbreak has followed a decreasing trend. Incidence at daycare centers and preschools has been steadily increasing over consecutive years.
Conclusion: The steady number of patients and decreasing number of cases per outbreak, even as the number of outbreaks has been increasing, suggest that the KCDC's professional management system is operating effectively. It is necessary to continue improving the objectivity and efficiency of the management system and to carefully examine the increasing number of outbreaks in smaller-scale group catering facilities, such as daycare centers and preschools. Outbreaks can be prevented by closely examining those caused by unidentified pathogens and group outbreaks caused by other diseases, identifying problems, and supplementing the management system.

Keywords: Foodborne diseases; Korea; Outbreaks; Waterborne disease

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Introduction

Since 2007, the Korea Centers for Disease Control and Prevention (KCDC) has managed outbreaks of waterborne and foodborne infectious diseases that occur in South Korea (hereafter, Korea), while also collecting the results of epidemiological investigations. The World Health Organization defines a waterborne or foodborne disease outbreak as "a case in which two or more people experienced the same disease after eating the same food or drinking water from the same source" [1]. In Korea, the occurrence of waterborne and foodborne infectious diseases is defined as the appearance of gastroenteritis symptoms, such as diarrhea or vomiting, in a group of 2 or more people, with epidemiological associations (e.g., time and place) [2]. A status analysis provides basic, critical data that may be used to prepare policies for the prevention of infectious diseases. Unlike previous studies, this study subdivided outbreaks according to their place of occurrence and analyzed their timing and the causative pathogens. The purpose of this study was to analyze the status of outbreaks of waterborne and foodborne infectious diseases that occurred in Korea from 2015 to 2019 and to examine trends in those outbreaks.

Materials and Methods

This study analyzed outbreaks of waterborne and foodborne infectious diseases reported through the KCDC's web reporting system from 2015 to 2019. Reports on the results of all epidemiological investigations must be submitted to the KCDC within 14 days after the end of the outbreak, and the reports submitted are reviewed by a KCDC Epidemic Intelligence Service officer, evaluated, and managed as data.

Outbreaks were excluded from the analysis if they were not reported in the results of an epidemiological investigation or if an epidemiological connection had not yet been confirmed. We analyzed the trends and epidemiological aspects of outbreaks by month, place of occurrence, and causative pathogens. Microsoft Excel was used for the analysis. The study protocol was approved by the KCDC Institutional Review Board (IRB No: 2020-08-03-PE-A). Informed consent was confirmed by the IRB.

Results

From 2015 to 2019, a total of 2,815 waterborne and foodborne disease outbreaks involving 48,032 cases were reported to the KCDC (Figure 1). There was an increase from 2015 to 2018, but the number of outbreaks decreased in 2019. However, the number of cases per outbreak followed a decreasing trend. In 2018, there was an increase of 29.3% in the number of outbreaks ($n = 697$) compared to the previous year ($n = 539$), and the number of cases approximately doubled compared to the previous year. With the exception of a peak in 2018, the number of outbreaks has been steadily increasing over the last 5 years.

Outbreaks occurred most intensively between May and September (9.5%, 9.2%, 9.3%, 9.8%, and 10.2%, respectively) (Table 1), accounting for 48% of the total annual outbreaks. However, May and June 2015 accounted for a lower percentage of outbreaks (6.9%) than the corresponding months in other years (Figure 2). Outbreaks most commonly occurred in March and June in elementary, middle, and high schools and least commonly in January and February. July and August, which are the summer vacation period, accounted for 16.4% of outbreaks among elementary, middle, and high school groups, likely due to active after-school learning activities. The highest incidence in daycare centers occurred in winter (November, December, and January) and the lowest occurred in summer (July and August). Similarly, the incidence of outbreaks in preschools was highest in winter, while it was relatively low in summer. For restaurants, the highest incidence was during summer,

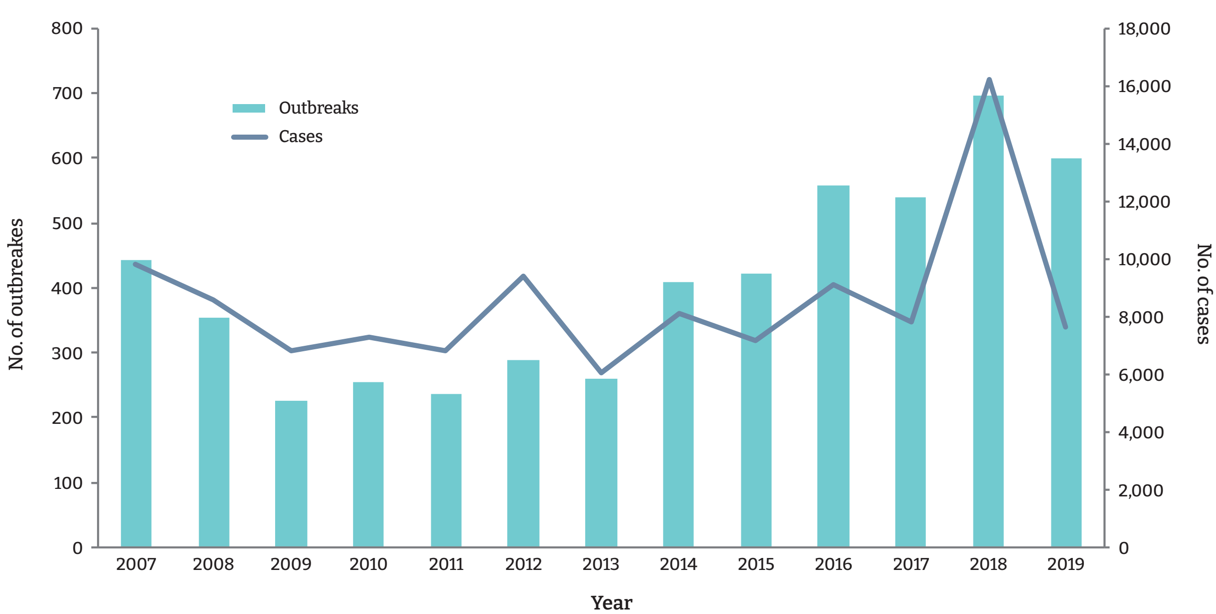

Figure 1. Number of reported waterborne and foodborne disease outbreaks and cases.

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Table 1. Number of reported waterborne and foodborne disease outbreaks and cases by month

Month	2015		2016		2017		2018		2019		Total (%)	
	Outbreak	Case	Outbreak	Case	Outbreak	Case	Outbreak	Case	Outbreak	Case	Outbreak	Case
January	52	537	22	192	38	296	28	178	48	503	188 (6.7)	1,706 (3.6)
February	17	217	17	89	33	215	37	557	35	275	139 (4.9)	1,353 (2.8)
March	35	414	33	452	33	351	61	1,334	56	988	218 (7.7)	3,539 (7.4)
April	33	490	49	567	50	858	47	848	67	1,012	246 (8.7)	3,775 (7.9)
May	29	500	53	871	51	691	62	1,213	72	873	267 (9.5)	4,148 (8.6)
June	29	732	48	766	65	904	51	1,068	66	952	259 (9.2)	4,422 (9.2)
July	45	612	34	459	56	753	69	979	58	772	262 (9.3)	3,575 (7.4)
August	42	2,212	72	2,516	65	1,346	50	1,586	48	517	277 (9.8)	8,177 (17.0)
September	41	477	53	576	50	1,179	96	5,762	48	315	288 (10.2)	8,309 (17.3)
October	38	308	56	795	25	379	79	970	29	344	227 (8.1)	2,796 (5.8)
November	32	276	57	929	30	369	62	880	35	577	216 (7.7)	3,031 (6.3)
December	29	400	63	927	43	471	55	872	38	531	228 (8.1)	3,201 (6.7)
Total	422	7,175	557	9,139	539	7,812	697	16,247	600	7,659	2,815 (100)	48,032 (100)

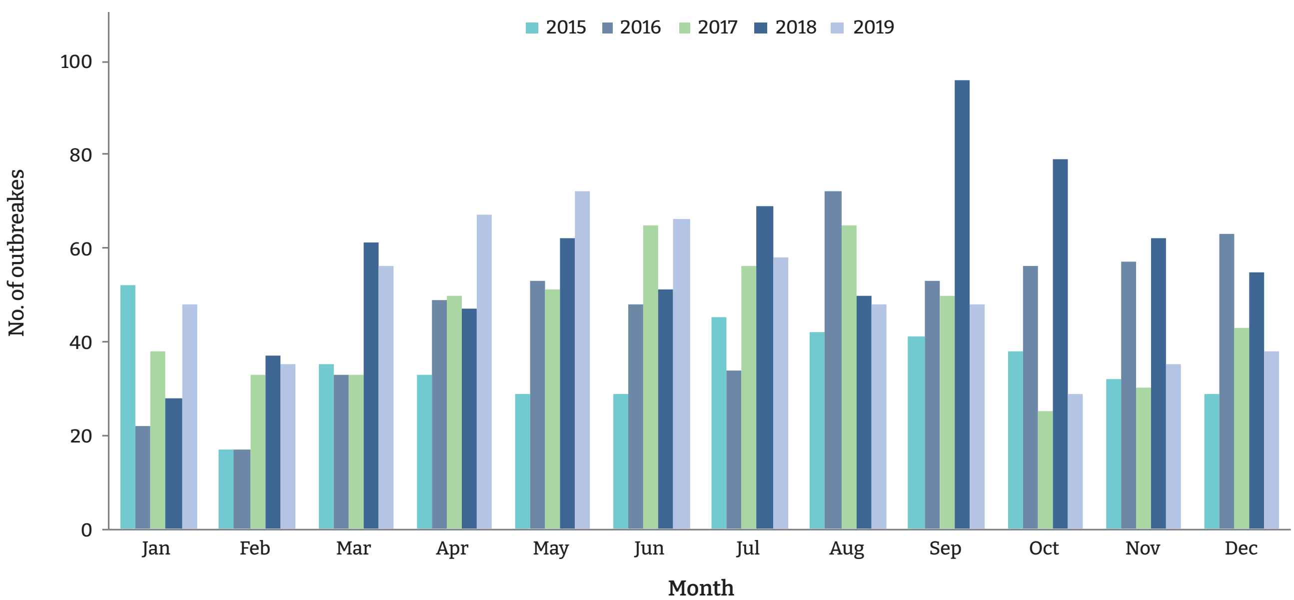

Figure 2. Number of reported waterborne and foodborne disease outbreaks by month.

between June and August (data not shown).

The causative pathogens were only identified in 58.7% of cases, of which norovirus was the most frequent, at 21.6% (Table 2). Aside from norovirus, the category of "others" accounted for 11.9%, pathogenic *Escherichia coli* for 6.3%, and *Salmonella* spp. for 3.5%. "Others" included pathogens that are not legally defined as communicable diseases, such as *Kudoa septempunctata* and intestinal coliform infection. Two or more pathogens were involved in 3.2% of outbreaks between 2015 and 2019. The majority (80.4%) of outbreaks involving bacterial pathogens, such as pathogenic *E. coli*, occurred from May to October. Norovirus infections occurred most commonly in winter (January and December), accounting for 33.5% of the yearly incidence, with 22.7% of norovirus cases occurring from May to October.

Of the total norovirus outbreaks, 37.8% occurred in elementary, middle, and high schools, and 25.6% occurred in daycare centers and preschools. That is, 63.4% of norovirus outbreaks occurred in group facilities with minors. Norovirus displayed a yearly increasing trend, which was especially evident in 2018, with an increase of 77.2% compared to the previous year.

The causative pathogens classified as "others" also increased annually due to an increase in the yearly number of outbreaks

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Table 2. Number of reported waterborne and foodborne outbreaks and cases by the causative pathogen

Causative pathogen	2015			2016			2017			2018			2019		
	Outbreak	Case	Case/outbreak	Outbreak	Case	Case/outbreak	Outbreak	Case	Case/outbreak	Outbreak	Case	Case/outbreak	Outbreak	Case	Case/outbreak
Norovirus	79	1,504	19.0	99	2,138	21.6	101	2,054	20.3	178	4,184	23.5	152	3,300	21.7
Pathogenic *Escherichia coli*	26	1,830	70.4	37	686	18.5	57	2,512	44.1	38	962	25.3	18	361	20.1
Salmonella spp.	10	136	13.6	23	282	12.3	23	711	30.9	22	3,596	163.5	21	606	28.9
Vibrio parahaemolyticus	3	16	5.3	22	322	14.6	10	357	35.7	15	239	15.9	5	25	5.0
Staphylococcus aureus	8	151	18.9	2	8	4.0	2	10	5.0	4	50	12.5	8	82	10.3
Campylobacter spp.	22	747	34.0	18	902	50.1	7	103	14.7	19	542	28.5	12	270	22.5
Shigella spp.	2	7	3.5	0	0	0	0	0	0	0	0	0	0	0	0
EHEC	1	5	5.0	3	12	4.0	0	0	0	0	0	0	1	2	2.0
Hepatitis A	0	0	0	1	10	10.0	2	15	7.5	0	0	0	77	557	7.1
Bacillus cereus	6	33	5.5	7	29	4.1	9	64	7.1	13	186	14.3	5	75	15.0
Clostridium perfringens	14	419	29.9	10	451	45.1	9	68	7.6	16	694	43.4	10	236	23.6
Others	19	222	11.7	80	2,094	26.2	75	448	6.0	96	1,855	19.3	66	514	7.8
Superinfection	17	644	37.9	20	804	40.2	5	294	58.8	29	1,939	66.9	18	422	23.4
Unknown	215	1,461	6.8	235	1,401	6.0	239	1,176	4.9	267	2,000	7.5	207	1,209	5.8
Total	422	7,175	17.0	557	9,139	16.4	539	7,812	14.5	697	16,247	23.3	600	7,659	12.8

EHEC, enterohemorrhagic *Escherichia coli*.

caused by *K. septempunctata*. In addition, there were 77 outbreaks related to hepatitis A in 2019, accounting for 3.7% of the total outbreaks that year. Notably, hepatitis A was previously not prominent in outbreaks. The proportion of outbreaks for which the causative pathogens could not be identified was 41.3%, corresponding to approximately 200 outbreaks every year. The proportion of outbreaks for which the causative pathogen was classified as "unknown" decreased gradually over time (2015, 50.9%; 2016, 42.2%; 2017, 44.3%; 2018, 38.3%; 2019, 39.5%). The places with the highest proportion of "unknown" pathogens were homes (60.3%) and restaurants (56.1%), and those with the fewest were preschools (5.4%) and daycare centers (9.3%).

General restaurants accounted for the highest proportion of outbreaks (48.0%), although this category accounted for only 18.0% of total cases (Table 3). Conversely, the proportion of outbreaks in elementary, middle, and high schools was low (18.6%), but the number of cases was approximately 50%, or roughly half of all cases. The proportion of outbreaks occurring in daycare centers and preschools was 7.2%, and the proportion of cases was 6.6%. The proportion of outbreaks with unidentifiable locations was 5.4%, and the proportion of cases was 2.4%. Outbreaks in elementary, middle, and high schools and in restaurants showed increasing and decreasing trends similar to those of outbreaks overall, but the proportion of outbreaks at daycare centers and preschools steadily increased (2015, 4.0%; 2016, 6.3%; 2017, 5.4%; 2018, 7.9%; 2019, 11%) (Table 4). Conversely, the proportion of outbreaks occurring at home decreased over the study period (2015, 19.4%; 2016, 4.5%; 2017, 2.0%; 2018, 2.4%; 2019, 4.8%).

Discussion

The incidence of waterborne and foodborne infectious diseases in Korea exhibited an increasing trend over the past 5 years. From 2007 to 2009, the incidence of outbreaks gradually decreased, and the number of patients increased, prompting the suggestion that professional management of outbreaks was required [3]. In contrast, the findings of the present study show that despite the increase in the number of outbreaks in recent years, the number of cases has been relatively consistent every year, and the number of cases per outbreak has been decreasing. This can be interpreted as reflecting a lower incidence of outbreaks in group facilities, such as major catering facilities, which often have a major effect when they occur. These results also suggest that the professional management system is operating effectively. Since 2003, the KCDC has been monitoring the outbreak of waterborne and foodborne infectious diseases

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Table 3. Number of reported waterborne and foodborne outbreaks and cases by causative pathogen and place of occurrence

Causative pathogen	Daycare center	Preschool	Elementary–high school	College	Work	Facility	Restaurant	Home	Others	Unknown	Total (%)
Norovirus	97	59	230	7	18	42	97	14	26	19	609 (21.6)
Pathogenic *Escherichia coli*	1	1	62	7	13	8	69	2	6	7	176 (6.3)
Salmonella spp.	1	2	7	2	5	6	53	10	8	5	99 (3.5)
Vibrio parahaemolyticus	0	0	1	1	0	2	44	4	1	2	55 (2.0)
Staphylococcus aureus	1	0	4	1	2	3	10	1	1	1	24 (0.9)
Campylobacter spp.	1	2	31	2	12	5	11	1	12	1	78 (2.8)
Shigella spp.	2	0	0	0	0	0	0	0	0	0	2 (0.1)
EHEC	0	0	0	0	0	0	3	2	0	0	5 (0.2)
Hepatitis A	1	0	0	0	19	4	31	10	0	15	80 (2.8)
Bacillus cereus	2	1	3	0	2	0	28	2	0	2	40 (1.4)
Clostridium perfringens	0	0	13	6	5	6	19	1	4	5	59 (2.1)
Others	6	2	25	0	8	57	210	17	5	6	336 (11.9)
Superinfection	4	3	39	3	8	7	19	1	2	3	89 (3.2)
Unknown	12	4	109	6	50	18	758	99	20	87	1,163 (41.3)
Total	128	74	524	35	142	158	1,352	164	85	153	2,815 (100)

EHEC, enterohemorrhagic *Escherichia coli*.

Table 4. Number of reported waterborne and foodborne disease outbreaks and cases per outbreak by place of occurrence

Year	Division	Daycare center	Preschools	Elementary–high school	College	Work	Facility	Restaurant	Home	Other	Unknown	Total
2015	Outbreak (%)	9 (2.1)	8 (1.9)	88 (20.9)	12 (2.8)	58 (13.7)	10 (2.4)	88 (20.9)	82 (19.4)	19 (4.5)	48 (11.4)	422 (100)
	Case/outbreak	5.9	18.6	35.8	21.9	13.1	17.0	6.5	3.8	80.1	4.6	17.0
2016	Outbreak (%)	20 (3.6)	15 (2.7)	104 (18.7)	6 (1.1)	24 (4.3)	30 (5.4)	265 (47.6)	25 (4.5)	25 (4.5)	43 (7.7)	557 (100)
	Case/outbreak	17.6	20.0	43.8	17.8	16.5	18.3	5.7	3.6	39.1	7.0	16.4
2017	Outbreak (%)	18 (3.3)	11 (2.0)	87 (16.1)	5 (0.9)	12 (2.2)	48 (8.9)	327 (60.7)	11 (2.0)	7 (1.3)	13 (2.4)	539 (100)
	Case/outbreak	19.0	12.1	43.9	34.8	15.4	13.6	6.1	5.6	32.6	15.8	14.5
2018	Outbreak (%)	36 (5.2)	19 (2.7)	136 (19.5)	8 (1.1)	17 (2.4)	48 (6.9)	377 (54.1)	17 (2.4)	25 (3.6)	14 (2.0)	697 (100)
	Case/outbreak	15.0	21.0	66.7	41.5	40.1	36.7	6.5	3.5	32.2	9.1	23.3
2019	Outbreak (%)	45 (7.5)	21 (3.5)	109 (18.2)	4 (0.7)	31 (5.2)	22 (3.7)	295 (49.2)	29 (4.8)	9 (1.5)	35 (5.8)	600 (100)
	Case/outbreak	11.5	17.2	31.0	30.5	12.7	14.2	7.1	3.2	12.8	7.9	12.8

with real-time information through the Enteric Pathogens Active Surveillance Network (Enter-Net). Since 2012, efforts have also been made to prevent collective outbreaks of waterborne and foodborne infectious disease by expanding the monitoring of bacterial pathogens from 5 to 10 species [4].

Approximately 100 outbreaks occurred each year from 1995 to 2005, but the number of outbreaks increased to 259 in 2006 and 510 in 2007. The reason for these outbreaks was an increase in the use of group catering services, and the peak in 2007, in particular, occurred due to a change in the criteria used to define outbreaks from 5 to 2 persons affected [3]. However, approximately 540 outbreaks occurred recently, and the numbers are increasing over time. This may be caused by an increase in the culture of dining out and food delivery, the increasing use of group catering facilities, and improvements in the competence of health staff and the reporting system.

Approximately half of the outbreaks occurred between May and September each year. However, May and June of 2015 showed a lower proportion (6.9%) than the corresponding months in the other years included in this study. This was likely caused by the outbreak of Middle East respiratory syndrome in Korea in 2015, which reduced activities outside the home and increased personal hygiene awareness, resulting in a decrease in the number of outbreaks occurring in restaurants and catering facilities. The KCDC conducts intensive monitoring from May to September every year to prevent outbreaks in the summer. This is because the high temperature and highly humid environment facilitate the proliferation of bacteria or viruses that cause outbreaks. Normally, outbreaks occurring from May to September account for approximately 57% of the yearly total [3], but in recent years, outbreaks occurring from April to September have accounted for approximately the same proportion. This could be related to climate change causing the weather to be relatively warm in April. A 1°C rise in temperature increases the incidence of foodborne outbreaks by approximately 5% [5]. According to data from the Korea Meteorological Administration, the average temperature in April from 2015 to 2019 was higher than the average temperature in April from 2007 to 2009 (2007, 11.7°C; 2008, 13.0°C; 2009, 12.6°C; 2015, 12.7°C; 2016, 13.8°C; 2017, 13.9°C; 2018, 13.3°C; 2019, 12.0°C). This indicates that there is a correlation between the rise in temperature and outbreaks of waterborne and foodborne infectious diseases.

Norovirus is the most common pathogen that causes waterborne and foodborne infectious diseases. Furthermore, 16.5% of the outbreaks that occurred between 2007 and 2009 were caused by norovirus, 13.9% were caused by intestinal infections, and 39.9% were caused by unidentified pathogens [3]. The number of outbreaks caused by norovirus has been higher in recent years than previously. Moreover, the proportion of the total outbreaks attributed to norovirus among those with identified pathogens was very high, at 36.9%. The proportion of norovirus outbreaks worldwide is also high. For example, in the United States, norovirus accounted for approximately half (46%) of all pathogen outbreaks between 2009 and 2015. More than half of the norovirus outbreaks occurred in group catering facilities related to minors and during summer. Due to the nature of norovirus, which is transmitted through contact, it occurs predominantly in groups involving minors. In addition, with the increase in after-school activities, norovirus, which was once mainly prevalent only in winter, is now showing a trend to spread in summer.

Outbreaks of pathogenic *E. coli* decreased by 6.3%, but the number of cases for which the cause could not be identified rose to 41.3%. The proportions of other causative pathogens, such as *K. septempunctata*, also significantly increased. In particular, outbreaks caused by *K. septempunctata* accounted for 80% of “other” pathogens and are increasing consistently on a yearly basis. Previously, outbreaks due to hepatitis A were uncommon in Korea. However, 17,598 cases occurred in Korea during 2019. Seventy-seven hepatitis A-related group outbreaks were reported, including 2 outbreaks with more than 100 cases each.

The proportion of outbreaks of *Salmonella* has significantly decreased. *Salmonella* outbreaks accounted for 12.9% of all outbreaks from 2003 to 2006 [6] and 7.7% from 2007 to 2009 [3]. This decrease is due to the systemic management of *Salmonella* bacteria from the egg laying process to the egg distribution process by the Ministry of Agriculture, Food and Rural Affairs and the Ministry of Food and Drug Safety. However, cases associated with *Salmonella* outbreaks have increased steadily. In particular, in 2018, cases attributed to *Salmonella* outbreaks were approximately 5 times more numerous than in the previous year. The increase was attributed to the occurrence of *Salmonella* contamination in chocolate cakes, which are a popular product; this accounted for 2,975 cases in 2018.

Consistent with past trends, more than half of water and foodborne infectious disease outbreaks occurred in restaurants.

However, most of the group outbreaks that occurred in restaurants were small-scale outbreaks of 7 or fewer people, whereas large-scale outbreaks of more than 7 people frequently occurred in group catering facilities. In recent years, the frequency of outbreaks in group catering facilities, such as schools, has been increasing. The

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average proportion of outbreaks in schools was previously reported to be 14.5% [3], but the proportion of outbreaks occurring in elementary, middle, and high schools over the previous 5 years increased to 18.6%. In particular, the proportion of outbreaks in daycare centers and preschools exhibited a steadily increasing trend every year from 2015 to 2019. However, according to statistics from the National Statistical Office, the number of children who attend daycare in Korea is gradually decreasing. That is, the number of children who use daycare centers is decreasing, but the number of outbreaks occurring in daycare centers is increasing. Therefore, it is necessary to strengthen the management system for daycare centers and preschools, which appear to be a blind spot with respect to waterborne and foodborne infectious diseases, and to decrease the incidence in these locations to the same level as in elementary, middle, and high schools.

In addition, the proportion of "unknown" cases, in which the causal pathogen was not identified, increased from 39.9% (2007–2009) to 41.3% (2015–2019). However, the number of patients per outbreak in "unknown" cases almost halved, from 11.1 (2007–2009) to 6.2 (2015–2019) [3]. "Unknown" cases were less frequent in preschools and daycare centers than in homes and restaurants. This indicates that places such as schools have better management systems for infectious diseases than do homes and restaurants. These results suggest that the professional management system is operating effectively.

Conclusion

The incidence of outbreaks of waterborne and foodborne infectious diseases in Korea has fluctuated in recent years, but showed an overall increase compared to the past. However, the present findings confirmed that the number of cases per outbreak decreased, while the number of overall patients remained relatively constant. These results indicate the positive effect of intensively managing large-scale group catering facilities, such as schools, through professional human resources to prevent outbreaks. It is necessary to carefully examine the increasing number of outbreaks in smaller-scale group catering facilities, such as daycare centers and preschools. Group outbreaks among preschool children who cannot ensure their own personal hygiene must be systematically managed in collaboration with related ministries. In addition, outbreaks of waterborne and foodborne infectious diseases can be prevented by closely examining outbreaks due to unidentified pathogens and group outbreaks caused by other diseases; that is, steps should be taken to determine the cause of incidents, identify causative problems, and supplement the management system.

Notes

Ethics Approval

The study protocol was approved by the Institutional Review Board (IRB) of the Korea Centers for Disease Control and Prevention (IRB No: 2020-08-03-PE-A). Informed consent was confirmed by the IRB.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

All data generated or analysed during this study are included in this published article.

Authors' Contributions

Conceptualization: DHL; Data curation: SHL, JWY, JHL, YHJ; Formal analysis: SHL; Investigation: All author; Methodology: DHL, SHL; Project administration: JHL; Resources: SHL; Visualization: JHL; Writing–original draft: SHL, DHL; Writing–review & editing: All authors.

Additional Contributions

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Original Article

Psychological outcomes of the COVID-19 pandemic among pregnant women in Indonesia: a cross-sectional study

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ABSTRACT

Objectives: The objective of this study was to analyze the psychological outcomes of pregnant women during the coronavirus disease 2019 (COVID-19) pandemic in several areas that are epicenters for the spread of the severe acute respiratory syndrome coronavirus 2 in Indonesia.
Methods: This cross-sectional study used data obtained from an online survey administered to 120 women who were pregnant and gave birth during the COVID-19 pandemic in Indonesia. The psychological condition of pregnant women was measured using the Depression, Anxiety, and Stress Scale-21 questionnaire which was modified for conditions experienced during the COVID-19 pandemic. We classified pregnant women into 2 groups according to their psychological condition: pregnant women who experienced anxiety and pregnant women who did not experience anxiety or felt normal. Receiver operating characteristic (ROC) analysis was undertaken for the 2 groups. This study also used univariate analysis and bivariate analysis.
Results: The results of the ROC analysis resulted in a cutoff score of 3.56. The proportion of respondents who felt anxious was 53.3% and the proportion of respondents who did not feel anxious or felt normal was 46.7%. Anxiety was most common among pregnant women with high education levels, gestational age <19 weeks, and working pregnant women.
Conclusion: Maternal health services need to be performed with strict health protocols, complemented by pregnancy counseling services. This will provide a feeling of comfort and safety as pregnant women receive health services and give birth.

Keywords: COVID-19; Pregnant women; Psychological outcomes

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Introduction

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus first broke out in China in December 2019, it has continued to spread [1,2]. The resultant coronavirus disease

2019 (COVID-19) pandemic [3], which has had an extremely negative impact on public health [4]. The health care system faces numerous disruptions as the death toll from the virus continues to increase and becomes increasingly more difficult to control [5]. The COVID-19 pandemic has also taken a significant toll on the world economy [6]. Millions of people have experienced layoffs and poverty as a result of the pandemic [7,8], which has led to an increase in psychological disorders in some communities [9–11].

Mental health problems as a result of the COVID-19 pandemic also afflict pregnant women [12,13], which are one of the pandemic's most vulnerable groups [14,15]. In addition to the risk of infection, pandemic conditions result in limited physical activity and a disruption of maternal health services which in turn affect the mental health of pregnant women [16,17]. Poor mental health in pregnant women poses risks for adverse birth outcomes, such as miscarriage, premature birth, complications during childbirth, and death [18,19].

Pregnant women need psychological support to carry out pregnancy and childbirth during the COVID-19 pandemic [20,21]. Maternal health services need to be implemented with strict health protocols so that pregnant women can obtain health services with a low risk of COVID-19 infection. These services must also be supplemented by pregnancy counseling services, which improve the mental health of pregnant women [22]. In addition, psychological support needs to be provided by the family, especially by their partners [23], which can provide a feeling of comfort for pregnant women [24].

However, these standards have been difficult to meet during the COVID-19 pandemic in Indonesia. The accessibility of safe maternal health services is still not optimal, especially in areas that are considered epicenters of the SARS-CoV-2 virus, such as Jakarta, where health services are more focused on treating COVID-19 patients. Thus, non-COVID-19 health services have faced many disruptions [25]. Many pregnant women struggle to access maternal health services at all, and if they do, they may encounter inadequate health protocols. This increases the risk of pregnant women becoming infected [26].

People have also faced economic pressure also during the COVID-19 pandemic. Many people have lost their jobs and income, including people in households with pregnant women. This further increases the mental health burden of pregnant women [27–29]. In addition, pregnant women who work also face severe psychological stress [30]. There is no extended leave policy for pregnant women during the COVID-19 pandemic. Even working hours are generally reduced, pregnant women do continue to work. Of course, working while pregnant during pandemic conditions is very difficult for pregnant women, many of whom experience mental health problems [31].

This study analyzed the psychological condition of pregnant women during the COVID-19 pandemic in Indonesia. The purpose of this study was to analyze the psychological outcomes of pregnant women during the COVID-19 pandemic in several areas that have become epicenters for the spread of SARS-CoV-2 in Indonesia. The results of this study are expected to help pregnant women overcome psychological health problems and help health workers provide maternal health services that can promote a feeling of security for pregnant women.

Materials and Methods

Study Design

This cross-sectional study used data obtained from online surveys. An online survey was conducted to avoid face-to-face or physical data collection between researchers and respondents. Face-to-face or physical data collection would have a high risk of SARS-CoV-2 transmission between researchers and respondents. In addition, Indonesian regulations also restrict public and social activities, including field research. As a result, we decided to use an online survey in this study to examine the psychological outcomes of pregnant women during the COVID-19 pandemic in Indonesia.

Data and Study Sample

Data were collected online using an online questionnaire. The data collection period was carried out from October 19, 2020 to November 19, 2020. Questionnaires were distributed through the community networks of pregnant women, whose contact numbers were obtained from various sources, such as health personnel, lecturer networks, and community members. Questionnaires were also distributed through social media.

The samples in this study were women who were pregnant or gave birth during the COVID-19 pandemic. COVID-19 was declared to be a pandemic by the World Health Organization in March 2020. The study locations were the epicenters for the spread of SARS-CoV-2 in Indonesia, including Jakarta, Bogor, Depok, Tangerang, and Bekasi. These 5 regions are integrated with each other and considered 1 regional unit, referred to as the *Jabodetabek* area. The sample selection method is shown in Figure 1.

Method of Measurement and Analysis

We developed a new questionnaire to assess the psychological outcomes of pregnant women during the COVID-19 pandemic. This questionnaire was developed by referring to the Depression, Anxiety, and Stress Scale-21 questionnaire,

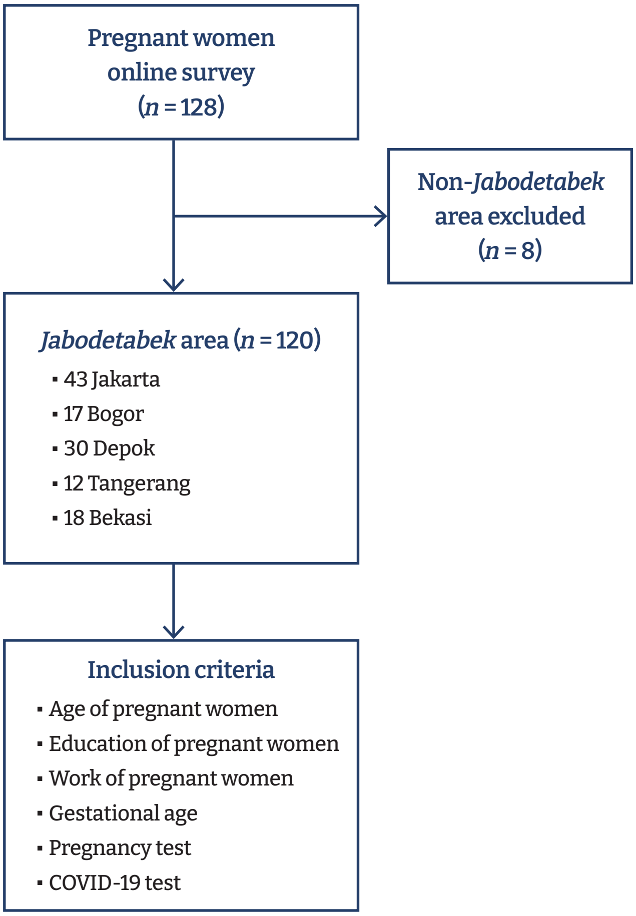

Figure 1. Flow chart of study sample selection.

in particular the anxiety component of the instrument [32]. We used 8 variables: (1) feeling unable to obtain maternal health services; (2) feeling unable to take care of household needs; (3) feeling worried about the condition of their pregnancy and the fetus; (4) feeling afraid of the childbirth process; (5) feeling worried about being unable to carry out physical activities, such as sports, during pregnancy; (6) feeling worried about not getting childbirth assistance from their partner; (7) feeling worried about the condition of social relationships; and (8) feeling worried about not being able to adapt to normal life during the pandemic. Each variable was measured using a Likert scale: 1 (very high), 2 (high), 3 (moderate), 4 (low), and 5 (very low).

We calculated the total value of the 8 variables and determined the average value to quantify the psychological outcome of each respondent. We then dichotomized these values using a receiver operating characteristic (ROC) curve, which is a visual representation of the relationship between sensitivity and specificity. The ROC curve is generated based on the calculation of a confusion matrix between the false-positive rate and the true-positive rate, which is used to divide data based on a cutoff point [33,34]. We calculated the cutoff point of the ROC curve, and a mean value less than or equal to the cutoff point was categorized as not anxious or normal, while a mean value greater than the cutoff point was categorized as anxious. We also used univariate and bivariate analysis in this research.

Ethical Considerations

This study received ethical permission from the Ethics Committee of the Veterans National Development University of Jakarta (No. 2789/X/2020/KEPK).

Results

Table 1 shows the socio-demographic characteristics of the respondents. Univariate analysis showed that 35.8% of respondents lived in Jakarta, 14.2% in Bogor, 25.0% in Depok, 10.0% in Tangerang, and 15.0% in Bekasi. With regard to age, 30.0% of respondents were < 25 years of age, 22.5% between ≥ 25 and < 27 years old, 25.8% between ≥ 27 and < 30 years old, and 21.7% ≥ 30 years old.

Most of the participants had relatively high education levels; specifically, 0.8% of respondents had only completed elementary school, 12.5% had completed up to high school, 16.7% had completed a bachelor's degree, and 70.0% had completed their bachelor's, master's, or doctoral degrees. Slightly fewer than half (44.2%) of respondents worked, while 55.8% did not. The proportion of respondents whose gestational age was < 19 weeks was 15.8%, while 17.5% had a gestational age from ≥ 19 to < 28 weeks, 15.0% from ≥ 28 to < 35 weeks, and 15.0% ≥ 35 weeks. The proportion of those who had given birth was 36.7%.

Fully 93.3% of respondents had received antenatal care, while 6.7% had never had a prenatal examination. The proportion of respondents who had been tested/tested for COVID-19 (rapid test/swab test) during pregnancy was 52.5%, while 47.5% had never been tested for COVID-19 (Table 1).

The ROC results had a cutoff point of 3.56. The average value was 3.54 and the standard deviation was 0.51. Based on the ROC analysis, the proportion of respondents who felt anxious was 53.3% and the proportion of respondents who did not feel anxious or felt normal was 46.7% (Table 2).

The results of the bivariate analysis showed that the highest concentration of respondents feeling anxious was in Depok, with 58.1% of respondents from this region reporting anxiety, while the lowest concentration was in Bogor, with only 41.2% reporting anxiety. The group with the largest proportion of respondents experiencing anxiety was

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respondents ≥30 years old, with a total of 61.5% reporting feeling anxious. The group with the lowest anxiety rate was respondents <25 years old, of whom only 44.4% reported feeling anxious.

Furthermore, respondents with a higher education level (bachelor degree/master's degree/doctoral degree) had a higher anxiety rate (58.3%) than those with a secondary education or lower, of whom 37.5% reported feeling anxious. Working pregnant women were mostly in the anxious category as well, as 56.6% reported feeling anxious. Among pregnant women who did not work, 50.7% reported anxiety.

The lower the gestational age of the respondents, the greater the percentage of respondents who reported feeling anxious. The percentage of respondents with a gestational age <19 weeks who reported anxiety was 68.4%, whereas only 38.9% of respondents with a gestational age ≥35 weeks reported anxiety. However, for respondents who had given birth, the percentage of anxious respondents increased to 50.0%. Furthermore, respondents who had never had a prenatal check-up were more anxious, with 75.0% reporting anxiety. Meanwhile, only 51.8% of who had a prenatal check-up reported anxiety. Of respondents who had not been tested for COVID-19, 57.9% were in the anxious category, while only 49.2% of respondents who had been tested for COVID-19 reported feeling anxious (Table 3).

Table 1. Socio-demographic characteristics of the respondents (*n* = 120)

Characteristic	*n* (%)
City/district	
Jakarta	43 (35.8)
Bogor	17 (14.2)
Depok	30 (25.0)
Tangerang/Tangerang Selatan	12 (10.0)
Bekasi	18 (15.0)
Mother's age (y)	
<25	36 (30.0)
≥25 & <27	27 (22.5)
≥27 & <30	31 (25.8)
≥30	26 (21.7)
Mother's education	
Primary school	1 (0.8)
Junior high school	0
Senior high school	15 (12.5)
Diploma	20 (16.7)
Bachelor's degree/master's degree/doctoral degree	84 (70.0)
Mother's job	
Currently employed	53 (44.2)
Not currently employed	67 (55.8)
Gestational age (wk)	
<19	19 (15.8)
≥19 & <28	21 (17.5)
≥28 & <35	18 (15.0)
≥35	18 (15.0)
Has given birth	44 (36.7)
Has had a pregnancy check-up during the COVID-19 pandemic	
Yes	112 (93.3)
No	8 (6.7)
Has received a COVID-19 test (rapid test/swab test)	
Yes	63 (52.5)
No	57 (47.5)

COVID-19, coronavirus disease 2019.

Discussion

The rapid spread of the SARS-CoV-2 virus in the *Jabodetabek* area has disrupted maternal health services. Several maternal health facilities were closed to prevent the spread of SARS-CoV-2. The Indonesian government also limits physical activity (physical distancing) in public spaces to reduce the spread of the virus [35]. These measures have all had impacts on the psychological condition of pregnant women [12,13].

This study evaluated the psychological status of pregnant women during the COVID-19 pandemic, many of whom reported feelings of anxiety, which can have a negative

Table 2. Psychological outcomes according to variables (*n* = 120)

Variable	Mean ± SD
1. Feeling unable to meet the needs of maternal health services	3.32 ± 0.99
2. Feeling unable to take care of household needs	2.87 ± 1.05
3. Feeling worried about the condition of pregnancy and the fetus	3.95 ± 0.95
4. Feeling afraid of the childbirth process	3.85 ± 1.00
5. Feeling worried about not being able to carry out physical activities, such as sports, while pregnant	3.73 ± 0.96
6. Feeling worried about not getting childbirth assistance from the partner	4.37 ± 0.91
7. Feeling worried about the condition of social relationships	2.97 ± 1.00
8. Feeling worried about not being able to adapt to normal life again during the pandemic	3.31 ± 0.83
Total	3.54 ± 0.51

SD, standard deviation.

Table 3. Psychological outcomes by characteristics of the respondent ($n = 120$)

Characteristic	Psychological outcomes		p
	Anxious	Normal	
City/district			0.425
Jakarta	25 (58.1)	18 (41.9)	
Bogor	7 (41.2)	10 (58.8)	
Depok	19 (63.3)	11 (36.7)	
Tangerang	5 (41.7)	7 (58.3)	
Bekasi	8 (44.4)	10 (55.6)	
Mother's age (y)			0.586
< 25	16 (44.4)	20 (55.6)	
≥ 25 & < 27	15 (55.6)	12 (44.4)	
≥ 27 & < 30	17 (54.8)	14 (45.2)	
≥ 30	16 (61.5)	10 (38.5)	
Mother's education			0.261
Primary/secondary school	6 (37.5)	10 (62.5)	
Diploma	9 (45.0)	11 (55.0)	
Bachelor's degree/master's degree/doctoral degree	49 (58.3)	35 (41.7)	
Mother's job			0.523
Currently employed	30 (56.6)	23 (43.4)	
Not currently employed	34 (50.7)	33 (49.3)	
Gestational age (wk)			0.379
< 19	13 (68.4)	6 (31.6)	
≥ 19 & < 28	13 (61.9)	8 (38.1)	
≥ 28 & < 35	9 (50.0)	9 (50.0)	
≥ 35	7 (38.9)	11 (61.1)	
Has given birth	22 (50.0)	22 (50.0)	
Has had a pregnancy check-up during the COVID-19 pandemic			0.192
Yes	58 (51.8)	54 (48.2)	
No	6 (75.0)	2 (25.0)	
Has received a COVID-19 test (rapid test/swab test)			0.340
Yes	31 (49.2)	32 (50.8)	
No	33 (57.9)	24 (42.1)	

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

effect on the health condition of pregnant women and increase the risk of adverse birth outcomes [36–38]. Several findings of this study are noteworthy. First, the likelihood of experiencing psychological distress was higher in areas with a high rate of spread of the virus and fewer available health facilities, such as Depok. This can be explained by the greater likelihood of being infected with the virus in general, making it difficult to access maternal health services.

Education level also affected the psychological health of pregnant women. Mothers with higher education levels tended to have more feelings of anxiety than mothers with lower education levels. This may be because higher levels of awareness of the threat posed by the virus increase anxiety. However, precisely this knowledge should also allow a person to better adapt to pandemic conditions [39].

The rate of experiencing anxiety was also higher among pregnant women who worked, who have a higher risk of psychological distress than pregnant women who do not work [40]. This may be due to having to carry out work-related activities in pandemic conditions, in addition to experiencing pregnancy [41]. Moreover, pregnant women can experience emotional instability. These factors result in increased feelings of anxiety during pregnancy for women who work, for whom it is unsafe to perform work activities outside the home. As a result, it is encouraged for pregnant women who work and working women who recently gave birth to take time off work during the pandemic.

Pregnant women with a gestational age <19 weeks experience greater psychological problems than those with a gestational ≥19 weeks. Anxiety in early pregnancy occurs

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because pregnant women feel worried about not receiving high-quality maternal services during the COVID-19 pandemic. At the beginning of pregnancy, pregnant women want to make sure that their pregnancy is in good condition and that the fetus is healthy, so they need to receive a prenatal check-up. However, as a result of psychological distress, pregnant women may choose not to receive antenatal care at health facilities due to worries about being infected with SARS-CoV-2 [42].

Psychological distress is also caused in part by information regarding the high risk and effects of SARS-CoV-2 in pregnant women. Pregnant women with COVID-19 can experience health problems such as acute respiratory infection, pneumonia, high fever, lymphocytopenia, and fatigue [43–45]. The clinical symptoms of COVID-19 may require intensive care for pregnant women with the virus [46]. COVID-19 can also have an effect on obstetric outcomes, such as premature births, the need for cesarean sections, a low birth weight, and neonatal death [47–49]. This information often causes anxiety in pregnant women.

The COVID-19 pandemic seriously disrupted the maternal health service system, especially at the onset of the pandemic.

Health protocols in the maternal health service system were designed and implemented very slowly by the government, which resulted in low access to maternal health services for pregnant women [50]. The high risk level of infection for pregnant women and the disruption of access to maternal health services caused pregnant women to experience psychological problems during pregnancy [51]. Therefore, efforts to improve health protocols and maternal health services that are comfortable and safe are necessary for pregnant women during the COVID-19 pandemic [52].

In addition, the role of the family is very important for providing comfort to pregnant women during the pandemic. Comfort plays an important role in reducing the likelihood of psychological disorders in pregnant women [53,54]. This includes family members showing discipline in their application of health protocols during interactions with pregnant women.

Conclusion

The COVID-19 pandemic has caused psychological problems for many pregnant women. Therefore, it is necessary to provide psychological guidance to reduce the likelihood of severe psychological disorders. Providers of maternal health services for pregnant women must also provide security and a sense of comfort for pregnant women by devising and adhering to strict health protocols. Likewise, family support is very important for the psychological condition of pregnant women. A government policy is also needed to provide a longer leave for working pregnant women and working women who gave birth during the COVID-19 pandemic. Such a policy would allow working women to experience pregnancy and childbirth comfortably with fewer psychological problems.

Notes

Ethics Approval

This study received ethical permission from the Ethics Committee of the Veterans National Development University of Jakarta (No. 2789/X/2020/KEPK). Participants were given consent form prior to data collection and all data were completely anonymized after obtaining their permission.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

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.

Additional Contributions

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Original Article

Seroprevalence of antibodies to SARS-CoV-2 and predictors of seropositivity among employees of a teaching hospital in New Delhi, India

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Objectives: Healthcare workers (HCWs) are at a high risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to the increased likelihood of clinical exposure during patient management. The study objective was to determine the seroprevalence of antibodies to SARS-CoV-2 and its predictors among hospital employees.
Methods: The cross-sectional study was conducted at a teaching hospital from August 2020 to September 2020 among 1,401 employees, including 1,217 HCWs, in New Delhi, India. The serum samples were examined for immunoglobulin G (IgG) antibodies to SARS-CoV-2 using the COVID Kavach-Anti-SARS-CoV-2 IgG Antibody Detection enzyme-linked immunosorbent assay kit. Data were collected electronically using the EpiCollect mobile platform. A $p<0.05$ was considered to indicate statistical significance.
Results: A total of 169 participants (12.1%) had detectable IgG antibodies to SARS-CoV-2. The highest seropositivity rate was observed in the administrative staff (20.1%), while it was lowest among medical doctors (5.5%, $p<0.001$). Male sex and ever having lived in a containment zone were independently associated with past infection with SARS-CoV-2.
Conclusion: The seroprevalence of SARS-CoV-2 infection in health workers may be lower than in the general population in New Delhi. However, nonpharmaceutical interventions were not associated with a reduction in the risk of acquisition of SARS-CoV-2.

Keywords: Communicable diseases; COVID-19; Occupational health

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a global pandemic since its initial identification in December 2019 [1]. The clinical spectrum of coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2, ranges from asymptomatic to severe respiratory symptoms and death, with significantly higher mortality in individuals with comorbidities and among elderly patients [2]. In India, the second-most populous country of the world, 6.7 million cases and 104,555 deaths attributed to COVID-19 have been recorded as of October 7, 2020. In the state of New Delhi, the Indian capital city; 295,236 cases and 5,581 deaths were observed during the same period [3].

It is well-established that healthcare workers (HCWs) comprise a population subgroup that is at a high risk of contracting SARS-CoV-2 infection due to clinical exposure during the management of suspected or confirmed COVID-19 patients [4]. The risk is further accentuated due to the incorrect use of personal protective equipment (PPE) and nonadherence to the recommended infection prevention and control guidelines [5].

The World Health Organization has estimated that 1.4 million COVID-19 infections occurred among HCWs worldwide as of August 2020 [6]. In India, according to an unofficial estimate, a total of 2,174 and 382 COVID-19 related infections and deaths, respectively, have been reported among medical doctors as of September 10, 2020, highlighting a 16-fold higher case fatality rate compared to the general population [7].

Early identification, isolation, and treatment of HCWs are indispensable tools for limiting the spread of SARS-CoV-2 among co-workers and non-COVID-19 patients within a healthcare facility. Understanding the risk factors related to the transmission of infection within healthcare settings can guide effective planning and implementation of evidence-based strategies for protecting HCWs.

Establishing the true infection rate of SARS-CoV-2 among HCWs requires an assessment of antibody seroprevalence since asymptomatic cases constitute approximately 40% to 45% of all SARS-CoV-2 infections [8]. Therefore, we conducted this study to determine the seroprevalence of antibodies to SARS-CoV-2 and its predictors among employees of a teaching hospital in New Delhi, India.

Materials and Methods

Study Design and Setting

We conducted a cross-sectional study from August 2020 to September 2020 at a teaching hospital located in New Delhi, India. The tertiary care hospital was designated as a dedicated COVID-19 hospital in April 2020, and has since treated more than 9,000 moderate to severe cases of COVID-19 [9]. No non-COVID-19 patients were admitted or treated at the hospital during the pandemic.

HCWs at the hospital deployed to the COVID-19 isolation wards currently work 15-day shifts, followed by 7 days of quarantine and another 7 days of home isolation. All HCWs working at the hospital could opt to be tested for COVID-19 if they self-reported any breach in PPE or developing symptoms suggestive of the disease. Medical personnel attending to COVID-19 patients in the wards and intensive care units were provided complete PPE kits including gowns, gloves, and N95 respirators. Administrative staff who were unlikely to come in contact with suspected COVID-19 patients were provided with surgical masks. Wearing an N95 or a surgical mask was mandatory for all hospital employees. Furthermore, employees of the hospital without any preexisting cardiac abnormalities were recommended the to receive the Indian Council of Medical Research-approved hydroxychloroquine (HCQ) prophylaxis regimen, the intake of which was completely voluntary [10].

Sampling Strategy

Sites for immunoglobulin G (IgG) SARS-CoV-2 antibody testing were organized at different locations in the medical school and the hospital complex, and information about testing sites was disseminated through notice boards, banners, flyers, and WhatsApp groups. All the employees were invited to participate in the study. The hospital campus includes a medical college, a dental college, an eye hospital, and a tertiary care hospital with approximately 3,000 employees. Participation in this study was a one-time activity, and seronegative participants were not retested subsequently.

Inclusion Criteria

We included doctors, nurses, housekeeping staff, biomedical waste collectors, and administrative staff in the study.

Methodology

The participants were informed that seropositivity would indicate past infection. A blood sample (3 mL) was collected in a serum separator tube under aseptic conditions and transported to the testing facility upright in a transport box within 3 hours after collection. The serum samples were tested for qualitative detection of IgG antibodies to SARS-CoV-2 using the COVID Kavach-Anti-SARS-CoV-2 Human IgG ELISA Kit (ICMR-NIV, Pune, India). The sensitivity and specificity of the assay have been reported to be 92.4% and 97.9%, respectively [11].

Data Collection

We collected participant information on sociodemographic variables and on occupational exposure-related risk factors (Suppl. 1) through face-to-face interviews, and the data were captured using the paperless mobile EpiCollect platform [12].

Operational Definitions

Participants were characterized as high-risk if they were directly involved in the care of COVID-19 patients or handling of their clinical samples, and were considered low-risk otherwise. Containment zones were defined by the local administration, usually as places within a 1-km radius where 3 or more cases were detected. Within these zones, movement and access to the neighborhood were significantly restricted with exemptions for essential services staff [13].

Statistical Analysis

Data were analyzed with IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). The results were expressed as frequency and proportions for categorical variables, and mean and standard deviation for continuous variables. Associations between categorical variables were assessed using the chi-square test. The variables that were significantly associated with the presence of the IgG antibody to SARS-CoV-2 were included in a binary logistic regression model. A $p<0.05$ was considered to statistical significance.

Results

Sociodemographic Characteristics

We enrolled a total of 1,401 participants, including 769 males (54.9%) and 632 females (45.1%). The median age of the participants was 33 years (interquartile range, 27–45 years). The participants comprised doctors (43.8%), nursing personnel (18.1%), auxiliary health workers (25.1%), and administrative staff (13.1%). A total of 466 participants (33.3%) reported engaging in high-risk activities.

Seroprevalence of IgG Antibodies to SARS-CoV-2

A total of 169 (12.1%; 95% confidence interval [CI], 10.4–13.8) participants, and 132 (10.8%; 95% CI, 9.1–12.6) ($n=1{,}217$) HCWs (doctors and nurses), had detectable IgG antibodies against SARS-CoV-2. Among the various categories of participants, administrative staff (20.1%) had the highest seropositivity rate, followed by auxiliary staff (18.5%), nursing staff (13.0%), and doctors (5.5%; $p<0.001$). The seroprevalence of SARS-CoV-2 among the healthcare employees observed in this study was less than half of that observed in the general population in the state during a similar period (Figure 1).

In the bivariate analysis, the seropositivity was significantly higher in participants aged ≥34 years, of the male sex, performing administrative duties, having low body mass index (<18.5 kg/m^2), with a history of COVID-19 diagnosis through real-time polymerase chain reaction (PCR) or rapid antigen test, and a history of having ever consumed any alternative medication (Table 1). Although not statistically significant, the seropositivity was higher in participants with any self-reported preexisting chronic illness ($p=0.062$) and in those who did not undertake the HCQ prophylaxis regimen ($p=0.246$).

Among the 101 participants with a previous history of COVID-19 infection diagnosed with real-time PCR or rapid antigen test, 42 participants (41.6%) were IgG-seropositive. In the participants with an absence of documented COVID-19 infection ($n=1{,}300$), 127 (9.76%) were IgG-seropositive. Moreover, the proportion of health workers with seropositivity was higher in those who reported a breach of PPE during patient management compared to those who did not, but this difference did not reach statistical significance ($p=0.139$) (Table 2).

We conducted a binary logistic regression analysis by

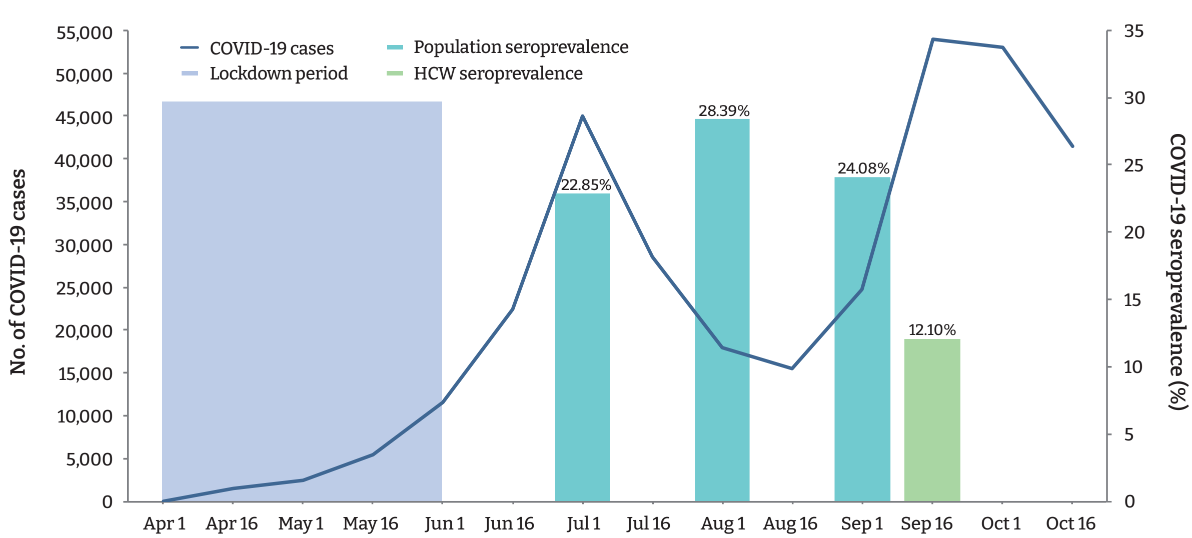

Figure 1. Epidemic curve of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Delhi (April–October 2020).
COVID-19, coronavirus disease 2019; HCW, healthcare worker.

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Table 1. Distribution of factors associated with IgG seropositivity to SARS-CoV-2 ($n = 1,401$)

Characteristic	Total	IgG-positive	Unadjusted odds	*p*
Age (y)				0.011
< 33	668 (47.7)	65 (9.7)	1	
≥ 33	733 (52.3)	104 (14.2)	1.53 (1.10–2.13)	
Sex				0.001
Male	769 (54.9)	113 (14.7)	1.77 (1.26–2.49)	
Female	632 (45.1)	56 (8.9)	1	
Containment zone				0.063
Living or ever lived	156 (11.1)	26 (16.7)	1.54 (0.98–2.43)	
Never lived	1,245 (88.9)	143 (11.5)	1	
Occupation				< 0.001
Doctor	613 (43.8)	34 (5.5)	1	
Nurse	253 (18.1)	33 (13.0)	2.55 (1.54–4.23)	
Auxiliary HCW	351 (25.1)	65 (18.5)	3.87 (2.50–6.00)	
Administrative staff	184 (13.1)	37 (20.1)	4.29 (2.60–7.06)	
Risk profile				0.210
High risk	466 (33.3)	49 (10.5)	0.80 (0.56–1.14)	
Low risk	935 (66.7)	120 (12.8)	1	
Chronic illness				0.062
Present	163 (11.6)	27 (16.6)	1.53 (0.98–2.40)	
Absent	1,238 (88.4)	142 (11.5)	1	
Smoker				0.952
Yes	108 (7.7)	12 (11.1)	0.90 (0.49–1.69)	
No	1,293 (92.3)	157 (12.1)	1	
Alternative medicines				0.004
Yes	418 (29.8)	67 (16.0)	1.65 (1.18–2.30)	
No	983 (70.2)	102 (10.4)	1	
Hand hygiene adherence				0.573
Always	1,090 (77.8)	127 (11.7)	1	
Sometimes	226 (16.1)	32 (14.2)	1.25 (0.82–1.90)	
Rarely	85 (6.1)	10 (11.8)	1.01 (0.51–2.01)	
Social distancing				0.886
Always	1,015 (72.4)	125 (12.3)	1	
Sometimes	286 (20.4)	33 (11.5)	0.93 (0.62–1.40)	
Rarely	100 (7.1)	11 (11.0)	0.88 (0.46–1.70)	
Body mass index (kg/m^2)				0.107
< 18.5	42 (3.0)	8 (19.0)	1	
≥ 18.5	1,359 (97.0)	161 (11.8)	0.52 (0.24–1.15)	
HCQ intake				0.251
Complete regimen	228 (16.3)	20 (8.8)	1	
Partial regimen	114 (8.1)	14 (12.3)	1.46 (0.71–3.00)	
None	1,059 (75.6)	135 (12.7)	1.52 (0.93–2.49)	
History of COVID-19				< 0.001
Present	101 (7.2)	42 (41.6)	6.57 (4.25–10.17)	
Absent	1,300 (92.8)	127 (9.8)	1	

Data are presented as *n* (%) or odds ratio (95% confidence interval).
IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HCW, healthcare worker; HCQ, hydroxychloroquine; COVID-19, coronavirus disease 2019.

including variables that were statistically significant in the bivariate analysis ($p < 0.05$). The model was found to be statistically significant ($\chi^2(4) = 69.76$; $p < 0.001$). The model correctly classified 87.9% of cases. The Hosmer-Lemeshow goodness of fit test-statistic had a p-value of 0.415, from which we concluded that the model estimated the data

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Table 2. Distribution of exposure characteristics among healthcare workers and association with IgG seropositivity to SARS-CoV-2 ($n = 1,217$)

Characteristic	Total	IgG-positive	OR (95% CI)	p
Direct skin contact				0.610
Reported	54 (4.4)	7 (13.0)	1.24 (0.55–2.80)	
Not reported	1,163 (95.6)	125 (10.7)	1	
Direct fluid contact				0.370
Reported	17 (1.4)	3 (17.6)	1.78 (0.50–6.27)	
Not reported	1,200 (98.6)	129 (10.8)	1	
PPE breach (~1 m)				0.133
Reported	105 (8.6)	16 (15.2)	1.54 (0.88–2.72)	
Not reported	1,112 (91.4)	116 (10.4)	1	
PPE breach during COVID-19 care				0.930
Reported	29 (2.4)	3 (10.3)	0.95 (0.28–3.17)	
Not reported	1,188 (97.6)	129 (10.8)	1	
PPE breach when conducting an aerosol-generating procedure				0.355
Reported	22 (1.8)	1 (4.5)	0.39 (0.05–2.90)	
Not reported	1,195 (98.2)	131 (11.0)	1	
PPE breach and contact with the patient environment				0.358
Reported	78 (6.4)	6 (7.7)	0.67 (0.29–1.57)	
Not reported	1,139 (93.6)	126 (11.1)	1	
Hand hygiene after PPE removal				0.355
Missed	22 (1.8)	1 (4.5)	0.39 (0.05–2.90)	
Not missed/uncertain	1,195 (98.2)	131 (11.0)	1	
Post-duty hand hygiene				0.357
Always	958 (78.7)	100 (10.4)	1	
Sometimes	190 (15.6)	26 (13.7)	1.36 (0.86–2.16)	
Rarely	69 (5.7)	6 (8.7)	0.82 (0.34–1.94)	
Post-duty social distancing				0.641
Always	893 (73.4)	101 (11.3)	1	
Sometimes	241 (19.8)	24 (10.0)	0.87 (0.54–1.39)	
Rarely	83 (6.8)	7 (8.4)	0.72 (0.32–1.61)	

Data are presented as *n* (%) or OR (95% CI). Contact with body fluids (urine, blood, saliva) of a confirmed COVID-19 patient. Within a 1-m distance of a confirmed COVID-19 patient who was not wearing a mask/respirator.
IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; CI, confidence interval; PPE, personal protective equipment; COVID-19, coronavirus disease 2019.

acceptably. Among the variables that were found to be statistically significant in the bivariate analysis, only male sex and the type of occupation were found to be independently associated with seropositivity in the logistic regression analysis (Table 3). The administrative staff had 3.8-fold higher odds of being IgG-seropositive than the doctors.

Discussion

The present study conducted among employees of a teaching hospital in New Delhi observed that the IgG antibody to SARS-CoV-2 was present in 12.1% of participants, indicating past infection with the virus. A large community-based repeated serosurvey conducted in Delhi during the same period reported detectable IgG antibodies in 24.08% to 28.39% of the population [14]. Surprisingly, in our study, the seropositivity was significantly higher among administrative staff who had a considerably lower risk of exposure to the virus than HCWs. These findings suggest that the likelihood of exposure to SARS-CoV-2 was high in the community. Furthermore, although the administrative staff were provided with face-masks and instructed to adhere to hand hygiene and social distancing measures, a lack of effective training in correctly using PPE may have disproportionately accentuated their risk compared to the HCWs.

Previous studies in India have shown variable rates of seropositivity among HCWs ranging from 2.5% in the Srinagar district [15] to 16% in Southern Rajasthan, with most cases being asymptomatic [16]. In Europe, various Italian studies have reported COVID-19 IgG seroprevalence

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Table 3. Logistic regression analysis of factors associated with IgG seropositivity to SARS-CoV-2

Characteristic	Adjusted OR (95% CI)	*p*
Age (y)		0.549
< 33	1 (reference)	
≥ 33	1.11 (0.79–1.57)	
Sex		0.049
Male	1.45 (1.00–2.10)	
Female	1 (reference)	
Occupation		
Doctor	1 (reference)	< 0.001
Nurse	2.59 (1.54–4.35)	
Auxiliary	3.34 (2.09–5.31)	
Administrative staff	3.77 (2.25–6.31)	
Body mass index (kg/m^2)		0.226
< 18.5	1 (reference)	
≥ 18.5	0.60 (0.27–1.37)	

IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; CI, confidence interval.

among hospital personnel to range from 5.1% to 7.4% [17,18]. In Denmark, the seropositivity among HCWs was 4.04%, with a significant association observed with a history of exposure to COVID-19 patients [19]. Another study in the USA reported 6% of HCWs within a multistate hospital network had detectable SARS-CoV-2 antibodies, and within the seropositive subgroup, 69% had no prior microbiological confirmation of COVID-19 disease [20]. However, a study among a large cohort of HCWs in New York City (NYC) who were voluntarily tested reported a higher seroprevalence of antibodies (13.7%), which was correlated with the high COVID-19 burden [21].

Similar to the present study, men were reported to be at a higher risk of SARS-CoV-2 infection in the studies conducted in Milan and Denmark [17,19]. Age was not found to be a significant predictor of seropositivity among HCWs in the NYC study, which corroborates the findings of this study [20]. Acquisition of SARS-CoV-2 infection locally from the community as the dominant mode of transmission among HCWs was also previously reported in a Dutch study [22].

In the present study, the intake of an HCQ prophylaxis regimen did not have any protective effect on the risk of contracting the SARS-CoV-2 infection. Although some early observational studies indicated protective efficacy of HCQ against COVID-19, evidence generated from later clinical trials showed that daily HCQ does not prevent SARS-CoV-2 infection [23-25].

In this study, the use of immunity boosters based on alternative systems of medicine, such as indigenous systems of Indian medicine and homeopathy, was associated with a significantly higher risk of seropositivity. The findings suggest that while immunity boosters probably offered no protection against the acquisition of SARS-CoV-2 infection, they might instill a false sense of security leading to reduced adherence to preventive measures, with increased risk of infection. Nonetheless, the potential impact of alternative systems of medicine in the management of COVID-19, including disease progression and severity, needs further evaluation.

The strengths of the study include a large sample size and collection of data through face-to-face interviews with the employees of the largest state-run teaching hospital in Northern India catering only to COVID-19 patients. However, the study has several limitations. These include the use of a cross-sectional analysis, which precluded the assessment of any temporal or causal relationships, especially changes in seroprevalence with the progression of the pandemic, which would require a prospective study design. The study was conducted in a single institutional setting, limiting the generalizability of the findings. Furthermore, the employees who did not participate in the study may have differed in their sociodemographic and clinical characteristics, leading to potential selection bias. Finally, the data on adherence to preventive measures against COVID-19 were self-reported, which may have led to recall bias.

In conclusion, the present study conducted at a teaching hospital in New Delhi observed that nearly 1 in 10 HCWs without any prior microbiological confirmation had detectable IgG antibodies to SARS-CoV-2. Considering that the doctors had the lowest seropositivity for SARS-CoV-2, whereas administrative staff had the highest seropositivity, the probability of HCW-to-HCW or patient-to-HCW transmission may be lower than the risk of transmission from other sources including the general population. However, non-pharmaceutical interventions were not associated with a reduction in the risk of acquisition of SARS-CoV-2, implying the necessity to improve training techniques among all hospital employees for maintaining the correct use of PPE on all occasions involving the risk of contracting the infection.

Supplementary Material

Table S1. All indicators except public transportation. Supplementary data is available at https://doi.org/10.24171/j.phrp.2021.12.2.06.

Notes

Ethics Approval

The study protocol was approved by the Institutional Ethics Committee (F.1/IEC/MAMC/(77/05/2020/No 202). Written and informed consent was obtained from all the participants.

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

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None.

Availability of Data
The anonymized dataset that support the findings of this study will be made available by the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: PS, RC, RB, SS, PL, MD, SKB; Data curation: PS, RC, RB, PKB; Formal analysis: SB; Funding acquisition: Nil; Investigation: PS, RC, RB, PKB; Methodology PS, RC, RB, SB, MD; Project administration: PS, RC, PKB; Resources: PS, RC, SS, MD, SKS; Supervision: PS, SS, PL; Validation: PS, SS, MD; Visualization: SB; Writing–original draft: SB; Writing–review & editing: all authors.

Additional Contributions
Mr. Kumar Dushyant (research associate) contributed to creating the figure for the manuscript.

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Original Article

Sex differences in weight perception and weight gain among Black college students in the USA

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ABSTRACT

Objectives: The aims of this study were to examine the prevalence of overweight/obesity and to explore sex differences in body weight perceptions and correlates of weight gain among Black students at 2 historically Black colleges and universities (HBCUs) in the USA.
Methods: Participants completed a paper-based survey, and their height and weight were measured (67% completion rate).
Results: The overweight and obesity rates were 33.8% and 26.9%, respectively. More females than males accurately assessed their weight ($p<0.05$). Body weight underestimation was associated with male sex, excellent/very good perceived overall health, and not being informed by a doctor of having overweight or obesity ($p<0.01$). Higher odds of ≥5% weight gain were related to female sex, living on campus, and not being informed by a doctor of having overweight or obesity ($p<0.05$).
Conclusion: Given the high overweight and obesity rates among Black students, HBCUs in the USA should develop intervention strategies for the prevention and management of overweight and obesity. College health educators at HBCUs need to provide regular check-ups or health screenings that help male students perceive their weight accurately and prevent weight underestimation. It is important for HBCUs to monitor and address weight gain among Black students as early as possible.

Keywords: Obesity; Sex characteristics; Students; Universities; Weight gain; Weight perception

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Introduction

The prevalence of overweight/obesity among college students in the USA increased from

31.3% in 2008 to 39.7% in 2019 [1,2]. Overweight/obesity and weight gain during adulthood are related to an increased risk of diabetes, cardiovascular disease, and some forms of cancer [3]. Given that the prevalence of overweight/obesity in adults aged 20 to 39 years is about twice as high as that in adolescents aged 12 to 19 years [4], the transition from adolescence to adulthood is a critical period for weight gain [5,6], and college years may be a time of particular risk for overweight and obesity [7]. Maintaining an active lifestyle and healthy eating habits could be challenging for college students due to a lack of family support and established routines [7]. Thus, when students transition from high school to college, many face drastic changes in their environment and residence that may influence health behaviors such as diet and exercise [5]. The health behaviors of college students are important because health habits established during their college years could affect life-long weight struggles and future health problems [5]. Despite reports of rapid weight gain during the college years [7], investigations of weight gain among college students have been scarce [8].

Unlike investigations of overweight and obesity among US adults that have provided race/ethnicity-specific rates of overweight and obesity, very few studies have examined racial/ethnic differences in overweight and obesity among US college students [9]. In 2007, a US national study of 24,613 students from 119 four-year colleges reported that non-Hispanic Blacks had higher rates (38.3%) of overweight and obesity than non-Hispanic Whites (26.7%), non-Hispanic Asians (16.4%), and Hispanics (30.2%) [9]. The high rates of overweight/obesity in Black college students may be due, in part, to body weight perceptions [10] and associated weight management behaviors [11]. Evidence shows that accurate weight perception plays an important role in weight loss attempts [11]. Furthermore, weight underestimation is a predictor of weight gain over time [10] and a barrier to weight management behaviors among adults [12].

Sex [13] and race/ethnicity [14] are crucial determinants of body weight perception. In a statewide school-based survey, 24.5% of male adolescents underestimated their weight, which was 3 times higher than the prevalence reported in female adolescents [13]. A similar sex difference was reported in Black college students [15]. In addition, weight underestimation was more prevalent in Black female adolescents than in their White counterparts [13]. To date, however, a paucity of research exists on weight perception in Black college students [16] despite their higher rates of overweight and obesity than other racial/ethnic groups [9]. Thus, the current study aimed to investigate the prevalence of overweight/obesity and to examine sex differences in body weight perceptions and correlates of weight gain among Black college students at 2 historically Black colleges and universities (HBCUs).

Materials and Methods

Participants

A purposive sample of Black students from 2 HBCUs in the USA was recruited for this cross-sectional study. After the Institutional Review Boards at Tennessee State University (IRB No: HS2015-3675) and University of Maryland Eastern Shore (IRB No: #2016-016) approved the protocol, 325 undergraduate students enrolled in health courses were invited to participate in a paper-based survey in March 2016. A total of 318 students completed the survey. All participants provided written consent for their personal data to be used. Twenty-five participants at each university were randomly selected and each of them received a $25 gift card as reimbursement. This sample initially consisted of 278 Black students, 4 Native Hawaiian or Pacific Islander students, 25 White students, and 11 students of other racial backgrounds. Data from 278 Black students, our population of interest, were used for the current study. We excluded 59 participants who did not report anthropometric characteristics (n=1) or socio-demographic data (n=10). The present study focused on investigating the health-related variables that are correlated with weight gain. Thus, participants (n=48) with missing responses pertinent to the health-related items were excluded. The final sample was composed of 219 participants, reflecting a completion rate of 67%.

Measures

We developed a 34-item paper questionnaire adapted from the following previously validated and reliable instruments: the American College Health Association-National College Health Assessment [17], National Longitudinal Survey of Youth [18], and National Health and Nutrition Examination Survey [19]. The questionnaire was pilot-tested with 10 Black students at the 2 HBCUs to evaluate the questionnaire wording and respondents' understanding of questions. Data from the pilot test were not included in the study.

To measure body mass index (BMI), anthropomorphic data were collected using a Detecto scale (Detecto Scale Company, Webb City, MO, USA). After completing the questionnaire, participants stood on the scale, wearing light clothes/no shoes, and their height and weight were measured twice. The mean of each measurement was recorded. BMI was calculated as weight (kilograms) divided by height (meters squared) [20]. Participants' BMI status

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was classified as follows: (1) underweight, < 18.5 kg/m²; (2) normal weight, 18.5–24.9 kg/m²; (3) overweight, 25.0–29.9 kg/m²; and (4) obesity, ≥ 30 kg/m².

Body weight perception was measured by the question, "Do you consider yourself now to be…?" Response options were "underweight," "about the right weight," and "overweight." Body weight perceptions were divided into 3 categories based on the concordance, or lack thereof, between perceived weight status and actual BMI status, which was objectively measured and computed by the lead author: (1) underestimation (perceived weight status < BMI status); (2) accurate estimation (perceived weight status = BMI status); and (3) overestimation (perceived weight status > BMI status) [21]. Each student's weight change was computed by subtracting his/her self-reported weight in the previous year from his/her self-reported current weight. Weight gain was defined as a ≥ 5% increase in weight relative to weight 1 year ago [22,23]. Participants were categorized as having ≥ 5% or < 5% weight gain.

Questions on sociodemographic characteristics included the type of residence (on-campus vs. off-campus) and annual household income. The poverty threshold level was computed using the 2015 federal poverty level guidelines to determine poverty status [24]. Health behavior questions were asked to assess participants' dietary intake of alcohol, fruits, vegetables, soda, and fast foods. Questions about sedentary behavior were asked to measure time sitting on a typical day and daily television/video/computer screen time use. Health status questions were asked to gauge students' perceived health status and whether or not a doctor had ever informed them of their overweight status. Physical activity questions were asked to measure the number of days/week and minutes/day participants engaged in the following physical activities for 10 minutes: (1) walking or bicycling; (2) moderate-intensity sports, fitness, or recreational activities causing small increases in the breathing or heart rate; and (3) vigorous-intensity sports, fitness, or recreational activities causing large increases in the breathing or heart rate. These physical activity questions were used to create a metabolic equivalent (MET) variable that was calculated by multiplying walking/bicycling by 4.0, moderate-intensity activities by 4.0, and vigorous-intensity activities by 8.0 [25]. Based on these MET values, participants' activity level was classified into 2 categories, inactive (< 500 MET-min/wk) and active (≥ 500 MET-min/wk) [23,25].

Data Analysis

The chi-square test and the Cramer's V-test were performed to investigate the significance of differences in categorical variables (e.g., sociodemographic characteristics and health behaviors) and weight perceptions between male and female participants. Multivariable logistic regression models were developed to identify correlates of weight underestimation and ≥ 5% weight gain over 1 year among students with overweight or obesity. Independent variables in the multivariable logistic regression models were selected based on previous research that found associations with weight underestimation and weight gain [11,12,26,27]. All analyses were conducted with Stata ver. 13 (StataCorp., College Station, TX, USA). We set the level of significance at 0.05.

Results

This study included a total of 219 participants with a mean age of 19.8 years (standard deviation, 1.5 years), of whom 54.8% were male. As shown in Table 1, 37.9% of participants had an annual income ≥ $60,000, 27.4% had an annual income between $30,000 and $59,999, and 14.6% had an annual income < $30,000. Almost 3 out of 4 participants lived on campus (74.0%). The campus setting was a rural town for 64.8% of participants, while 35.2% of them were in a very large city.

The proportions of weight status were as follows: underweight, 2.3%; normal weight, 37.0%; overweight, 33.8%; and obesity, 26.9%. Sex was moderately associated with perceived overall health (Cramer's V = 0.283). More females than males (27.3% vs. 10.8%; $p = 0.001$) perceived their overall health as fair or poor. More males than females (93.5% vs. 83.0%; $p = 0.025$) reported ≥ 500 MET-minutes/week of physical activity. Only 22.4% of participants consumed ≥ 3 daily servings of fruits and vegetables. Almost half of participants (49.3% and 46.6%, respectively) consumed fast food ≥ 3 times and drank a soft drink ≥ 3 times in the past 7 days (Table 1).

As shown in Table 2, sex was moderately associated with body weight perceptions in all weight status categories: (1) normal weight group, Cramer's V = 0.399; (2) overweight group, Cramer's V = 0.290; and (3) obese group, Cramer's V = 0.352. Among participants with normal weight, more females than males (88.1% vs. 66.7%; $p = 0.001$) estimated their body weight accurately. We observed similar results in participants with overweight or obesity, indicating that females had more accurate weight perceptions than males, regardless of their weight categories (Table 2).

Higher odds of body weight underestimation were associated with (1) male sex, (2) not being informed of being overweight by a doctor, and (3) being physically active (≥ 500 MET-min/wk; $p < 0.05$) (Table 3).

Higher odds of ≥ 5% weight gain were associated with (1)

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Table 1. Characteristics of participants

Variable	Total (n = 219)	Male (n = 120)	Female (n = 99)	Effect size[a)]	p
Annual household income				0.187	0.054
Don't know	44 (20.1)	31 (25.8)	13 (13.1)		
< $30,000	32 (14.6)	13 (10.8)	19 (19.2)		
≥ $30,000 & < $60,000	60 (27.4)	34 (28.3)	26 (26.3)		
≥ $60,000	83 (37.9)	42 (35.0)	41 (41.4)		
Poverty threshold (n = 205)				0.082	0.239
Above	177 (86.3)	97 (89.0)	80 (83.3)		
Below	28 (13.7)	12 (11.0)	16 (16.7)		
Type of residence				0.047	0.490
On-campus	162 (74.0)	91 (75.8)	71 (71.7)		
Off-campus	57 (26.0)	29 (24.2)	28 (28.3)		
Campus setting				0.112	0.099
Very large city	77 (35.2)	48 (40.0)	29 (29.3)		
Rural town	142 (64.8)	72 (60.0)	70 (70.7)		
Weight status				0.138	0.239
Underweight	5 (2.3)	2 (1.7)	3 (3.0)		
Normal	81 (37.0)	39 (32.5)	42 (42.4)		
Overweight	74 (33.8)	47 (39.2)	27 (27.3)		
Obese	59 (26.9)	32 (26.7)	27 (27.3)		
Informed of being overweight by a doctor				0.072	0.345
Yes	55 (24.9)	26 (22.0)	28 (28.3)		
No	164 (75.1)	94 (78.0)	71 (71.7)		
Perceived overall health				0.283	0.001
Excellent	27 (12.3)	15 (12.5)	12 (12.1)		
Very good	64 (29.2)	47 (39.2)	17 (17.2)		
Good	88 (40.2)	45 (37.5)	43 (43.4)		
Fair/poor	40 (18.3)	13 (10.8)	27 (27.3)		
Metabolic equivalent (min/wk)				0.149	0.025
< 500	26 (11.8)	8 (6.5)	17 (17.0)		
≥ 500	193 (88.2)	112 (93.5)	82 (83.0)		
Monthly frequency of alcohol use (d)				0.015	0.976
0	89 (40.6)	48 (40.0)	41 (41.4)		
1–14	119 (54.3)	66 (55.0)	53 (53.5)		
15–30	11 (5.0)	6 (5.0)	5 (5.1)		
Daily fruit and vegetable consumption (serving)				0.042	0.822
0	22 (10.0)	13 (10.8)	9 (9.1)		
1–2	148 (67.6)	79 (65.8)	69 (69.7)		
≥ 3	49 (22.4)	28 (23.3)	21 (21.2)		
Weekly frequency of eating fast foods (time)				0.123	0.193
0	44 (20.1)	20 (16.7)	24 (24.2)		
1–2	67 (30.6)	42 (35.0)	25 (25.3)		
≥ 3	108 (49.3)	58 (48.3)	50 (50.5)		
Weekly frequency of drinking a soft drink or soda containing sugar (time)				0.094	0.379
0	59 (26.9)	30 (25.0)	29 (29.3)		
1–2	58 (26.5)	29 (24.2)	29 (29.3)		
≥ 3	102 (46.6)	61 (50.8)	41 (41.4)		
Daily sitting hours	5.8 ± 3.7	5.7 ± 3.4	5.9 ± 4.0	-	0.640
Daily screen time	8.4 ± 7.2	9.1 ± 7.4	7.5 ± 6.9	-	0.141

Data are presented as n (%) or mean ± SD. The percentages may not add to 100 because of a lack of responses or rounding errors.
[a)]Cramer's V effect sizes were judged as negligible associations if < 0.1, weak associations if between 0.1 and < 0.2, moderate associations if between 0.2 and < 0.4, and strong if ≥ 0.4.

Table 2. Body weight perceptions by sex

Variable	Total	Male	Female	Effect size[a)]	p
Normal weight ($n=81$)				0.399	0.001
Underestimation	15 (18.5)	13 (33.3)	2 (4.8)		
Accurate estimation	63 (77.8)	26 (66.7)	37 (88.1)		
Overestimation	3 (3.7)	0 (0.0)	3 (7.1)		
Overweight ($n=74$)				0.290	0.013
Underestimation	56 (75.7)	40 (85.1)	16 (59.3)		
Accurate estimation	18 (24.3)	7 (14.9)	11 (40.7)		
Obese ($n=59$)				0.352	0.007
Underestimation	11 (18.6)	10 (31.3)	1 (3.7)		
Accurate estimation	48 (81.4)	22 (68.8)	26 (96.3)		

Data are presented as n (%). Underweight participants were not included in this table due to the small sample size ($n=5$).
[a)]Cramer's V effect sizes were judged as negligible associations if <0.1, weak associations if between 0.1 and <0.2, moderate associations if between 0.2 and <0.4, and strong if ≥0.4.

living on campus, (2) household income ($30,000–$59,999), (3) being below the poverty threshold, (4) having fair or poor perceived health, (5) not being informed of being overweight by a doctor, (6) longer daily screen time, (7) eating fast food ≥3 times/week, and (8) drinking a soft drink ≥3 times/week ($p<0.05$). Lower odds of weight gain were associated with male sex and eating ≥3 servings of fruits and vegetables ($p<0.05$) (Table 4).

Discussion

The present study aimed to fill a research gap by examining the prevalence of overweight/obesity and investigating sex differences in body weight perception and correlates of ≥5% weight gain in the past year in a sample of students at HBCUs. The overweight/obesity rate of students at HBCUs was found to be 60.7%, which was much higher than that (38.3%) of a nationally representative sample of Black college students in the USA [9]. In addition, the overweight/obesity rate (60.7%) in the current study was markedly higher than that (36.8%) of a nationally representative sample of US college students who completed the American College Health Association-National College Health Assessment in 2016 [28].

Similar to other studies of college students finding that females estimated their body weight more correctly than males [11,15], the females in this study were significantly more likely than the males to accurately estimate their body weight, regardless of their weight categories. A previous study reported that among US adults with overweight or obesity, males were less likely than females to perceive their weight accurately [29]. A possible explanation is that males perceive a more muscular and athletic body type as an ideal shape because social norms among males may shape preferences for a heavier body [30,31]. Moreover, females may be scrutinized more intensely than males regarding social standards of beauty and in response may be more diligent at keeping records of their weight [32,33]. The present study showed that the prevalence of overweight/obesity among male students in 2016 was 65.9%, which was much higher than that of overweight/obesity (42.2%) among male students who completed the American College Health Association-National College Health Assessment in the same year [28]. The higher overweight/obesity prevalence among male students in the current sample may be due, in part, to inaccurate body weight perceptions [34]. Research has shown that accurate weight perception is associated with the desire to lose weight [35] and plays an important role in maintaining a healthy weight [14,36]. There is a need to establish effective programs to prevent or rectify body weight misperceptions, especially in Black male college students at HBCUs. Thus, it is important for college health professionals at HBCUs to develop health education programs that help their male students perceive their weight accurately, which may result in a lower overweight/obesity rate.

Excellent or very good perceived overall health was predictive of weight underestimation. Another possible cause of weight underestimation is visual weight status misperceptions, but this factor was not directly measured in the current study. Oldham and Robinson [37] found that frequent visual exposure to people with obesity can alter one's perception of how a healthy body weight appears and lead to an underestimation of weight. Therefore, given the high rates of overweight and obesity in Black communities [38,39], it is possible that heavy weights may appear normal and healthy in these settings and that those who underestimate their weight may also have a false sense of perceived good health [40]. In addition to

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Table 3. Correlates of body weight underestimation ($n = 82$) compared to correct body weight estimation ($n = 129$)

Variable	OR (95% CI)
Age (y)	
18–19	1.02 (0.59–1.78)
≥ 20	1.00
Sex	
Male	4.46 (2.40–8.30)***
Female	1.00
Campus setting	
Very large city	0.94 (0.52–1.67)
Rural town	1.00
Type of residence	
On-campus	1.43 (0.75–2.73)
Off-campus	1.00
Poverty threshold	
Above	1.00
Below	1.04 (0.46–2.35)
Perceived overall health	
Excellent/very good	1.00
Good	0.72 (0.39–1.31)
Fair/poor	0.15 (0.06–0.43)***
Informed of being overweight by a doctor	
Yes	1.00
No	2.81 (1.37–5.74)**
Metabolic equivalent (min/wk)	
< 500	1.00
≥ 500	3.21 (1.05–9.85)*
Daily sitting hours	1.04 (0.96–1.12)
Daily screen time	1.05 (0.99–1.11)
Monthly frequency of alcohol use (d)	
0	1.00
1–14	0.91 (0.51–1.62)
15–30	1.86 (0.52–6.57)
Daily fruit and vegetable consumption (serving)	
0	1.00
1–2	0.88 (0.35–2.27)
≥ 3	0.45 (0.15–1.35)
Weekly frequency of eating fast foods (time)	
0	1.00
1–2	2.01 (0.88–4.61)
≥ 3	1.75 (0.81–3.79)
Weekly frequency of drinking a soft drink or soda containing sugar (time)	
0	1.00
1–2	1.33 (0.61–2.90)
≥ 3	1.77 (0.89–3.51)

We excluded underweight participants ($n = 5$) and normal weight participants who overestimated their body weight ($n = 3$) due to the small cell size.
OR, odds ratio; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

the aforementioned correlate of weight underestimation, not being informed by a doctor of having overweight or obesity was associated with weight underestimation. This underscores the important role that health care providers at student health centers can play when it comes to openly speaking about weight-related issues with Black students who underestimate their weight. Weight underestimation was reported to be more prevalent in Black college students than in other racial/ ethnic groups in a nationally representative sample of college students, thereby highlighting racial/ethnic differences in weight underestimation among US college students [14]. Therefore, it is important for college health educators at HBCUs to understand more correlates of weight underestimation and to provide regular check-ups or health screenings for their students. In addition, future research should include a large sample of Black students at HBCUs using probability sampling techniques.

This study found that 62.9% of participants who had overweight or obesity experienced weight gain, defined as a 5% or greater weight increase relative to weight 1 year ago, which is in accord with previous evidence that weight gain is one of the most common negative health consequences among college students [7]. Living on campus and not having been informed by a doctor of having overweight or obesity were associated with weight gain. The present study findings reinforce the importance of college health care providers, who can provide effective communication about weight gain for college students and, in particular, those at HBCUs. Overweight and obesity in college can be a powerful determinant of excess body weight in middle adulthood [41]. Colleges and universities are an ideal place to educate students on health behaviors and to promote healthy weight maintenance [9]. Considering that most colleges and universities have resources (e.g., student wellness programs and fitness centers) on campus, it is necessary for college health staff and campus administrators at HBCUs to promote healthy weight-related behaviors by encouraging students living on campus to use those resources. Moreover, it is imperative that HBCUs monitor and address weight gain among students as early as possible.

Limitations of this study include the cross-sectional nature of the data, which prevents a determination of causality between sociodemographic or behavioral factors and perceived weight or weight gain. Second, survey data were based on self-reports, which are susceptible to recall bias. However, unlike previous college obesity studies [11,14,42] that were based on self-reported height and weight, this study used measured height and weight. A previous study reported that BMI values computed from

Table 4. Correlates of weight gain[a)] among overweight and obese students ($n = 132$)

Variable	≥5% weight gain (%)	OR (95% CI)
Total	58.3	
Age (y)		
18–19	62.9	1.48 (0.73–3.00)
≥20	53.2	1.00
Sex		
Male	50.0	0.43 (0.20–0.94)*
Female	70.4	1.00
Campus setting		
Very large city	58.7	1.35 (0.64–2.87)
Rural town	58.1	1.00
Type of residence		
On-campus	62.5	2.46 (1.12–5.38)*
Off-campus	47.2	1.00
Poverty threshold		
Above	54.8	1.00
Below	78.9	5.99 (1.32–27.29)*
Perceived overall health		
Excellent/very good	41.9	1.00
Good	58.3	1.81 (0.82–4.01)
Fair/poor	82.8	5.03 (1.62–15.63)**
Informed of being overweight by a doctor		
Yes	51.0	1.00
No	63.7	2.07 (1.01–4.30)*
Metabolic equivalent (min/wk)		
<500	81.8	1.00
≥500	55.9	0.35 (0.07–1.69)
Daily sitting hours	-	1.02 (0.92–1.12)
Daily screen time	-	1.02 (1.01–1.05)*
Monthly frequency of alcohol use (d)		
0	45.7	1.00
1–14	64.1	0.73 (0.30–1.81)
15–30	75.0	1.39 (0.45–4.29)
Daily fruit and vegetable consumption (serving)		
0	85.7	1.00
1–2	57.3	0.16 (0.02–1.35)
≥3	48.3	0.09 (0.01–0.83)*
Weekly frequency of eating fast foods (time)		
0	44.0	1.00
1–2	59.5	2.55 (0.98, 7.04)
≥3	63.1	2.67 (1.04, 6.86)*
Weekly frequency of drinking a soft drink or soda containing sugar (time)		
0	46.9	1.00
1–2	58.3	1.88 (0.65–5.38)
≥3	64.1	3.21 (1.21–8.55)*
Body weight perception		
Underestimation	62.7	0.98 (0.49–1.99)
Accurate estimation	63.1	1.00

OR, odds ratio; CI, confidence interval.
a)Defined as a 5% or greater weight increase relative to weight 1 year ago.
*$p < 0.05$, **$p < 0.01$.

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self-reported height and weight were 1.16 kg/m^2 lower than measured BMI values. In the current study, participants' BMI was accurately measured, and self-reporting bias of BMI was not present. Third, caution is needed to generalize our findings to students at other HBCUs as the study data were collected at only 2 HBCUs with a small sample size. Fourth, multivariable logistic regression in this study could not take covariates into account because it produced unstable adjusted ratios and 95% confidence intervals due to the small sample size. Finally, residual confounding by unmeasured variables is always a possibility when dealing with observational studies, and a broader list of correlates of weight perception and weight gain may be needed.

Despite these limitations, the present study adds to the knowledge base by reporting the prevalence of overweight/obesity and investigating sex differences in body weight perceptions and correlates of weight gain (defined as a 5% or greater weight increase in comparison with weight 1 year ago) in students at 2 HBCUs. The college years are associated with many life changes that can impact behaviors in a way that is conducive to weight gain [5]. Examples include unhealthy eating behaviors, reduced physical activity, increased sedentary behavior including screen time, and high levels of stress [27,43,44]. More importantly, the factors that can lead to weight gain can be quite different between individuals [5]. A one-size-fits-all approach aimed at addressing the barriers to healthy behaviors and contributors to weight gain is unlikely to work in such a context. Instead, it is important to develop individualized health promotion programs for college students and to address the root causes of the problem to maximize success.

Notes

Ethics Approval

The study was approved by the Institutional Review Board of Tennessee State University (IRB No: HS2015-3675) and University of Maryland Eastern Shore (IRB No: #2016-016). All participants provided written consent for their personal data to be used.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

All data generated or analysed during this study are included in this published article.

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Original Article

Sex differences in the relationship between depression and cardiovascular disease risk: a nationwide study in Korea

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ABSTRACT

Objectives: This study aimed to identify sex differences in the association between depression and the risk of developing cardiovascular disease (CVD).
Methods: A secondary analysis was conducted of data from the fifth to seventh waves (2010–2018) of the Korea National Health and Nutrition Examination Survey. The participants were adults aged 30–74 years who had no diagnosis of CVD. The CVD risk was calculated using the Framingham Risk Score algorithm. Multiple linear regression analysis was conducted to identify the association between depression and CVD risk using a complex sample design.
Results: The mean CVD risk was higher in males and females with current depression (14.72% vs. 6.35%, respectively) than in males without current depression (11.67% and 4.42%, respectively). Current depression showed a significant association with CVD risk after controlling for only health-related characteristics, but the significance disappeared in both males and females when demographic characteristics were additionally controlled.
Conclusion: The presence of depression was not associated with CVD risk regardless of sex after controlling for confounding factors. Further studies are recommended to investigate the relationship between depression and CVD risk in a larger sample of both males and females with depression.

Keywords: Cardiovascular diseases; Depression; Risk; Sex

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Introduction

Cardiovascular disease (CVD) refers to a range of conditions such as ischemic heart disease, stroke, heart failure, atrial fibrillation, and rheumatic heart disease [1], and was the top cause of death worldwide in 2015 [2] and the second leading cause of death in South Korea, with 108.3 deaths per 100,000 people in 2017 [3]. The prevalence of CVD in Korea was 12.2% (16.0% in males, 17.4% in females); it was higher in males than in females below 50 years of age, but its prevalence significantly increased in females at ages over 50 [4]. Meanwhile, CVD risk in

Korea is higher in males than in females [5]. Hypertension, dyslipidemia, diabetes, obesity, and poor health behaviors such as smoking, drinking, and lack of physical activity are major risk factors for CVD [1]. Social factors (e.g., marital status, education level, and social status) and psychological factors (e.g., stress, social support, and depression) are also considered to be important risk factors for CVD [6–8].

Depression is experienced by more than 300 million people globally [9]. In Korea, the lifetime prevalence of major depressive disorder in Korea was found to be 5.0% (3.0% for males and 6.9% for females), making it the second most common mental illness in 2016 after alcohol and nicotine abuse [10]. Depression may be linked to CVD through various factors, including lifestyle factors, autonomic nervous system disturbances, endocrine disruption, inflammatory diseases, platelet aggregation, and endothelial dysfunction [11,12]. More specifically, many patients with depression show poor lifestyle habits that increase the risk of CVD, including sleep deprivation, smoking, drinking, lack of physical activity, poor hygiene, and lack of adherence to medication [13].

Several studies have investigated the relationships between depression and CVD occurrence and/or risks [11–15], and some of them have shown significant associations between these variables [8,14,15]. However, studies of the relationships between these variables according to sex did not show consistent results [15–17]. In Korea, few studies have examined the relationship between depression and CVD risk factors [18–20]. Moreover, no study has directly identified the relationship between depression and CVD occurrence or CVD risk; in particular, no analytical study has explored these variables separately in males and females. In addition, in a meta-analysis of the relationship between depression and the onset of coronary atherosclerosis, most studies were conducted in Western countries [21]. Therefore, this study investigated the relationship between depression and CVD risk using data from the Korea National Health and Nutrition Survey (KNHANES), with the aim of filling the existing gap by examining that relationship by sex in an Asian population.

Materials and Methods

Participants

We conducted a secondary analysis of data collected from 5th to 7th waves (2010–2018) of the KNHANES, which is conducted by the Korea Centers for Disease Control and Prevention. The KNHANES is an ongoing national survey system conducted to assess the health and nutritional status of Koreans, monitor changes in health risk factors and the prevalence of major diseases, and provide evidence to develop health policies and programs in Korea [22,23]. It was initiated in 1998, and the seventh survey has been completed. It was a triannual survey up to the third KNHANES, after which it was conducted annually (from 2007 onwards). The sample of KNHANES VII was selected using 2-stage stratified cluster sampling for enumeration districts and households, and a health survey, health examination, and nutrition survey were conducted among appropriate household members.

The inclusion criteria for this study were as follows: no missing data for sampling weight, age between 30 and 74 years, the availability of depression data, no history of CVD (e.g., stroke, angina pectoris, or myocardial infarction), and no missing data on socio-demographics, health-related characteristics, depression, and CVD risk. Among 72,751 participants in the fifth to seventh survey, a total of 24,537 (10,183 males and 14,354 females) met those inclusion criteria (Figure 1).

Variables and Definitions

CVD risk, as the main outcome variable, was assessed using the Framingham Risk Score (FRS), which is a sex-specific algorithm used to estimate the 10-year CVD risk of an individual based on the Framingham Heart Study [24]. The formulas for males and females are presented separately so that the probability of developing CVD in the next 10 years can be predicted as a percentage according to sex (Table S1). There are 2 models for calculating the risk of CVD: the primary model (P model) and the simple office-based non-laboratory model (S model). Common variables in both models are sex, age, systolic blood pressure (SBP) (with/without treatment), current smoking, and diabetes. Additional variables are total cholesterol or high-density lipoprotein (HDL) cholesterol (mg/dL) for the P model, and body mass index for the S model [25]. We used the P model for the FRS, as the laboratory results were available. SBP was measured by taking the average of 3 readings. People without diagnosed hypertension were regarded as "not treated."

Depression, as the major explanatory variable, was categorized as "never," "past," and "current" according to the responses to the survey question on the history of diagnosed depression ("I have been diagnosed [with depression] by a doctor" and "I am currently suffering [from depression]"). Confounding variables included socio-demographic factors (age, employment, and household income) and health-related characteristics (alcohol intake, current smoking, physical activity, perceived stress, and comorbidities) known to be associated with depression [26–31] or CVD risk [32,33]. The variables were categorized

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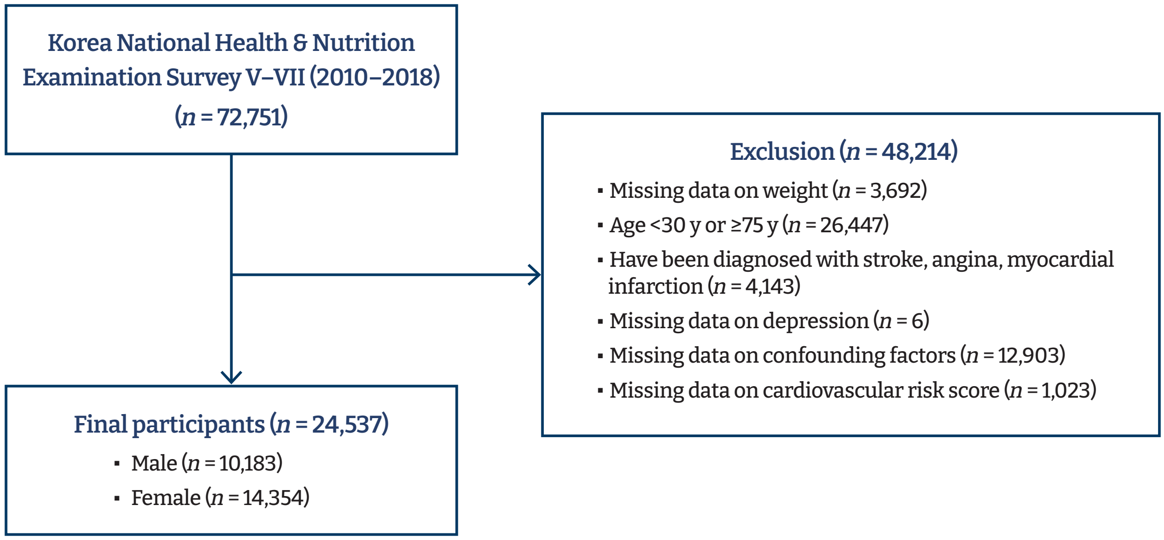

Figure 1. The selection process of study subjects.

as follows: "30–39," "40–49," "50–59," "60–69," and "over 70 years old" for age; "no," "yes, regular job," and "yes, irregular job" for employment; quartiles 1–4 for household income; "less than once per month," "1–4 times per month," and "2 times and higher per week" for alcohol intake; "yes" and "no" for current smoking; "yes" or "no" for engagement in high-or moderate-intensity physical activity during work or leisure for physical activity; and "much" and "little" for perceived stress. Comorbidities consisted of hypertension, diabetes, and dyslipidemia, and each disease was classified as "yes" or "no" depending on whether it had been diagnosed by a physician or not.

Data Analysis

The data were analyzed with IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA) using a complex sample design considering strata, cluster, and the combined sampling weight of 2 years. A 2-tailed test was performed with a significance level (α) of 0.05. The variables in the study were calculated using non-weighted frequency, weighted percentage, or mean and standard error according to sex. The distribution of CVD risk according to characteristics of the participants was analyzed using the chi-square test. As the CVD risk data did not satisfy the assumption of normality, CVD risk was classified as "lower risk" and "higher risk" based on the top 25% (15% for males and 5% for females). Multiple logistic regression analyses were conducted to evaluate the association of depression and CVD risk after controlling for confounding factors. We considered 4 models according to confounding factors input in the models: age (continuous) only in model 1; age (continuous), income, and occupation in model 2; drinking, smoking, physical activity, stress, and comorbidities in model 3; and all factors in model 4. Multi-collinearity was assessed based on a correlation coefficient ≥0.85. Meanwhile, we performed a sensitivity analysis to check the robustness of the findings on the impact of depression on CVD risk using the S model, which is used to calculate the FRS using body mass index instead of laboratory tests with total and HDL cholesterol results [24].

Ethical Considerations

This study was conducted after receiving permission for the use of data from the website of the KNHANES, and approval of exemption from review (IRB No: 2019_141_HR) from the Pusan National University Institutional Review Board.

Results

Characteristics and CVD Risk of the Participants

Table 1 shows participants' socio-demographic and health-related characteristics according to sex. Most of the 10,183 males were under 50 years old (61.2%), currently employed (80.8%), and in the third and fourth quartile income groups (65.3%); 43.2% were current smokers; and 1.1% had current depression. The majority of the 14,354 females were under 50 years old (60.6%), currently unemployed (53.8%), and in the third and fourth quartile income groups (61.0%); only 6.4% were current smokers; and 3.2% had current depression. All characteristics of the participants were significantly different according to sex. The distribution of CVD risk and its components is presented in Table 2. The

Table 1. Characteristics of the study participants according to sex

Characteristic	Male (*n* = 10,183)	Female (n = 14,354)	*p*
Age group (y)			0.005
30–39	2,725 (32.8)	4,055 (31.0)	
40–49	2,484 (28.4)	3,717 (29.6)	
50–59	2,112 (21.6)	3,254 (22.8)	
≥ 60	2,862 (17.1)	3,328 (16.6)	
Employment			< 0.001
No	2,491 (19.2)	8,003 (53.8)	
Yes, irregular	1,281 (12.8)	2,124 (15.4)	
Yes, regular	6,411 (68.0)	4,227 (30.8)	
Household income (quartile)			< 0.001
1st	1,286 (10.3)	2,031 (12.5)	
2nd	2,516 (24.4)	3,724 (26.5)	
3rd	3,151 (32.8)	4,328 (31.0)	
4th	3,230 (32.5)	4,271 (30.0)	
Alcohol intake			< 0.001
< 1 time/mo	2,317 (21.9)	7,636 (50.9)	
1–4 times/mo	3,905 (39.2)	5,063 (36.9)	
≥ 2 times/wk	3,961 (38.9)	1,655 (12.2)	
Smoking			< 0.001
Never	1,843 (18.8)	12,723 (87.5)	
Past	4,256 (37.8)	826 (6.1)	
Current	4,084 (43.3)	802 (6.4)	
Physical activity	3,415 (35.7)	3,586 (26.1)	< 0.001
Perceived stress			0.005
Much	2,429 (25.3)	3,777 (27.2)	
Little	7,754 (74.7)	10,577 (72.8)	
Comorbidities			
Hypertension	2,194 (17.2)	2,374 (13.6)	< 0.001
Diabetes	891 (6.7)	794 (4.6)	< 0.001
Dyslipidemia	1,261 (11.1)	2,139 (12.8)	< 0.001
Depression diagnosed			< 0.001
Never	9,983 (98.0)	13,454 (93.9)	
Past	85 (0.9)	409 (2.9)	
Current	115 (1.1)	491 (3.2)	

Data are unweighted number and weighted proportions.

mean CVD risk was 11.70% among males and 4.48% among females, reflecting a significant difference.

The Association between Depression and CVD Risk

According to the bivariate analysis, as shown in Tables 3 and 4, current depression was associated with CVD risk in both males and females. The mean CVD risk was higher in males and females with current depression (14.72% vs. 6.35%, respectively) than in males without current depression (11.67% and 4.42%, respectively). The prevalence of current depression among those with higher CVD risk was 1.6% in males and 5.0% in females, which was significantly higher than the prevalence among those with lower CVD risk. According to multiple logistic regression analysis, current depression showed a significant association with CVD risk after controlling for health-related characteristics, but the significance disappeared in both males and females when demographic characteristics were additionally controlled (Table 5).

Sensitivity Analysis

In the sensitivity analysis of CVD risk calculated using the S model, the mean CVD risk was 13.11% for males and 4.93% for females (Table S2). In the bivariate analysis, CVD

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Table 2. Distribution of cardiovascular disease risk and its components according to sex

Characteristic	Male (*n* = 10,183)	Female (*n* = 14,354)	*p*
Age (y)	47.00 ± 0.15	47.19 ± 0.13	0.210
Total cholesterol (mg/dL)	194.24 ± 0.42	193.37 ± 0.36	0.104
HDL cholesterol (mg/dL)	47.07 ± 0.13	54.51 ± 0.13	< 0.001
SBP (mmHg)	120.13 ± 0.18	113.84 ± 0.18	< 0.001
Hypertension treatment	1,935 (14.8)	2,185 (12.4)	< 0.001
Diabetes	891 (6.7)	794 (4.6)	< 0.001
Current smoking	4,069 (43.2)	773 (6.2)	< 0.001
CVD risk (%)			< 0.001
< 5	2,820 (33.4)	9,462 (71.6)	
5–9	2,294 (25.5)	2,744 (17.1)	
10–19	2,600 (24.1)	1,674 (9.1)	
≥ 20	2,468 (17.0)	473 (2.2)	
Mean ± SE	11.70 ± 0.13	4.48 ± 0.05	< 0.001

Data are presented as mean ± SE or *n* (%). Data are unweighted number and weighted proportions.

HDL, high-density lipoprotein; SBP, systolic blood pressure; CVD, cardiovascular disease; SE, standard error.

risk was higher in subjects with current depression than in subjects without current depression both for males ($p = 0.032$) and for females ($p < 0.001$). However, there was no significant association between depression and CVD risk after controlling for confounding factors, which showed similar trends to the results obtained by using the P model for CVD risk calculation (Table S3).

Discussion

This study aimed to investigate the relationship between depression and CVD risk by sex using data from a representative community-based health survey in Korea. The prevalence of current depression was 1.1% in males and 3.2% in females, and it increased to 2.0% in males and 6.1% in females when including past depression. This figure is slightly lower than the prevalence of 5.0% (3.0% in males, 6.9% in females) reported in a previous survey in 2016 [10], where depression was measured with the Korean version of Composite International Diagnostic Interview (CIDI). Since depression was identified by a self-reported physician's diagnosis in this study, those who show depressive moods but have never been diagnosed by a physician were classified as "not depressed," resulting in a potential underestimation of the prevalence of depression.

The CVD risk was measured with the FRS, which is a well-known measure of 10-year CVD risk, and its validity has been established in various populations including Koreans [34,35]. The CVD risk was higher in males than in females, which is consistent with a previous finding in a French cohort where CVD risk was measured by the FRS [36]. The CVD risk by sex also showed a similar trend in a sensitivity analysis with non-laboratory data, although CVD risk with non-laboratory data was consistently higher than CVD risk with laboratory data (Figure S1).

Without controlling for confounding factors, males and females with current depression showed 1.62 and 2.09 times higher CVD risk than those without depression, respectively, corresponding to a slightly higher effect size than that of 1.46 (95% confidence interval [CI], 1.37–1.55) reported in a meta-analysis [37]. However, depression was no longer associated with CVD risk after controlling for well-known confounding factors, including socio-demographic and health-related characteristics [26–33]. Nonetheless, an independent association between depression and CVD risk was found after controlling for only health-related characteristics for both males and females, with CVD risk calculated by the P model and S model. Health behaviors are important factors that explain the relationship between depression and CVD [11,12]. The prevalence of risk factors of CVD such as obesity, smoking, diabetes, and hypertension was found to be high in individuals with severe mental health disorders such as depression in a previous study [38]. According to our additional stratified analyses according to these categories, some health-related characteristics (e.g., alcohol intake, current smoking, and perceived stress) seem to act as effect modifiers, not as confounding factors, between the 2 variables (Table S4). For instance, males with depression who drank more than twice a week, smoked cigarettes, and experienced a high level of stress had higher CVD risk than their counterparts without depression. Unlike males, females with depression who drank fewer than 4 times a month and did not smoke had a higher CVD risk than those

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Table 3. Relationship between the characteristics of the participants and cardiovascular disease risk among males (n=10,183)

Characteristic	Mean ± SE	Lower risk (n = 6,624)	Higher risk (n = 3,559)	p[a)]
Age group (y)				< 0.001
30–39	3.70 ± 0.05	2,715 (44.3)	10 (0.4)	
40–49	8.40 ± 0.12	2,266 (35.0)	218 (9.9)	
50–59	15.90 ± 0.23	1,187 (16.7)	925 (35.4)	
≥ 60	27.21 ± 0.31	456 (4.0)	2,406 (54.3)	
Employment				< 0.001
No	20.35 ± 0.36	769 (11.2)	1,722 (41.9)	
Yes, irregular	14.12 ± 0.35	708 (11.3)	473 (17.1)	
Yes, regular	8.80 ± 0.12	5,147 (77.5)	1,264 (41.0)	
Household income (quartile)				< 0.001
1st	20.43 ± 0.50	424 (6.4)	862 (21.3)	
2nd	12.33 ± 0.26	1,514 (23.7)	1,002 (26.6)	
3rd	10.11 ± 0.19	2,287 (35.2)	864 (26.1)	
4th	10.05 ± 0.17	2,399 (34.7)	831 (26.0)	
Alcohol intake				< 0.001
< 1 time/mo	12.77 ± 0.28	1,392 (21.1)	925 (24.1)	
1–4 times/mo	9.97 ± 0.18	2,803 (42.4)	1,102 (30.3)	
≥ 2 times/wk	12.84 ± 0.20	2,429 (36.5)	1,532 (45.6)	
Current smoking				< 0.001
No	10.04 ± 0.14	4,152 (60.1)	1,962 (47.7)	
Yes	13.89 ± 0.22	2,472 (39.9)	1,597 (52.3)	
Physical activity				< 0.001
No	12.71 ± 0.17	4,154 (61.2)	2,614 (72.8)	
Yes	9.88 ± 0.17	2,470 (38.8)	945 (27.2)	
Perceived stress				< 0.001
Much	9.64 ± 0.21	1,852 (28.0)	577 (17.7)	
Little	12.40 ± 0.15	4,772 (72.0)	2,982 (82.3)	
Comorbidities				< 0.001
No	8.48 ± 0.10	5,645 (86.1)	1,488 (43.7)	
Yes	21.36 ± 0.31	979 (13.9)	2,071 (56.3)	
Current depression				0.030
No	11.67 ± 0.13	6,563 (99.0)	3,505 (98.4)	
Yes	14.72 ± 1.17	61 (1.0)	54 (1.6)	

Data are presented as mean ± SE or n (%). Data are unweighted number and weighted proportions.
SE, standard error.
[a)]The value was obtained by the chi-square test.

who did not have depression. This finding may be related to a lack of statistical power due to the small sample of heavy drinkers and smokers in females.

Meanwhile, the findings on the relationship between depression and CVD risk by sex are not consistent among studies [15–17]. In a cohort study of United States (US) middle-aged and older adults who had never been diagnosed with stroke or heart disease, CVD occurred 1.39 times (95% CI, 1.20–1.61) more often in males and 1.19 times (95% CI, 1.05–1.35) more often in females who had depressive symptoms than in those who did not have depression, showing a significant correlation in both sexes [15]. According to the study of Holt et al. [16] using cohort data in the United Kingdom, CVD incidence increased by 1.130 times (95% CI, 1.034–1.235; p = 0.007) in males with high depression scores, but no significant relationship was found in females. However, the study of Kouvari et al. [17] using cohort data in healthy populations without chronic diseases showed

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Table 4. Relationship between the characteristics of the participants and cardiovascular disease risk among females (*n*=14,354)

Characteristic	Mean ± SE	Lower risk (*n* = 9,462)	Higher risk (*n* = 4,892)	p[a)]
Age group (y)				< 0.001
30–39	1.18 ± 0.01	4,036 (43.1)	19 (0.6)	
40–49	2.67 ± 0.03	3,416 (37.7)	301 (9.1)	
50–59	5.93 ± 0.08	1,670 (16.6)	1,584 (38.3)	
≥ 60	11.90 ± 0.15	340 (2.6)	2,988 (52.0)	
Employment				< 0.001
No	5.12 ± 0.08	4,787 (50.3)	3,216 (62.9)	
Yes, irregular	4.83 ± 0.12	1,297 (14.4)	827 (17.9)	
Yes, regular	3.19 ± 0.06	3,378 (35.4)	849 (19.2)	
Household income (quartile)				< 0.001
1st	8.66 ± 0.20	656 (7.3)	1,375 (25.5)	
2nd	4.74 ± 0.10	2,266 (25.2)	1,458 (29.8)	
3rd	3.60 ± 0.07	3,235 (34.0)	1,093 (23.6)	
4th	3.43 ± 0.06	3,305 (33.5)	966 (21.1)	
Alcohol intake				< 0.001
< 1 time/mo	5.11 ± 0.07	4,588 (47.2)	3,048 (59.9)	
1–4 times/mo	3.87 ± 0.07	3,642 (39.4)	1,421 (30.7)	
≥ 2 times/wk	3.74 ± 0.12	1,232 (13.4)	423 (9.4)	
Current smoking				< 0.001
No	4.37 ± 0.05	9,024 (94.7)	4,557 (91.7)	
Yes	6.17 ± 0.26	438 (5.3)	335 (8.3)	
Physical activity				< 0.001
No	4.78 ± 0.06	6,801 (71.3)	3,967 (80.3)	
Yes	3.65 ± 0.07	2,661 (28.7)	925 (19.7)	
Perceived stress				< 0.001
Much	4.27 ± 0.09	2,586 (28.1)	1,191 (25.0)	
Little	4.56 ± 0.06	6,876 (71.9)	3,701 (75.0)	
Comorbidities				< 0.001
No	2.93 ± 0.03	8,675 (92.1)	2,023 (42.7)	
Yes	10.02 ± 0.14	787 (7.9)	2,869 (57.3)	
Current depression				< 0.001
No	4.42 ± 0.05	9,231 (97.5)	4,632 (95.0)	
Yes	6.35 ± 0.29	231 (2.5)	260 (5.0)	

Data are presented as mean ± SE or *n* (%). Data are unweighted number and weighted proportions.
[a)]The value was obtained by the chi-square test.

Table 5. Multiple logistic regression results on the association between depression and cardiovascular disease risk by sex

Model[a)]	Male (*n* = 10,183)			Female (*n* = 14,354)		
	OR (95% CI)	p	R^{2}[b)]	OR (95% CI)	p	R^{2}[b)]
0	1.62 (1.04–2.53)	0.032	0.001	2.09 (1.69–2.60)	< 0.001	0.004
1	1.26 (0.67–2.37)	0.469	0.417	1.28 (0.88–1.87)	0.203	0.457
2	1.06 (0.55–2.01	0.869	0.418	1.17 (0.79–1.71)	0.433	0.459
3	1.81 (1.12–2.94)	0.016	0.201	1.62 (1.24–2.13)	< 0.001	0.253
4	1.07 (0.55–2.08)	0.837	0.511	0.92 (0.64–1.33)	0.671	0.494

OR, odds ratio; CI, confidence interval.
[a)]Each model was adjusted as follows: 0, no adjustment; 1, by age (continuous); 2, by age (continuous), income, and occupation; 3, by drinking, smoking, physical activity, stress, and comorbidities; 4, by all factors. [b)]Cox & Sneel R^2.

that depression was only associated with the incidence and recurrence of CVD in females. The inconsistent findings of studies on the relationship between depression and CVD risk by sex underscore the importance of further replication studies.

Strengths and Limitations

To our knowledge, this is the first study to identify the relationship between depression and CVD risk by sex using nationwide community-based data. This study has many strengths. First, we identified the relationship between depression and CVD risk after controlling for socio-demographic and health-related characteristics that are known to affect the relationship. Second, we used a large, nationally representative dataset for the entire country during 9 years, which increases the generalizability of our findings.

However, the following limitations need to be taken into account when interpreting the results. First, this study did not control for the effects of variables such as potential biomarkers that affect CVD risk, since this was a secondary data analysis study and that information was not available. Second, as depression is defined by the subject's reported diagnosis, the actual prevalence of depression may have been underestimated due to the possibility of undiagnosed depression. According to a nationwide survey of mental disorders in 2016, the use of mental health service over the past year was 9.6% [10], which was much lower than the rates of 14.2% in the US, 39.5% in Belgium, 35.5% in Spain, and 20% in Japan [39,40]. This underestimation leads to misclassification bias, as subjects with strong depressive symptoms who were undiagnosed by a physician were classified as not having depression, thereby weakening the strength of the association between the 2 variables. Third, CVD risk is a predicted value and may differ from the actual occurrence of CVD. In particular, CVD risk reflects the probability of CVD occurrence within 10 years. If the values used to calculate CVD risk change over time, CVD risk also changes, which may result in a difference in the actual incidence of CVD. Finally, study subjects with CVD, as well as those under 30 years old or over 75 years old, were excluded from the study, impeding the generalizability of the study results to these subjects.

Conclusion

According to our findings, the prevalence of depression was 3 times higher in females than in males, and CVD risk was more than 2.5 times as high in males as in females. The presence of depression was not associated with CVD risk in either males or females after controlling for confounding factors. This finding may be related to the small sample with depression and misclassification bias, as depression was defined according to a subject's reported diagnosis. Therefore, we recommend that further research should investigate the relationship between depression and CVD risk in a larger sample of individuals with depression and take steps to minimize the underestimation of depression by using both subjects' reported diagnoses and depressive symptoms in both males and females.

Supplementary Material

Table S1. The cardiovascular risk functions; **Table S2.** The distribution of cardiovascular disease risk calculated by simple office-based non-laboratory model; **Table S3.** Multiple logistic regression results on the association between depression and cardiovascular disease risk by the simple office-based non-laboratory model; **Table S4.** Additional analysis results on the association between depression and cardiovascular disease risk after stratifying according to categories; **Figure S1.** Agreement of cardiovascular risk calculated by primary model and simple office-based non-laboratory model according to sex. Supplementary data is available at https://doi.org/10.24171/j.phrp.2021.12.2.08.

Notes

Ethics Approval

This study was conducted after receiving permission for the use of data from the website of the KNHANES, and approval of exemption from review (IRB No: 2019_141_HR) from the Pusan University Institutional Review Board.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

All the data supporting the results of this study are included in the article and the supplementary file.

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Original Article

Impact of fatigue on quality of life among breast cancer patients receiving chemotherapy

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ABSTRACT

Objectives: Fatigue is the most frequently reported symptom experienced by cancer patients and has a profound effect on their quality of life (QOL). The study aimed to determine the impact of fatigue on QOL among breast cancer patients receiving chemotherapy and to identify the risk factors associated with severe fatigue incidence.
Methods: This was an observational prospective study carried out at multiple centers. In total, 172 breast cancer patients were included. The Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire was used to measure QOL, while the Brief Fatigue Inventory (BFI) was used to assess the severity of fatigue.
Results: The total average mean and standard deviation of QOL were 84.58±18.07 and 4.65±1.14 for BFI scores, respectively. A significant association between fatigue and QOL was found in linear and multiple regression analyses. The relationships between fatigue severity and cancer stage, chemotherapy dose delay, dose reduction, chemotherapy regimen, and ethnicity were determined using binary logistic regression analysis.
Conclusion: The findings of this study are believed to be useful for helping oncologists effectively evaluate, monitor, and treat fatigue related to QOL changes.

Keywords: Breast neoplasms; Chemotherapy; Fatigue; Quality of life

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Introduction

Breast cancer is the most common malignancy among women globally, particularly among women over the age of 40 [1]. In Malaysia, breast cancer is the most commonly diagnosed cancer in women, followed by colorectal cancer, and it is the second leading cause of cancer death among Malaysians after colorectal cancer [2]. Cancer-related fatigue (CRF) is a multidimensional concept reported to be the most common side effect experienced by cancer patients [3]; it has a profound negative effect on patients' quality of life (QOL) [4]. The fatigue reported by cancer patients is usually described as an unusual, excessive, whole-body experience that is unrelated to activity or exertion and is not relieved by rest or sleep [5,6].

The prevalence of fatigue among cancer patients has been estimated to be between 10% to 99% [7] and reaches as high as 90.3% among patients receiving chemotherapy [8], with a marked effect on patients' QOL [4,9]. Most studies have reported relatively high rates of moderate to severe fatigue (30%–60%), which may lead to treatment discontinuation [10]. It has been found that the QOL among cancer patients is significantly and negatively affected from the moment of diagnosis with cancer or once they hear the word "cancer" [11]. A study of the scientific literature demonstrated a strong relationship between fatigue and poor QOL in cancer patients [12]. There is a growing interest in using QOL data in clinical studies to help clinicians improve health services among cancer survivors [13]. Recently, QOL has been introduced as a point of comparison between treatments for many types of cancer, particularly in advanced stages [14]. QOL has also been used as an early indicator of disease progression that could help oncologists and healthcare providers more closely monitor patients in their daily routines [15].

Several factors play a significant role in the incidence of severe fatigue in cancer patients. The predominant factors are demographic characteristics such as obesity [16–18], pre-menopausal status [18], age [17,19,20], and level of education [17,20]. In addition, the development of severe fatigue is associated with pathological factors such as the presence of interleukin (IL)-6, tumor necrosis factor, IL-1 receptor antagonist (IL-1RA), and especially IL-8, which is a significant factor related to pain and fatigue in cancer patients [21], the types of cancer [19], and anticancer treatment schedules [22–24]. Still other factors include illness-related characteristics (pain, inflammation, and joint damage), physical function (sleep disturbance and disability), emotional impairment (depression and anxiety), and personal conditions (gender, work, social relationships, education, and whether the patient has a partner) [25]. In addition, patient-related factors, treatment-related factors, inflammatory cytokines, and metabolic and/or endocrine dysregulation play significant roles in the incidence and/or severity of fatigue among breast cancer patients [26,27].

Improving the QOL of cancer patients is expected to have significant benefits for their adaptation and motivation to continue receiving and completing chemotherapy with fewer side effects and to increase the chances of cancer patients being cured and surviving [28]. Hence, this study aimed to determine the effect of CRF on the QOL of Malaysian breast cancer patients and to detect the risk factors associated with fatigue severity. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale was used to assess the impact of fatigue on QOL, and the Brief Fatigue Inventory (BFI) scale was used to measure fatigue severity among breast cancer patients. The outcome of this study will significantly help improve the techniques used by healthcare providers and medical staff to care for cancer patients. Future studies that focus on improving the QOL of cancer patients are highly recommended because such research will help cancer patients to overcome the disease itself [29–31].

Materials and Methods

This prospective observational multi-center study was carried out at the oncology department and daycare clinics of Institute Kanser Negara, Putrajaya, Hospital Kuala Lumpur, and University of Malaya Medical Center, Malaysia, from July 2019 to April 2020. Patients were recruited based on the following criteria: (1) being diagnosed with breast cancer at any stage and receiving chemotherapy; (2) not having received radiation treatment and hormonal therapy; (3) having a fatigue score of 2 or above after cancer diagnosis based on the Eastern Cooperative Oncology Group Performance Status (ECOG PS) and BFI; (4) not having chronic diseases, such as hypertension, renal disease, cardiac disease, and diabetes mellitus, or being in a poor psychological state; (5) being able to complete the questionnaire unaided; and (6) being aged above 18 years old. Patients having any other malignancy and patients with an ECOG PS of 0–1 were excluded from the study.

Patients who experienced fatigue were identified based on the ECOG PS and BFI scores, which is used to determine the prognostic status of fatigue, as recorded in their medical files. The severity of fatigue was assessed by the BFI scale: 0–3 (mild), 4–7 (moderate), and 7–10 (severe) [32]. The patients were then briefed on the background of the study and given a consent form to sign once they agreed to participate. Prior permission was granted by the owners of the FACIT system to use their tool in this study. The test was conducted and scored using the instructions from version 4 of the FACIT Measurement System (www.facit.org). Patients were followed up on the same day after receiving chemotherapy to complete the FACIT-F (version 4) questionnaire in English and/or Malay language format (whichever was needed) and the BFI scale. The respondents were required to circle or mark 1 number per line to indicate their responses as they applied to the past 7 days. The response scale ranged from 0 (not at all) to 4 (very much). In addition, patients were instructed to answer the first 3 questions from the BFI scale to indicate the severity of fatigue during the previous 24

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hours. These patients were followed up with for another cycle of chemotherapy (totaling 2 cycles). With the aid of the medical staff, the BFI and FACIT-F QOL assessment were completed during each follow-up. It took about 10 to 20 minutes to complete the questionnaires. The 2 follow-up visits for fatigue patients were performed within 2 to 4 months.

Tools for Measurements and Procedure

Brief Fatigue Inventory

The BFI is a tool defined to assess the severity of fatigue in cancer patients over the previous 24 hours (Cronbach's alpha, 0.82–0.97) [33]. The BFI is also used to screen, detect, and measure the severity of daily fatigue. It has many advantages such as easily understandable language, simplicity, and a short completion time (up to 10 minutes), which makes it one of the best tools for measuring fatigue among cancer patients. Originally the BFI was used for patients who speak English, but it is now available and used in many other languages [34,35]. The BFI consists of 9 questions answered using an 11-point rating scale. The severity of fatigue is rated according to the first 3 questions (1. Rate your level of fatigue now?, 2. Rate your USUAL level of fatigue during the past 24 hours?, 3. Rate your WORST level of fatigue during the past 24 hours?) on a scale of 0 to 10, with 0 indicating no fatigue and 10 indicating the most severe level of fatigue. The next 6 questions are used to assess and detect the interference of fatigue with aspects of a patient's daily life such as the ability to walk, their mood, ability to work, their enjoyment of life, and connections with other people. In this study, only the first 3 questions were used to assess the severity of fatigue among breast cancer patients.

The Functional Assessment of Chronic Illness Therapy-Fatigue scale

The FACIT-F scale is a tool designed specifically to assess the impact of fatigue on QOL. The FACIT-F questionnaire consists of 40 items. Twenty-seven items are derived from version 4 of the Functional Assessment of Cancer Therapy-General (FACT-G), which contains 4 QOL domains: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The other 13 items are from the fatigue subscale (FS) [36]. Each question had an equal value and the QOL was quantified as the sum of the scores for all domains. The QOL domains scores were classified into 5 categories, which were 'not at all' (0), 'a little bit' (1), 'somewhat' (2), 'quite a bit' (3), and 'very much' (4). Patients were followed up and assessed during each of their chemotherapy cycles, starting from cycle 2, which varied from 3 to 4 weeks depending on the type of chemotherapy treatment that they received.

FACIT-F scoring

The FACIT-F (version 4) contains 40 self-reported items, including 27 items from the core FACT-G scale and 13 items from the additional FS.

FACT-G 27 items = PWB 7 items + SWB 7 items + EWB 6 items + FWB 7 items
FS 13 items = Fatigue 13 items
FACIT-F 40 items = FACT-G 27 items+ FS 13 items

The final score is obtained by adding the scores from the 4 FACT-G domains (PWB, SWB, EWB, and FWB) to the score from the additional FS (13 items). The final score for fatigue patients (FACIT-F) ranges from 0 to 160 (Table 1). Negatively stated items are reversed by subtracting the response from 4. After reversing the necessary items, all subscale items are tabulated, the result of which is the subscale score.

Subscale scores are prorated if more than 50% of the items are answered (e.g., a minimum of 4 of 6 items or 4 of 7 items) and any number of unanswered or missing questions remained. This is done using the following formula: prorated subscale score = (sum of item scores) × (no. of items in subscale) / (no. of items answered)

The total score is then calculated as the sum of the subscale scores. The FACIT-F scale is considered to be an acceptable indicator of the QOL among cancer patients as long as the overall item response rate was greater than 80%. To achieve this result, at least 22 of 27 FACT-G items must be completed [36]. High scores for all FACIT scales and symptom indices have been associated with higher health-related QOL [37]. Higher scores on the FACIT-F have been shown to correlate with lower BFI scores and better QOL among cancer patients [38].

Table 1. Distribution of QOL domains based on the number of items and total scores

QOL domain	No. of questions	Total score
Physical well-being	7	28
Social well-being	7	28
Emotional well-being	6	24
Functional well-being	7	28
Fatigue subscale	13	52
FACT-G	27	108
FACIT-F (total)	40	160

QOL, quality of life; FACT-G, Functional Assessment of Cancer Therapy-General; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire.

Statistical Analysis

The mean and standard deviation (SD) were used as descriptive statistics to present the demographic and clinical data in this study. Regression analysis was performed. Both simple and multiple regression analyses with Pearson correlation coefficients were conducted to determine the effect and association between the total average of BFI scores and total average QOL (FACIT-F) scores, as well as between the total average BFI scores and the corresponding total average QOL domain subgroup. Logistic regression analysis was used to determine the relationship between fatigue severity and its associated factors such as cancer stage, chemotherapy data, and demographic characteristics. The dependent variables in all models were the QOL and BFI scores, and the independent variables were CRF, as well as other factors such as age, cancer stage, marital status, body mass index, chemotherapy types, dose delay, and the number of chemotherapy regimens. A relationship was considered statistically significant if the *p* was < 0.05. Data were analyzed using IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA). Computation of the results was done according to the guidelines of the FACT-G group. In all analyses, the first measurement was taken as a reference baseline level and changes relative to the baseline measurement (in follow-up visits after cycle 1) were analyzed. The effect of fatigue on QOL among breast cancer patients receiving chemotherapy was represented by interaction terms between the variables of fatigue (BFI severity) and QOL at the second follow-up. The association between fatigue severity (BFI scores) from the first follow-up (the first reading taken on the same day of receiving chemotherapy) and upcoming assessments (the second reading) were calculated separately for these scales. In addition, changes in the mean value between both readings were also calculated. Multiple logistic regression analysis was conducted to determine the relationships between cofactors and the fatigue score.

Results

Out of 172 respondents, 91 of them (52.9%) were Malay. The majority of respondents ($n = 128$; 74.4%) were < 60 years old with a mean age of 52.63 years (SD, 11.27 years). The majority of the respondents were married ($n = 153$, 89%) and more than half of the respondents were working ($n = 110$, 64%). Sixty-four respondents (37.2%) had stage III breast cancer, and 53 respondents (30.8%) had stage II cancer. The distribution of demographic characteristics such as ethnicity, age, marital status, menstrual status, employment status, smoking status, and alcohol consumption is reported in Table 2.

Fatigue Severity

Based on the BFI, fatigue severity was classified into 3 main categories: mild (1–3), moderate (4–6), and severe (7–10) [32].

Table 2 shows that most of the patients suffered from moderate fatigue ($n = 123$, 71.5%) followed by mild fatigue ($n = 43$, 25%).

QOL Data

The average mean score and SD for total QOL was 84.58±18.07. The mean QOL score at the first follow-up (91.91±17.45) was higher than the mean QOL score at the second follow-up (77.25±22.19). The scores for total QOL clearly declined across the two follow-up visits, as shown in Table 2.

Chemotherapy Data

The majority of the patients ($n = 127$, 73.8%) received a combination of chemotherapy regimens, and the rest ($n = 45$, 26.2%) received only 1 regimen. In addition, 79 patients (45.9%) were prescribed fluorouracil, epirubicin, cyclophosphamide (FEC); 32 patients (18.6%) were prescribed with docetaxel; and 24 patients (14%) were prescribed with a combination regimen of FEC and docetaxel (FEC-T), as shown in Table 3.

The Severity of Fatigue according to BFI Score across the 2 Follow-up Visits

The average mean of the total BFI was 4.65±1.14. Most respondents reported moderate fatigue at the 2 follow-up visits ($n = 121$, 70.3%; and $n = 117$, 68%), followed by mild fatigue and severe fatigue.

Association between Total QOL and BFI Scores

Linear regression analysis showed a significant ($p < 0.05$) association at all follow-up visits between QOL and fatigue severity. Pearson correlation analysis revealed a moderate positive relationship between QOL and BFI scores regarding fatigue severity ($r = 0.604$). As the severity of fatigue increased, the QOL score dropped to a greater extent and vice versa. Linear regression was calculated to predict the total QOL FACIT-F score based on fatigue severity. A significant regression equation was found ($F(1,170) = 97.789$, $p < 0.001$, $R2 = 0.365$). The equation for predicting QOL followed the format $y = a+bx$ [39], where $y =$ QOL (dependent variable), $a =$ constant, $b =$ BFI constant, $x =$ BFI score (independent variable), the participants' predicted QOL was equal to 128.993−9.555 (BFI score). In other words, the QOL score decreased by 9.555 units for each 1-unit increase in fatigue severity, as shown in Table 4. Additionally, as QOL decreased, fatigue severity (BFI score) increased, confirming an inverse relationship between both variables.

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Table 2. Demographic characteristics of breast cancer patients experiencing fatigue ($n = 172$)

Demographic characteristic	Value
Age (y)	52.6 ± 11.3
≥ 60	44 (25.6)
< 60	128 (74.4)
Ethnicity	
Malay	91 (52.9)
Indian	26 (15.1)
Chinese	43 (25.0)
Others	12 (7.0)
Marital status	
Single	9 (5.2)
Married	153 (89.0)
Divorced	10 (5.8)
Body mass index (kg/m^2)	
Underweight (< 18)	6 (3.5)
Normal (18–24.9)	68 (39.5)
Overweight (25–29.9)	59 (34.3)
Obese (≥ 30)	39 (22.7)
Employment	
Working	110 (64.0)
Not working	62 (36.0)
Menstrual status	
Premenopause	35 (20.3)
Postmenopause	137 (79.7)
Stage of breast cancer	
I	15 (8.7)
II	53 (30.8)
III	64 (37.2)
IV	40 (23.3)
Severity of fatigue	
Mild (1–3)	43 (25)
Moderate (4–6)	123 (71.5)
QOL total (0–160)	84.58 ± 18.07
QOL FACIT-F first follow-up (0–160)	91.91 ± 17.45
QOL FACIT-F second follow-up (0–160)	77.25 ± 22.19

Data are presented as mean ± SD or *n* (%).
QOL, quality of life; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue.

The scatter plot also showed that QOL declined from the first follow-up to second follow-up, whereas BFI scores increased (Figure 1).

Association between QOL and BFI Scores in Both Follow-up Visits

Multiple regression was carried out to investigate the relationship between the total QOL change and BFI scores at both follow-up visits and to predict the total QOL based on the BFI scores. The scatter plot showed a moderate negative linear relationship between the 2 variables, as confirmed by the Pearson correlation coefficient ($r = 0.575$ at first follow-up and $r = 0.546$ at second follow-up). Multiple regression showed a significant relationship between QOL across different domains and the BFI score ($p < 0.05$). According to a predictive equation with the format $y = a + bx_1 + bx_2$, where y = QOL (dependent variable), a = constant, b = BFI constant, x = BFI score (independent variable), the participants' predicted QOL was equal to 128.730–5.816 (BFI score) for the first follow-up and 128.730–3.859 (BFI score) for the second follow-up. The QOL scores decreased by 5.816 units for each 1-unit increase in the BFI score at the first follow-up and declined by 3.859 units for each 1-unit increase in BFI score at the second follow-up (Table 5).

Table 3. Chemotherapy data among patients undergoing chemotherapy ($n = 172$)

Variable	*n* (%)
No. of regimens[a)]	
1	45 (26.2)
> 1	127 (73.8)
Dose reduction[b)]	
Reduced	31 (18.0)
Not reduced	134 (77.9)
Not detected	7 (4.1)
Dose delay[c)]	
Delayed	64 (37.2)
Not delayed	108 (62.8)
No. of chemotherapy medications[d)]	
1	45 (26.2)
2	24 (14.0)
3	79 (45.9)
4	24 (14.0)
FEC[a)]	79 (45.9)
Docetaxel	32 (18.6)
FEC-T[b)]	24 (14.0)
TC[c)]	10 (5.8)
Paclitaxel	7 (4.1)
AC[d)]	4 (2.3)

FEC, fluorouracil, epirubicin, cyclophosphamide; FEC-T, fluorouracil, epirubicin, cyclophosphamide, and docetaxel; TC, docetaxel, cyclophosphamide; AC, adriamycin, cyclophosphamide.
[a)]Chemotherapy regimen: FEC is considered 1 regimen but 3 chemotherapy medications. [b)]Chemotherapy dose reduction: when the dose was reduced at the second follow-up from the first follow-up. [c)]Chemotherapy dose delay was defined as delay of the second dose of chemotherapy. [d)]No. of chemotherapy medications was defined as number of drugs according to the regimen (e.g., FEC is 3 medications and 1 regimen).

Association between Fatigue Severity and Its Associated Risk Factors

A logistic binary regression test was used to determine the strength of the association between fatigue severity and risk factors, incorporating all variables with significance

Table 4. Association between QOL and fatigue severity

	Total QOL				
	R^2	t-stat	*r*	b (95% CI)	$p^{a)}$
BFI score	0.365	−9.889	0.604	−9.555 (−11.463 to −7.648)	< 0.001

QOL, quality of life; CI, confidence interval; r, Pearson correlation coefficient.
[a)]Level of significance.

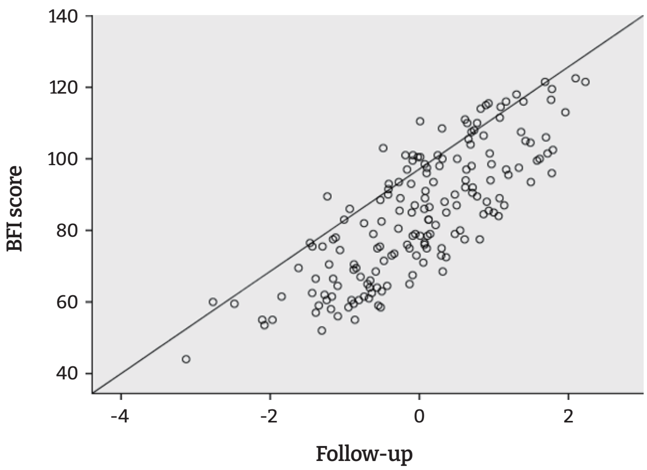

Figure 1. The linear relationship between Brief Fatigue Inventory (BFI) score and quality of life scores.

according to the chi-square test and performing logistic binary regression once for all factors. As shown in Table 6, cancer stage (p = 0.026), chemotherapy dose delay (p = 0.038), chemotherapy regimen (p = 0.003), chemotherapy dose reduction (p = 0.011), and ethnicity (p = 0.027) significantly predicted the magnitude of fatigue severity among breast cancer patients. There was a significant (p < 0.05) negative relationship between cancer stages (specifically stage II) with fatigue severity. Hence, as the cancer stage increased, the severity of fatigue also increased. Participants who experienced dose delay were 2.86 times less likely to experience severe fatigue compared to those with no chemotherapy dose delay. In addition, breast cancer patients who received a combination of chemotherapy regimens were 4 times more likely to develop a higher level of fatigue than those who took only a single chemotherapy regimen. Moreover, breast cancer patients with no chemotherapy dose reduction were 22.3 times more likely to experience severe fatigue compared to those with a dose reduction. Finally, Malay patients were 2.6 times more likely to develop severe fatigue than non-Malay patients (Table 6).

Discussion

CRF is a highly prevalent phenomenon in individuals with cancer who receive anti-neoplastic chemotherapy, radiation therapy, or biological response modifiers [40]. Almost every patient suffers from fatigue during cancer treatment, with a prevalence rate of up to 99% [41]. Despite growing evidence regarding fatigue occurring due to various anticancer treatments and how CRF affects patients' QOL, the severity of CRF is still not widely evaluated for cancer patients who are suffering from this distressing symptom. This study aimed to detect the factors associated with the severity of fatigue and how they affected QOL among cancer patients. To the best of the authors' knowledge, this is the first prospective longitudinal study conducted at multiple centers for cancer treatment in Malaysia with these objectives. The results showed that fatigue showed a moderate correlation with reduced overall QOL. This finding is similar to that of a recent study done in Malaysia in 2018 [30] and several studies conducted globally, which reported significant negative relationships between QOL and fatigue [38,42–50]. The majority of cancer patients reported that fatigue prevented them from engaging in their normal daily routine and partaking in social activities such as spending time with friends or going to a restaurant [51]. Fatigue was also associated with a wide range of symptoms consistent with psychological impairment, including lack of motivation, depression, cognition, and mood disturbance [52,53].

The results also revealed a moderate negative relationship between QOL and BFI scores. This finding is consistent with the findings of Butt et al. [54], who reported a strong significant correlation between fatigue and QOL. Despite the well-known negative effect of fatigue on the QOL of cancer patients, it is distressing to realize from this study that it remains a persistent problem that worsens patients' condition, significantly impacting their overall health status and the degree to which they experience physical symptoms. Cancer patients often describe their fatigue as a lack of energy, which could indicate that fatigue is caused by changes in metabolism and energy generation, particularly in skeletal muscles. In addition, fatigue might occur due to chemotherapy, which also exacerbates and induces various side effects that in turn negatively influence a patient's QOL. Furthermore, fear of metastasis and disappointment from treatment may result in a diminished QOL [55].

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Table 5. Associations between QOL and BFI score at both follow-up visits

Follow-up	Total QOL					*p*
	b	t-stat	95% CI	*r*	*p*	
BFI (first)	−5.816	−4.302	−8.485 to −3.147	−0.575	< 0.001	< 0.001
BFI (second)	−3.859	1.217	−6.261 to −1.456	−0.546	0.002	

QOL, quality of life; BFI, Brief Fatigue Inventory; CI, confidence interval; r, Pearson correlation.

Table 6. Association between risk factors and fatigue severity

Variable	Fatigue severity (BFI)		*p*
	B	OR (95% CI)	
Stage			
IV	Reference		
I	0.12	1.132 (0.158–8.133)	0.902
II	−1.47	4.34 (0.063–0.843)	0.026
III	−1.05	3.16 (0.088–1.138)	0.078
Dose delay			
Not delayed	Reference		
Delayed	−1.09	2.86 (0.130–0.942)	0.038
Regimen			
1	Reference		
> 1	1.39	4 (1.619–9.865)	0.003
Dose reduction			
Reduced	Reference		
Not reduced	3.10	22.3 (2.044–243.027)	0.011
Not detected	2.39	10.9 (1.342–88.319)	0.025
Ethnicity			
Non-Malay	Reference		
Malay	0.98	2.67 (1.116–6.398)	0.027

BFI, Brief Fatigue Inventory; OR, odds ratio; CI, confidence interval.

Our data also indicated a significant association between fatigue severity and QOL domains at both follow-up visits. The QOL scores decreased by 5.816 units for each 1-unit increase in the BFI score for the first follow-up and declined by 3.859 units for each 1-unit increase in BFI score at the second follow-up. In other words, about 36.8% of QOL was explained by fatigue BFI scores at both follow-up visits. A significant association was found between BFI scores and all QOL FACIT-F scales, indicating that higher BFI scores were associated with lower QOL. This finding was supported by many studies reporting that patients who demonstrated greater fatigue intensity showed lower QOL [38,56,57]. A similar conclusion was drawn by 2 large survey-based studies, each involving more than 1,900 breast cancer patients, which reported an inverse relationship between higher CRF and lower physical and social functioning with regard to QOL [42,58,59]. Understanding why CRF adversely impacts QOL could be achieved through a deeper understanding of the experiences of cancer survivors. The negative impact of fatigue on QOL did not only reduce patients' physical activity, but also affected them emotionally and functionally. Pappalardo and Reggio [60] found that fatigue diminished quality of life by interfering with the daily activities of patients. The study mentioned that 80% of fatigue patients lost their jobs (QOL, SWB) and reported a lack of ability to perform social tasks, work, and activities and to maintain a normal life [60]. Cancer patients often described their fatigue as a lack of energy, which suggested that fatigue resulted from changes in metabolism and energy generation, particularly in skeletal muscles [61]. In addition, patients undergoing chemotherapy often develop anorexia and reduce food intake, which could reduce their energy availability and contribute to fatigue [62].

There are several factors associated with the incidence of severe fatigue among cancer patients. In this study, the results showed a significant association between ethnicity (Malay) and CRF severity. This finding aligns with a previous study that revealed a significant relationship between the severity of fatigue and ethnicity among breast cancer survivors [17]. Hoh et al. [63] showed in their trial that the high association between the ethnicity of patients, particularly Malay patients, and fatigue severity might be due to the fact that Malays constitute the predominant racial group in Malaysia. The data also demonstrated a statistically significant ($p < 0.05$) association between fatigue severity and breast cancer stage. The intensity of CRF increased at higher breast cancer stages. According to Savina and Zaydiner [4], the 2 main factors that significantly affected the incidence and intensity of CRF among cancer patients were cancer stage and cancer status. The intensity of fatigue was hypothesized to be related to the level of disease burden rather than different fatigue profiles, such as the relationship between physical and mental health. The proposed explanation for this finding was that, due to a higher concentration of cancer cells in the body of patients with advanced-stage cancer, the condition of cancer itself causes patients to feel tired. Patients with advanced-stage cancer also eat less, receive more intense doses of chemotherapy, and are less active [64].

In addition, the data in this study showed that most cancer patients who received combination chemotherapy regimens developed moderate to severe fatigue. The logistic regression analysis demonstrated that breast cancer patients who received combination regimens were 4 times more likely to develop a high level of fatigue than those who received a single regimen. This finding is in agreement with a previous trial, which reported that breast cancer patients who received combinations of chemotherapy medications experienced more severe fatigue than those who received only 1 chemotherapy medication (paclitaxel) [65]. A similar finding was reported by Abrahams et al. [66], according to whom the prevalence of severe fatigue increased from 7% to 52% after patients received a combination of chemotherapy regimens. Another trial reported that patients who received a combination chemotherapy regimen (cyclophosphamide, fluorouracil, adriamycin [doxorubicin], and/or docetaxel) experienced more severe fatigue than those who received only Taxol (paclitaxel) [65]. Combined therapy regimens with 2 or more chemotherapy medications exacerbate fatigue more than any medication taken on its own. Fatigue tends to worsen with subsequent cycles of chemotherapy, which suggests a cumulative dose-related toxic effect that affects QOL.

A significant association was also found between dose reduction and the severity of fatigue. This finding is supported by Wang et al. [67], who pointed out that hematological, gastrointestinal tract, and neural toxicities related to chemotherapy might be significant factors in the development of severe fatigue, and suggested that fatigue could become a dose-limiting factor during chemotherapy. According to the logistic regression analysis, breast cancer patients with no dose reduction were 22.3 times more likely to develop severe fatigue than patients with dose reduction. Wyatt et al. [68] aimed to determine the relationship between chemotherapy interruption and the severity of associated symptoms. They found that the main reason for dose reduction or stoppage was disease progression. In other words, clinical judgment mainly determined the ability of these patients to continue medical therapy, while symptom-related reasons accounted for only 24% of withdrawals [68]. Furthermore, our results showed a statistically significant association between the severity of fatigue and chemotherapy dose delay. Logistic regression indicated that patients who did not experience dose delays were 2.86 times less likely to develop severe fatigue than those who experienced dose delays. This finding contradicts an earlier study that found no association between fatigue severity, chemotherapy dose delay, and dose reduction [68]. Wyatt et al. [68] also reported that pain severity (the main factor associated with fatigue in this study), was a predictor of dose delay or reduction in 385 breast cancer patients. Other studies found that the severity of pain depended on the severity of metastasis, which could indicate to an oncologist that it might be necessary to modify a dose to alleviate a terminal patient's fatigue levels [69,70].

Overall, the findings of our study suggest that fatigue among breast cancer patients was associated with demographic factors (Malaysian breast cancer survivors who suffered from fatigue were mostly Malay), chemotherapy-related factors (number of regimens, dose delay or dose reduction, receiving docetaxel), and advanced cancer stage. Thus, oncologists and health care professionals should pay particular attention to this specific group of patients. Future research should study additional variables related to fatigue following breast cancer treatment and their impact on QOL over time. Other factors, such as age, menstrual status, employment status, marital status, and type of chemotherapy were not significantly associated with the prevalence of severe CRT.

Conclusion

Fatigue is an important health issue influencing QOL among breast cancer patients. This study provided baseline information on the effect of fatigue on the QOL of Malaysian breast cancer patients. This study also demonstrated that the patients experienced CRF in different ways, and a deeper assessment is therefore needed to identify the main factors associated with fatigue. Appropriate treatments for

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cancer patients suffering from fatigue are important. The results we obtained showed a strong correlation between QOL and fatigue among breast cancer patients receiving chemotherapy. Since pharmacological medications are used widely in many countries including Malaysia, encouraging clinicians to consider a non-pharmacological management course may play an important role in the treatment outcome and QOL of cancer patients. We hope that these findings will contribute to a better understanding of CRF among cancer patients and facilitate the recognition, evaluation, monitoring, and documentation of prompt treatment.

Strengths of the Study

A major strength of this study is that it involved a moderate sample size of 172 breast cancer patients with no missing data on the fatigue subscales of the FACIT-F and BFI. Since it was conducted at multiple hospitals, the results could be used to standardize and improve clinical practice across multiple cancer treatment centers. Moreover, the patients recruited for the study were at different cancer stages, which provided a heterogeneous study population. This study also used credible questionnaires such as the FACIT-F and BFI scales, which were simple and easy to understand. The time it took to complete the questionnaires was no more than 10 minutes, which was very convenient for all respondents.

Notes

Ethics Approval

The research protocols and procedure of informed consent were approved by research ethics committee of Universiti Teknologi MARA (REC/392/19), Institute Kanser Negara (IKN/500-5/1/25 JId 4 (18), Hospital Kuala Lumpur (HCRC.IIR-2019-07-163), University Malaya Medical Centre & Medical Research Ethical Centre (MREC) (NMRR-18-3902-45218). Researcher adhered to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines. Participants were briefed about the purpose of the study, and informed consent was obtained from all participants involved in the study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

Data and materials are available upon request.

Additional Contributions

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Original Article

The 100 top-cited articles on scrub typhus: a bibliometric analysis

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ABSTRACT

Objectives: The aims of this study were to analyze the characteristics of the 100 top-cited articles on scrub typhus (ST), and to assess the present research landscape and future research directions using bibliometric analysis.
Methods: Web of Science was used to conduct a bibliometric analysis of the 100 top-cited articles on ST. The articles were analyzed by publication year, number of citations, document type, journals, keywords, institutions, country of origin, and authorship.
Results: The top 100 articles on ST were published between 1945 to 2017. The number of citations ranges from 39 to 227 and the interquartile range was 35.5. The United States published the highest number (n=21) of articles. Mahidol University was the most prolific institution in terms of articles (n=14). The *American Journal of Tropical Medicine and Hygiene* was the journal with the most articles (n=14), and Paris DH was the most productive author in terms of the Hirsh-index, which was 10 for that author. The study revealed a significant correlation between the total number of citations and the number of authors (r=0.668, $p<0.001$), number of institutions (r=0.692, $p<0.001$), number of years since publication (r=0.869, $p<0.001$), and number of countries involved (r=0.963, $p<0.001$).
Conclusion: The findings of this study provide landmarks in the publication and citation frequency of the most influential articles on ST. In addition, this study provides useful information for readers and health policy-makers in evaluating the literature on ST.

Keywords: Bibliometrics; Citation analysis; Scrub typhus

Introduction

Scrub typhus (ST), also known as tsutsugamushi disease [1], is a frequently neglected tropical disease most often transmitted through the bites of chiggers in rural areas [2]. The disease has been reported to be responsible for causing acute febrile illness, which is a serious public health burden throughout the wide endemic region known as the “tsutsugamushi triangle” [3].

More than 1 billion residents of rural areas across all age groups are estimated to be at risk, with approximately 1 million new cases reported annually [4,5]. Although there has been marked progress in antibiotics such as doxycycline, tetracycline, and chloramphenicol, which serve as the first-line treatment for ST, the risk of ST infection and reported cases have increased every year [6]. This suggests an urgent need for novel research regarding the development of an effective antibiotic and vaccine for the prevention and control of ST [7].

Bibliometric analysis can provide a macroscopic overview of a large volume of scientific literature in terms of historical background and help identify the most influential authors, journals, countries, institutions, and references in the historical development of scientific research in any field [8]. The use of bibliometrics as a technique can also help to identify a variety of research themes, illuminate the multidisciplinary character of a research domain, and determine research gaps, future research directions, and leading trends within in any particular field [9]. In addition, the technique enables assessment of active and influential authors, journals, countries, organizations and institutions in a given field, as well as annual publication trends [10].

Although there has been an increase in the amount of scientific research on ST, the disease is still remarkably neglected relative to other tropical diseases [11]. Today, more than 80 years after the end of the Second World War, there is still no effective human vaccine against ST infection [12], which may be due to the multiple antigenic strains of *Orientia tsutsugamushi* [13]. Thus, we applied bibliometric methods, which have been widely used by researchers across diverse scientific research fields, to assess and evaluate the development of the field and research trends in the study of ST since the end of World War II [9,14,15].

The purpose of this study was to perform a bibliometric analysis of the 100 most-cited articles on ST indexed in the Web of Science (WoS) from 1900 to December 2020. To our knowledge, this is the first bibliometric study conducted on the 100 most-cited ST articles.

Materials and Methods

Study Design and Data Source

We used the results of a search within the WoS database (Clarivate Analytics, Philadelphia, PA, USA) for the baseline data used in this study [16,17]. Bibliometric analyses have been undertaken in various research fields to monitor and evaluate the growth of scientific output and to provide support for designing suitable policies and making public health decisions [15–17]. Science Citation Index Expanded (SCIE) and Science Citation Index (SCI) were both used to identify the top 100 most-cited articles on ST.

Search methodology

As in other bibliometric studies [10,18], the overall searchz was conducted in a single day to avoid the possibility of daily citation updates to the database interfering with the results and leading to minor statistical changes over time [19]. Our search strategy was to use specific keywords on ST, which were obtained from the Medical Subject Headings (MeSH) index of biomedical literature (https://meshb.nlm.nih.gov/search). We restricted our search to the presence of keywords in the title (titles including: “Orientia tsutsugamushi infection*” or “Tsutsugamushi disease*” or “Tsutsugamushi fever*” or “Scrub typhus*”) and used the largest time span allowed in the WoS search function (“all years [1990–2020]”) (search date December 10, 2020). Only original articles and reviews were used in this study, while editorials, proceedings, corrections, meeting abstracts, news items, letters, notes, early access publications, and reprints were excluded from our final dataset.

The search was restricted to articles published in English. The entire retrieval and data extraction process was conducted by 2 independent researchers (THM, JK).

The eligible articles were arranged in decreasing order of their citation count, after which the 100 top-cited articles were downloaded in CSV format, plain text format, and tab-delimited (win) format for further analysis. The following characteristics were considered in our analysis: publication year, citation count, authorship, affiliation (institution and country), journal name, and keywords. The journal impact factor (JIF) for each journal was obtained from WoS through manual search.

Statistical Analysis

Bibliometric analysis was used to examine the production of scientific research in the ST field. The distribution of the most productive countries, institutions, authors, journals, and keywords, as well as impact factor and total global citations, were analyzed using HistCite and bibliometrix, an R tool for comprehensive science mapping analysis [20]. Research collaborations between authors, countries, and organizations were mapped using VOSviewer ver. 1.6.6 [21]. Given the distribution of variables and the presence of outliers, we preferred to use the median, range, and interquartile range (IQR) to describe some variables since these measures are less affected by extreme values [10].

For citation analysis, the Hirsh-index (h-index) was used, which is a measure of both the number of publications on ST and the number of citations they received, with higher h-index values suggesting a higher impact [19]. In addition, GraphPad Prism ver. 6 (GraphPad Software, San Diego, CA, USA) and IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA) were used for the statistical analysis. Spearman correlation coefficients were used to evaluate the associations between the number of citations and year of publication, authors, institutions, JIF, and countries. p of less than 0.05 were considered to indicate statistical significance.

Results

General Information

The study identified 1,217 articles from 1900 to 2020 during the initial WoS search, and the 100 top-cited articles were identified after restricting the results to articles written in English. The majority of articles in the top 100 were original research articles (n = 88), with a total of 5,632 citations. The remaining entries were reviews (n = 12), which had a total of 392 citations. Altogether they had an h-index of 63. Publication years ranged from 1945 to 2017. The 100 most-cited articles were published in 49 journals by authors from 21 countries. In total, 392 authors, approximately 3.92 per document, contributed to the top 100 articles. The general characteristics of the metadata are presented in Table S1.

Years of Publication

As seen in Figure 1, a continuous upward trend was observed in the citation of ST articles after 1975. The number of articles increased along with the number of citations reported for each year during the study period. Among the top 100 articles, the majority (n = 63) were published between 1990 and 2017, with the greatest number of highly cited ST articles (n = 40) being published between 2005 and 2017.

The 100 Most-Cited Articles

The 100 most-cited articles in the field of ST and the number of citations, year of publication, and adjusted citation index (ACI) are presented in Table S2. The overall number of citations of the 100 most-cited articles was 6,994, with a median of 56, range of 39 to 227, and IQR of 35.5. According to the global citations, the top-ranking article was published in 2003 by Watt and Parola [1] on ("Scrub Typhus and Tropical Rickettsioses"), followed by the 2009 article of Kelly et al. [3] entitled "Scrub Typhus: The Geographic Distribution of Phenotypic and Genotypic Variants of *tsutsugamushi*," both of which were cited more than 200 times.

In addition, the 100 most cited articles were indexed in many research categories including Public, Environmental and Occupational Health; Tropical Medicine; General and Internal Medicine; Microbiology; and Pathology among others.

Journal Citation and Impact Factor Analysis

The top 100 articles were published in 49 different journals. Fourteen journals that published at least 2 articles are

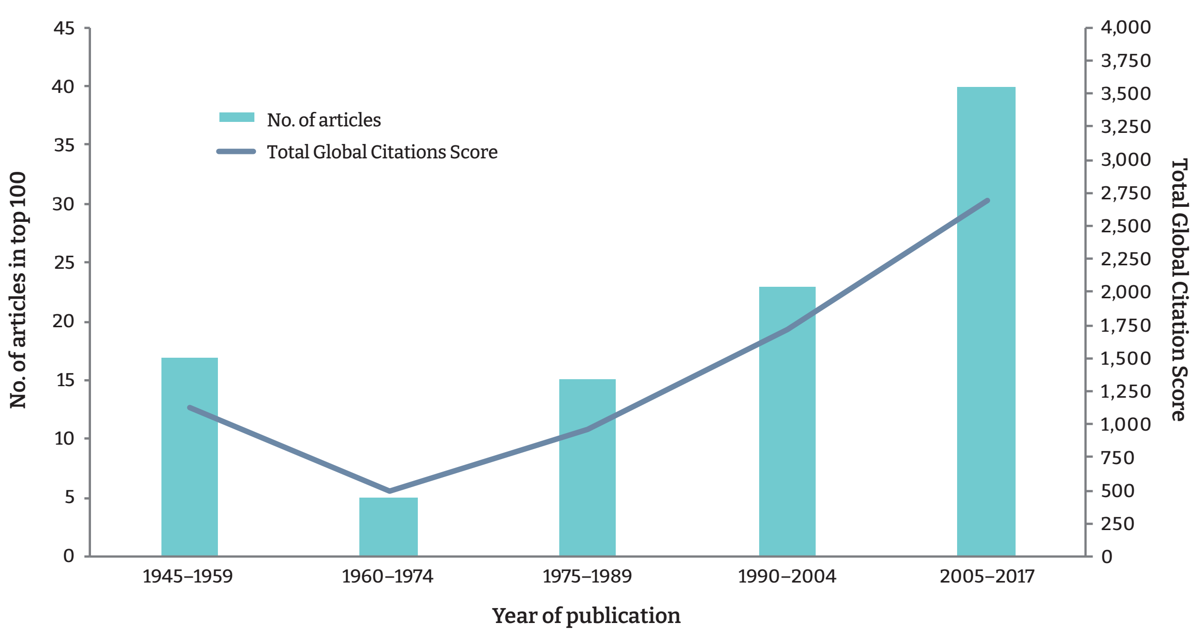

Figure 1. Graph showing the number of scrub typhus articles and Total Global Citations Score by year.

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shown in Table 1. These 14 journals altogether published 65 of the 100 top-cited ST articles. The *American Journal of Tropical Medicine and Hygiene*, with 14 articles (*n*), a median citations per article (MCA) of 55.0, and an IQR of 39 was the most represented journal, followed by *Clinical Infectious Diseases* (*n*, 7; MCA, 68.0; IQR, 77), and *Infection and Immunity* (*n*, 7; MCA, 59.0; IQR, 44). Notably, *The Lancet*, a journal with a JIF of over 60, published only 3 of the 100 top-cited articles on ST.

The earliest top-cited article was published in 1969 in *Transactions of the Royal Society of Tropical Medicine and Hygiene*, which published another one of the top 100 articles as recently as 2004.

Authorship and Institution Analysis

We identified 392 authors who contributed to the 100 top-cited articles. In terms of authorship, 13 authors contributed to 5 or more of the 100 top-cited articles on ST. The most productive author was Paris (h-index, 10; MCA, 73; IQR, 70), with 4 first-authorships and 10 articles in the top 100 (Table 2). Thirteen institutions contributed 3 or more of the top 100 articles, with Mahidol University in Thailand being the most prolific (h-index, 14; MCA, 60; IQR, 40), followed by the University of Oxford in England (h-index, 10; MCA, 60; IQR, 40) (Table 3).

Country of Origin

The countries with 2 or more top-cited articles, in terms of both single-country publications (intra-country collaborations), and multi-country publications (inter-country collaborations), are presented in Figure 2. The 100 most-cited ST articles originated from 21 countries, of which 9 countries originated more than 2 articles. The United States (US) was the most productive country with 21 articles, followed by South Korea and Thailand, both with 12 articles.

Keyword Analysis

The evaluation of keywords in terms of their frequency is shown in Figure 3. The analysis of author's keywords (Figure 3A) revealed the most popular themes in the diverse literature on ST. We found that 'scrub typhus' (*n* = 14), '*O. tsutsugamushi*' (*n* = 10), 'Rickettsia' (*n* = 4), 'children' (*n* = 2), and 'clinical manifestations' (*n* = 2) were the most frequent abstract keywords (Figure 3B). Among the top 100 KeyWords Plus results (Figure 3C) were 'doxycycline,' 'diagnosis,' 'polymerase chain reaction,' 'infection,' and 'outbreak,' among others.

Bibliographic Coupling Analysis

We used VOSviewer software to explore the bibliographic coupling (BC) between the authors, countries, and institutions that contributed to the 100 top-cited articles on ST (Figure 4). For BC analysis of authors, a minimum of 2 instances of authorship was required to meet the search criteria, and 72 authors reached this threshold. The top authors based on the number of links (L) and total link strength (TLS) were Paris (L, 70; TLS, 3,982), followed by Richards (L, 71; TLS, 3,019), Dasch (L, 69; TLS, 1,379), and Shirai (L, 65; TLS, 1,300) (Figure 4A). For the BC analysis between

Table 1. Journals that published at least 2 of the 100 most-cited scrub typhus papers

SCR	Source journal (*n* = 49)	Articles in top 100	TGCS (R)	MCA	IQR	2019 IF	Quartile[a)]	Publication[b)]
1st	*American Journal of Tropical Medicine and Hygiene*	14	965 (1)	55.0	39	2.126	Q2	1952–2013
2nd	*Clinical Infectious Diseases*	7	627 (2)	68.0	77	8.313	Q1	1997–2009
3rd	*Infection and Immunity*	7	461 (3)	59.0	44	2.970	Q2	1967–1982
4th	*Journal of Clinical Microbiology*	6	277 (7)	42.5	14	5.897	Q1	1977–2010
5th	*American Journal of Hygiene*	5	334 (4)	69.0	10	NA	NA	1945–1952
6th	*Plos Neglected Tropical Diseases*	5	315 (5)	63.0	11	3.885	Q1	2011–2017
7th	*Emerging Infectious Diseases*	4	235 (10)	27.5	38	6.259	Q1	2006–2016
8th	*Transactions of the Royal Society of Tropical Medicine and Hygiene*	4	258 (9)	55.5	23	1.868	Q3	1969–2004
9th	*The Lancet*	3	314 (6)	84.0	114	60.390	Q1	1996–2020
10th	*Antimicrobial Agents and Chemotherapy*	2	139 (11)	69.5	19	4.904	Q1	1995–2007
11th	*Current opinion in Infectious Diseases*	2	275 (8)	137.5	179	4.577	Q1	2003–2016
12th	*International Journal of Infectious Diseases*	2	112 (13)	56.0	26	3.202	Q2	2013–2014
13th	*Japanese Journal of Infectious Diseases*	2	112 (13)	56.0	8	3.202	Q4	2005–2006
14th	*Tropical Doctor*	2	118 (12)	59.0	38	0.523	Q4	2006–2010

SCR, Standard Competition Ranking; TGCS, Total Global Citation Score; MCA, median citations per article; IQR, interquartile range; IF, impact factor; NA, not available.
[a)]Journal quartile range. [b)]Time span: publication year for reported authors.

Table 2. Authors who contributed to at least 5 articles of the 100 most-cited scrub typhus papers

SCR	Author (*n* = 392)	h-index	Authorship position			TGCS	MCA	IQR	Publication year[a)]
			First	Second	Third or last				
1st	Paris DH	10	4	1	5	789	73	70	2007–2017
2nd	Osterman JV	9	0	5	4	579	46	43	1976–1982
3rd	Smadel JE	8	6	2	0	545	67	29	1948–1952
4th	Blacksell SD	7	2	1	4	518	57	80	2006–2016
5th	Abraham OC	6	0	2	4	365	56	37	2006–2015
6th	Ley HL	6	0	3	3	407	67	34	1948–1952
7th	Shiral A	6	1	3	2	397	64	43	1976–1983
8th	Chierakul W	5	1	2	2	259	44	15	2004–2011
9th	Dasch GA	5	1	0	4	368	50	9	1979–2006
10th	Day NP	5	0	0	5	348	57	35	2007–2012
11th	Richards AL	5	1	1	3	434	55	24	1997–2016
12th	Traub R	5	1	1	3	399	65	34	1948–1974
13th	Watt G	5	5	0	0	588	84	114	1996–2003

SCR, Standard Competition Ranking; h-index, Hirsh-index; TGCS, Total Global Citation Score; MCA, median citations per article; IQR, interquartile range.
[a)]Time span: publication year for reported authors.

Table 3. Institutions originating 3 or more of the 100 most-cited scrub typhus papers

SCR	Institution, country (*n* = 129)	Article in top 100[a)]	TLSC	TGCS	NA	MCA	IQR	Publication[b)]
1st	Mahidol University, Thailand	14	35	1,004	100	60	40	2004–2017
2nd	University of Oxford, England	10	31	715	72	60	40	2004–2017
3rd	University School of Nashville, USA	8	52	627	72	58	42	1973–2011
4th	Walter Reed Army Institute of Research, USA	8	39	550	69	68	38	1976–2000
5th	Christian Medical College & Hospital, India	6	17	365	46	58	37	2006–2015
6th	Chosun University, South Korea	4	13	252	32	57	31	2006–2010
7th	Seoul National University, South Korea	4	15	319	20	59	78	1993–2001
8th	Armed Forces Research Institute of Medical Sciences, USA	3	16	332	17	58	180	2000–2003
9th	Haenam General Hospital, South Korea	3	13	161	28	48	19	2006–2007
10th	Mahosot Hospital, Laos	3	7	270	13	83	61	2010–2017
11th	Seonam University, South Korea	3	13	161	28	48	19	2006–2007
12th	University of Texas Medical Branch, USA	3	6	230	33	68	74	2010–2017
13th	Walter Reed National Military Medical Center, USA	3	20	194	32	60	34	1995–2000

SCR, Standard Competition Ranking; TLSC, Total Local Citation Score; TGCS, Total Global Citation Score; NA, number of authors; MCA, median citations per article; IQR, interquartile range.
[a)]Total number of citations. [b)]Time span: publication year for reported authors.

countries, at least 2 must have originated in a country for it to be included in the analysis. Thirteen countries met this threshold and were visualized as 3 clusters. The country with the highest TLS was Thailand (L, 75; TLS, 3,631), followed by the US (L, 2,328; TLS, 3,468), England (L, 865; TLS, 2,667), South Korea (L, 793; TLS, 1,239), India (L, 601; TLS, 1,188), and Laos (L, 411; TLS, 1,137) (Figure 4B). For the BC analysis between institutions, at least 2 articles were required to have originated from an institution to be included, which resulted in 30 institutions visualized as 4 clusters. Mahidol University had the highest number of collaborations (L, 29; TLS, 2,783), followed by Naval Medical Research Center (L, 29; TLS, 999), and Christian Medical College & Hospital (L, 29; TLS, 810) (Figure 4C).

Funding Agencies

As shown in Figure 1, the annual number of articles on ST increased gradually, from just 23 in the 14-year range of 1990 to 2004, to 40 in the 12-year range of 2005 to 2017. This phenomenon may be the result of increased financial support from various funding sources such as Wellcome Trust, Global Emerging Infections Surveillance and Response System, and the United States Army Medical Research and Materiel Command and Naval Medical

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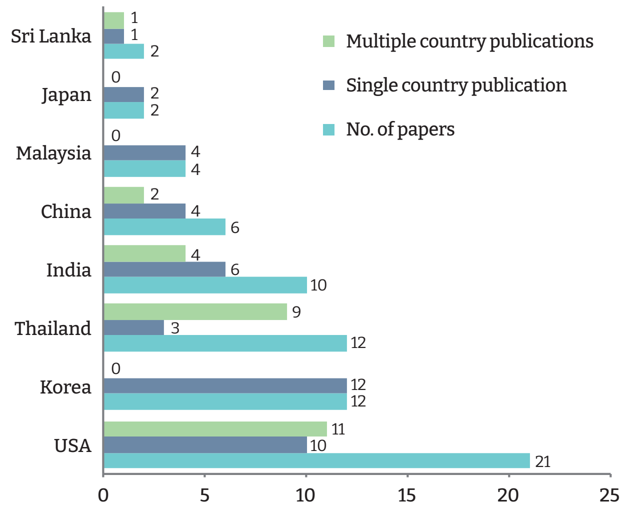

Figure 2. Most productive and influential countries on scrub typhus research with 2 or more articles, including both single-country publications (intra-country collaboration) and multiple-country publications (inter-country collaboration).

Research Center (Table S3). These, as well as other funding institutions, supported a total of 20 of the 100 top-cited ST articles.

Factors Influencing Citations Scores

The factors that determined the number of citations of the top-cited articles on ST are presented in Table 4. We explored possible correlations between the number of citations and study variables such as number of authors, number of institutions, years since publication, JIF, and number of countries. We observed a strong positive association between the citation score and number of years since publication ($r = 0.869$, $p < 0.001$), number of authors and number of citations ($r = 0.668$, $p < 0.001$), number of institutions and citation score ($r = 0.692$, $p < 0.001$), as well as number of countries and number of citations ($r = 0.963$, $p < 0.001$). However, there was not a significant correlation between the JIF and citations ($r = 0.158$, $p = 0.277$).

Discussion

The study provided insights into the trends of the most influential ST publications over the past 100–120 years using comprehensive bibliometric tools [10,17,18]. All 100 top-cited ST publications were written in English, and the majority were from US institutions, which produced more articles than those of any other country [18]. This may be because the US has a higher gross national product than other countries, which enables US researchers to be the more productive in ST research. Of the 100 most-cited articles, a total of 21 were from the US, followed by 12 articles from South Korea and 12 articles from Thailand [22].

A total of 392 authors from 21 countries contributed to the 100 top-cited articles with a citation range of 39 to 227 (MCA, 56; IQR, 35.5). The top 3 most-productive authors in this study were Paris, Osterman, and Smadel, who collectively contributed 27 articles as the first, second, or third or last author, and accrued a total of 1,913 citations. Overall, 13 key authors contributed to 82% of the top 100 articles in the ST field and were referred to in 5,996 citations during our study period. This number of citations, however, is less than is reported in some other medical fields such as islet transplantation, where the citation count ranged from 146 to 2,988 [23]. The difference in citation count could be a result of the number of researchers contributing to specific medical fields [24], or possibly due to there being less research interest in the field of ST compared to other diseases [11].

In addition, open access status may be another important factor in attracting citations, since open access articles are freely accessed and tend to be more cited than self-archived or closed access articles [24,25].

The most-cited and influential paper on ST was a review that discussed several key aspects of ST and tropical rickettsioses, published in 2003 in the *Journal of Current Opinion in Infectious Diseases*. The article indicated that modern developments in molecular taxonomic methods have led to a reclassification of rickettsial disease, and it estimated that 1 billion people are at risk, with 1 million cases occurring annually. Additionally, the review noted that the lack of professional or non-specialist physicians and disease misdiagnoses raise more questions than answers, implying the need for much more research on ST. As a result, this article became the most influential within the field, with 227 citations [1].

The second most-cited article received 216 citations and focused on the geographic distribution of phenotypic and genotypic variants of *O. tsutsugamushi*, published in *Clinical Infectious Diseases* as a review article. Our study indicates that a minority of articles on ST are responsible for the majority of citations, which is a similar result to other published bibliometric studies [18].

Other top-cited articles discussed key aspects and discoveries in ST research such as antibiotic use in the treatment of ST, including, for example, articles on chloromycetin [26], doxycycline compared to azithromycin [27], and chloramphenicol and tetracycline to treat patients with ST infection [28].

As shown in this study, there was a significant correlation between the number of citations and the number of years

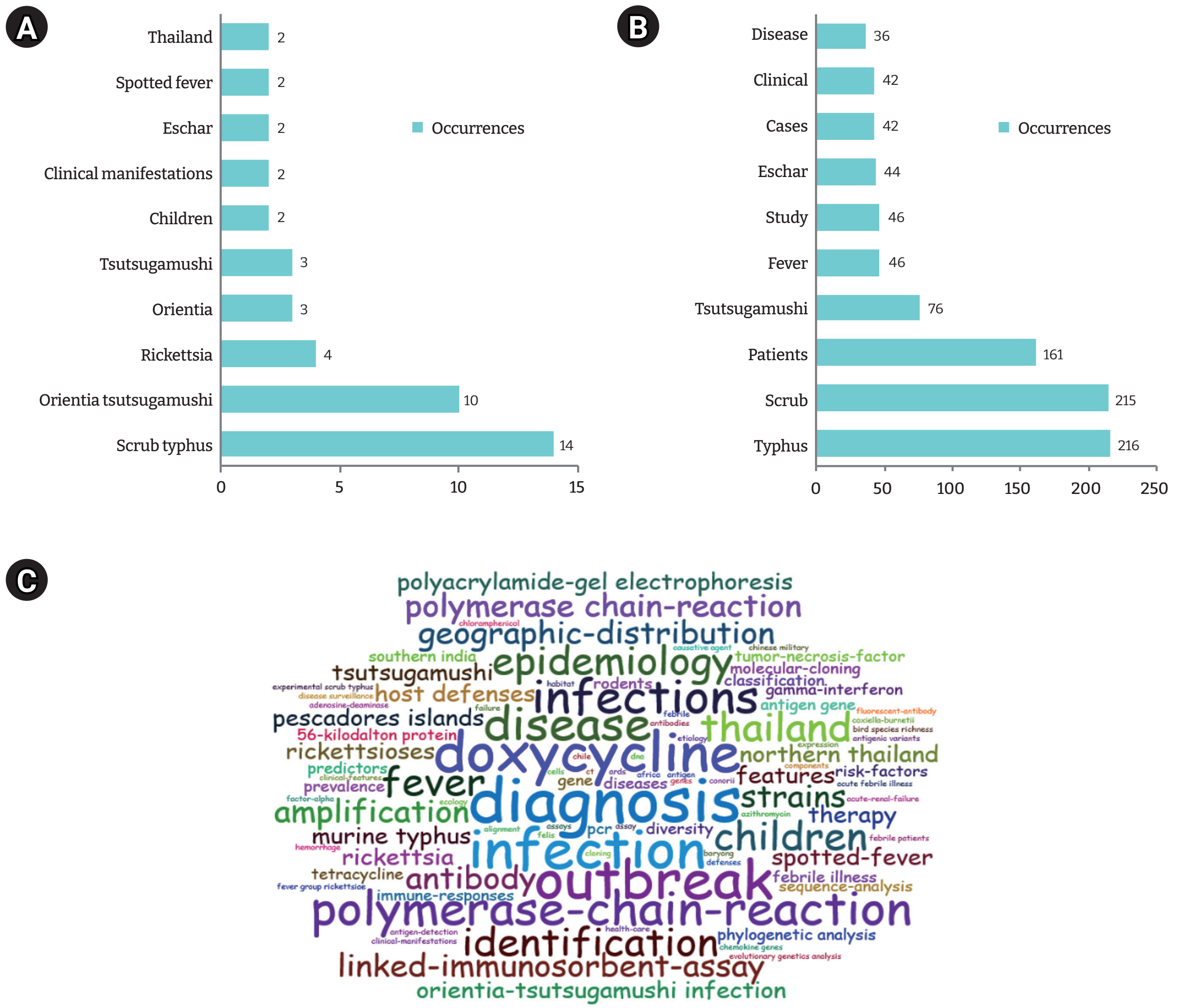

Figure 3. Keyword occurences of (A) author's keywords and (B) abstract keywords. (C) Word cloud visualization of KeyWords Plus.

since publication. This finding differs from bibliometric findings from other fields such as gastroenterology and hepatology, for which no significant correlations were found between the number of citations and the number of years since publication [17]. In addition, significant correlations were found between the number of institutions involved, the number of countries, and the number of citations. Similar associations were previously described by Azer and Azer [17] in 2016.

Across the 49 different journals that published ST research, the top-cited articles were published not only in journals with a high impact factor, but also in lower-impact journals [29]. Previous bibliometric studies have shown that the impact factor of particular journals is considered the best indicator used for journal citations. Our study also demonstrated that the JIF does not necessarily influence the citation performance of articles, and it is possible that highly cited articles can be published in journals with a low JIF. Examples of such articles are included in our references [28,30–34]. This indicates that most researchers focused on other factors aside from JIF when publishing ST research.

Regarding journal productivity, the *American Journal of Tropical Medicine and Hygiene* published the most papers related to ST. This can be seen as a pioneering journal that gave ST research particular attention. Furthermore, most of these journals belonged to the first and second quartiles,

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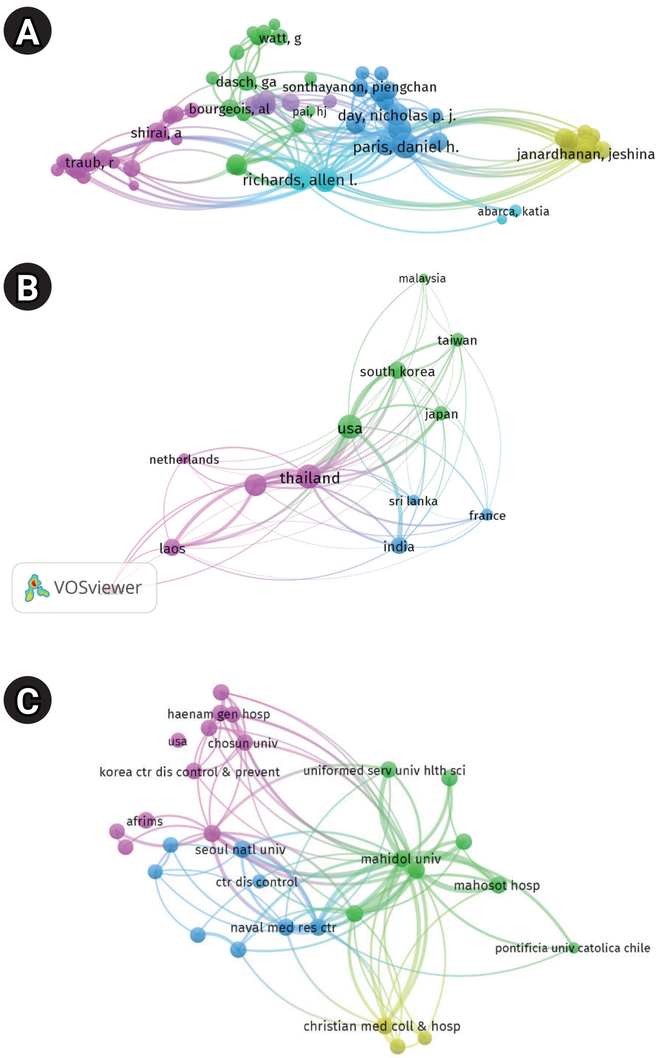

Figure 4. Bibliographic coupling of authors (A), countries (B), and organizations (C) that contributed to the 100 most-cited articles in scrub typhus research.

which confirms the quality of the ST research being published by these journals.

Our study shows that only 20% of the top-cited articles on ST reported funding. As previously reported, funding is a potential mechanism to encourage and increase productivity within a given field. Thus, to enable researchers to carry out more ST research in key fields such as the development of vaccines for ST prevention and control, increased funding is crucial [18].

The analysis of keywords indicated that the top-cited articles on ST covered various key aspects of ST including diagnosis, diseases symptoms, infection, its effect on children, clinical treatments, and advance diagnostic methods such as the use of polymerase chain reaction. These keywords

Table 4. Associations between citations and study variables

Characteristic	Research	Spearman r	*p*
No. of authors	392	0.668	< 0.001
No. of institutions	129	0.692	< 0.001
No. of years since publication	41	0.869	< 0.001
Journal impact factor (2019)	49	0.158	0.277
No. of countries	21	0.963	< 0.001

highlighted future trends and popular topics in ST research.

The institutions which produced the most research were primarily located in Asian countries such as Thailand, India, and South Korea, among others. This reflects the burden of the disease, as ST is endemic in the Asia-Pacific region and therefore influences research efforts in these countries. However, contributions from other regions and countries such as the US show the worldwide scope of ST research.

In terms of link strength, the 100 most-cited studies were produced through collaboration among different authors, countries, and institutions. From one perspective, this could imply the importance of collaborative efforts and partnerships in achieving research advances in the field and making them available in well-known databases. The results of the co-authorship network show the current state of collaboration and the most influential authors who produced the top-cited studies on ST. Evidence from the network analysis reveals a significant level of collaboration among authors in the field, visualized in 3 broad clusters. Collaboration is vital, as it enables the sharing of knowledge and scientific findings such as genome sequences and possible development of an ST vaccine.

Strengths and Limitations

By using bibliometric and visualization analyses, the present study furnishes deep insights into the 100 most-cited articles on ST. However, some limitations must be addressed. First, we analyzed results from a single database (WoS). Thus, there is a possibility of having missed key top-cited articles that are only available in other databases such as Scopus, PubMed, and Google Scholar. Therefore, the results of our assessment might not be fully comprehensive. Second, we only included studies published in the English language and overlooked studies published in other languages, which may themselves be highly cited. Third, it was not possible to search by category or to search for the top-cited articles in relevant fields, either manually or from the WoS website.

Conclusion

This study is the first bibliometric analysis of the 100 most-cited articles on ST indexed in WoS. We found that the trend and growth of most-cited articles on ST had a significant increase. The majority of articles originated in the US and various Asian countries, which showed a significant contribution to new research in the field, with strong research collaboration across authors, countries, and organizations. The *American Journal of Tropical Medicine and Hygiene* was the most prolific publisher of ST articles in terms of journals. Mahidol University in Thailand led the list of the most prolific institutions producing ST research. An article's citation count was significantly correlated with the number of authors, institution, years since publication, and countries involved, but not with JIF. In addition, only 20% of articles received funding, so adequate funding and institutional capacity-building are required to increase the impact of future developments in ST research. These findings may provide new insights for researchers and health policy-makers, thereby enabling a better understanding of the ST disease globally.

Supplementary Material

Table S1. Characteristics of metadata; **Table S2.** The 100 most-cited articles on scrub typhus; **Table S3.** The funding agencies that contributed to the 100 most-cited scrub typhus articles. Supplementary data is available at https://doi.org/10.24171/j.phrp.2021.12.2.10.

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 the data supporting the results of this study are included in the article and the supplementary file. The raw data on ST can also be directly obtained from the Web of Science Core Collection (https://webofknowledge.com/) using the appropriate search query.

Additional Contributions

The authors are grateful to the Southeast University electronic library for providing facilities and library resources for accessing the routine surveillance data used in this study.

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Instruction for authors

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