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PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

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Editorial

Which infectious diseases are currently posing problems in the Republic of Korea? One out of every two tuberculosis patients is over 65 years old

Jong-Koo Lee

National Academy of Medicine of Korea, Seoul, Republic of Korea

In this month's issue, we have published papers highlighting the importance of focusing on tuberculosis, the resurgence of coronavirus disease 2019 (COVID-19), and the post-COVID-19 increase in measles cases.

First, it is essential to evaluate whether the goal of eradicating tuberculosis by 2030 can be achieved. Our country has made significant strides in tuberculosis management compared to other countries globally. However, as of 2023, there are still 20,000 new cases and 1,000 deaths annually. The national tuberculosis management system, initiated in 1962, led to a dramatic decrease in the number of patients through nationwide screenings, early detection and treatment, and ongoing management via health centers. The effectiveness of these strong vertical health programs began to diminish when, following the expansion of national health insurance, private medical institutions increasingly assumed the role of treating patients, necessitating a new management model. As the prevalence dropped to less than 1%, the nationwide tuberculosis survey was replaced by patient reporting. However, it took 10 years to generate accurate statistics until the tuberculosis management infrastructure in the private sector, including reporting of patient treatment outcomes, was established. Fortunately, after a pilot project in 2007, accurate statistics became available by promoting the Private-Public Mix program starting in 2011. Consequently, the incidence of new cases in 2011 was confirmed to be 78.9 per 100,000 population, decreasing to 30.6 in 2023. The total number of patients is decreasing at an annual average of 7.6%. With this rate of decrease, achieving the 2030 Goal, elimination of tuberculosis, appears challenging. Notably, the proportion of patients over 65 years old has risen to 57.9%, and there is a need for targeted measures for groups with high incidence rates, such as those with chronic diseases, low income, and coexisting conditions. Additionally, there is a need to enhance early detection programs for latent tuberculosis. One global challenge is resistance to anti-tuberculosis drugs. Fortunately, the number of patients with multidrug-resistant/ rifampicin-resistant tuberculosis was 551 in 2023, representing 2.8% of the total reported tuberculosis cases of 19,540, a slight increase from 2.7% in 2022, but the situation remains relatively well-managed. However, while only 1.8% of new patients are drug-resistant, the proportion among retreatment cases is 6.8%, which is 3.8 times higher, underscoring the importance of continuous management and prevention of treatment dropout. Additionally, the proportion of imported cases among total tuberculosis cases

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continues to rise, reaching 5.7%, highlighting the need for focused prevention and early detection of imported cases [1].

Second, the possibility of a resurgence of COVID-19 in the 2024–2025 season remains a concern. Recent World Health Organization data indicates that the global number of new weekly COVID-19 cases rose by 10% during the 28-day period from August 19 to September 15, 2024, compared to the preceding 28 days, with over 270,000 new cases reported. Similarly, the number of new weekly deaths increased by 11%, totaling 5,700 fatalities. However, these reported cases may not accurately reflect the true infection rates due to a global reduction in testing and reporting. Currently, the variant of interest JN.1 is the most reported globally, identified in 140 countries and accounting for 16.0% of sequences in week 37, down from 19.4% in week 34 [2]. Despite these figures, it seems unlikely that we will experience a surge on the scale of 2022. Nevertheless, it is crucial to prepare for a potential resurgence this winter by addressing previously neglected policies—enhancing primary care, home care, critical patient treatment in intensive care units, and addressing excess mortality and collateral damage among patients. Recommendations include stockpiling treatments and increasing vaccination rates for those over 65 years old, along with promoting simultaneous vaccination for influenza. Although current vaccination rates are 1.7 times higher and simultaneous influenza vaccinations are 3.3 times higher than during the same period last year, it is still too early in the vaccination period to be fully reassured [3].

Lastly, It is important to note that there have been worldwide outbreaks of vaccine-preventable diseases (VPDs) following the COVID-19 pandemic. Specifically, from 2021 to 2022, global coverage for the first dose of the diphtheria-tetanus-pertussis–containing vaccine increased from 86% to 89%, and for the first dose of the measles-containing vaccine from 81% to 84%. However, these figures have not returned to the pre-pandemic coverage levels of 90% and 86%, respectively, recorded in 2019. The recovery in vaccination coverage has been uneven across different regions and countries, with low-income countries experiencing slower progress. In response, implementing strategies to provide catch-up vaccinations throughout childhood could effectively mitigate the increased risk of VPD outbreaks due to years of reduced vaccination coverage [4].

In particular, outbreaks of VPDs such as measles and pertussis were addressed at the 33rd WPRO Technical Advisory Group on Immunization Programmes. Fortunately, in our country (the Republic of Korea), neither economic nor geographic barriers disrupted access to the healthcare system during the COVID-19 pandemic, and vaccination rates remained stable, supported by the recall-reminder information technology program. However, despite implementing routine immunization programs and supplementary immunization activities, along with the surveillance and detection of measles virus genotypes, there has been a resurgence in endemic measles virus transmission in countries such as the Philippines and Malaysia, as well as large-scale import-related measles outbreaks in countries such as the Republic of Korea and Japan, which recently declared measles elimination, due to overseas influx. Additionally, endemic measles virus transmission has continued in countries such as Mongolia and Cambodia, where measles is prevalent. Overall, however, a report stated: "Notable progress towards measles and rubella elimination has been made in the Western Pacific Region in the last 10 years, despite the region-wide measles resurgence in 2013–2016, the global measles resurgence in 2018–2019, and the COVID-19 pandemic in 2020–2023 [5].

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
Jong-Koo Lee has been the editor-in-chief of *Osong Public Health and Research Perspectives* since October 2021.

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Original Article

Molecular characteristics of drug-susceptible *Mycobacterium tuberculosis* clinical isolates based on treatment duration

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ABSTRACT

Objectives: In this study, we performed comparative genomic and transcriptomic analysis of clinical isolates of *Mycobacterium tuberculosis* collected from patients with drug-susceptible tuberculosis (DS-TB). The clinical isolates were categorized based on treatment duration: standard 6 months or >6 months.
Methods: Study participants were recruited from a 2016 to 2018 tuberculosis cohort, and clinical *M. tuberculosis* isolates were collected from the sputum of patients with tuberculosis. We analyzed the genome and transcriptome of the isolated *M. tuberculosis*.
Results: Genomic analysis revealed a specific non-synonymous single-nucleotide polymorphism in *pe_pgrs9* and *ppe34*, exclusive to the group treated for >6 months. Transcriptomic analysis revealed increased expression of various virulence-associated protein family genes and decreased expression of ribosomal protein genes and *ppe38* genes in the group treated for >6 months.
Conclusion: The identified genetic variation and gene expression patterns may influence treatment outcomes by modulating host immune responses, increasing virulence, and potentially contributing to persister cell formation in *M. tuberculosis*. This study provides insights into the genetic and transcriptomic factors associated with prolonged DS-TB treatment. However, our study identified molecular characteristics using a small sample size, and further detailed studies are warranted.

Keywords: Clinical isolates; *Mycobacterium tuberculosis*; RNA sequencing; Whole-genome sequencing

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Introduction

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), which remains a major public health threat. However, the treatment of *M. tuberculosis* infections is a significant challenge. The World Health Organization (WHO) has estimated a treatment success rate of 85% in patients with drug-susceptible TB (DS-TB) who receive a 6-month treatment regimen consisting of 4 first-line TB drugs (i.e., isoniazid, rifampicin, pyrazinamide, and ethambutol) [1]. In general, the WHO does not recommend extending the duration of treatment beyond 6 months, as it does not significantly increase the efficacy of the drugs [2]. However, the treatment duration may need to be extended depending on the patient's age, comorbidities, and treatment progress [3].

Furthermore, the treatment is complicated by heterogeneity within *M. tuberculosis* populations [4,5]. Genetic diversity results in the formation of subpopulations within *M. tuberculosis* strains, and these subpopulations within a host can result from infection by multiple strains, reinfection with a new strain, or the microevolution of an infected strain within the host [6–8]. The heterogeneous *M. tuberculosis* subpopulations exhibit different phenotypes—for instance, the formation of persister cells, asymmetric cell growth and division, and variations at the transcriptional and posttranslational levels [9–11]. During pathogenesis, phenotypically diverse subpopulations exhibit varying levels of drug susceptibility and resistance, which is the primary reason for the prolonged treatment duration [9].

Persisters are a subpopulation without genetic resistance that temporarily halts their growth and sustains it in the presence of antibiotics and environmental stressors [10–15]. The presence of *M. tuberculosis* persister cells within the host hinders the effective eradication ability of therapeutic drugs and affects drug efficacy [16–18]. Several studies have been conducted to elucidate the mechanisms of persister formation. Transcriptome analysis of *M. tuberculosis* persisters revealed downregulation of metabolic and biosynthetic pathways and upregulation of toxin-antitoxin (TA) modules [10,19]. In addition, it has been shown that differential expression patterns of genes involved in stringent responses and catalase-peroxidase (*katG*) affect drug tolerance [20,21]. Using whole-genome sequencing and transcriptome analysis of the high persister mutants and clinical isolates of *M. tuberculosis*, a recent study showed that genes involved in lipid biosynthesis, carbon metabolism, TA systems, and transcriptional regulators are associated with persister formation [10]. Specifically, genetic variation of the genes involved in outer membrane lipid phthiocerol dimycocerosate biosynthesis increases drug tolerance [10,22].

HIGHLIGHTS

- This study investigated the genetic and transcriptional characteristics of *Mycobacterium tuberculosis* isolated from patients with drug-susceptible tuberculosis who underwent treatment for >6 months. The research identified key genetic variations in the form of a non-synonymous single-nucleotide polymorphism in *pe_pgrs9* and *ppe34*, as well as reduced expression of *ppe38* in the group treated for >6 months. Transcriptome analysis revealed an increase in *vapC26* expression and a decrease in the expression of rRNA and ribosomal protein genes in the group treated for >6 months. These features found in the prolonged treatment group suggest potential impacts on host immunity, treatment resistance, and bacterial persistence.

The persistence of the clinical isolates of *M. tuberculosis* has been confirmed after isolation from sputum samples *in vitro*. The isolation of *M. tuberculosis* clinical isolates from sputum samples requires several stages of subculture. The culture process can influence the population structure, such as variant genotypes and clonal composition, resulting in the loss of genetic diversity and modification of clinical specimens [23–25]. Moreover, drug treatment influences the population structure of *M. tuberculosis* [26]. Therefore, it is important to select the time point for isolation to properly characterize infected *M. tuberculosis*.

This study aimed to identify the molecular factors that contribute to prolonged DS-TB treatment using genomic and transcriptomic profiling. Clinical isolates of *M. tuberculosis* were collected from the first mycobacterial growth indicator tube (MGIT) culture medium inoculated directly into sputum samples to characterize the infected *M. tuberculosis*.

Materials and Methods

Patients, Samples, and Culture Conditions

Clinical isolates of *M. tuberculosis* were obtained from patients' sputum before the standard treatment regimen or 2 weeks after treatment. *M. tuberculosis* clinical isolates were identified from sputum samples using both Löwenstein-Jensen medium and the MGIT culture system. Acid-fast bacilli (AFB) staining with Ziehl-Neelsen stain and MPT64 antigen detection using Bioline TB Ag MPT64 (Abbott) were used to confirm positive culture isolates. AFB-stained samples or MPT64 detection-negative samples were assessed by polymerase chain reaction (PCR) using a PowerChek *M.*

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tuberculosis/nontuberculous mycobacteria (MTB/NTM) Real-time PCR Kit (Kogene Biotech). DS-TB and drug-resistant (DR)-TB were differentiated using GeneXpert MTB/RIF (Cepheid), GenoType MTBDR*plus* (Hain Lifescience GmbH), and traditional minimum inhibitory concentration measurements. In addition, 13 and 9 clinical isolates were subjected to genome and transcriptome analyses, respectively. The patient details are presented in Table 1. To maintain the population structure of the clinical isolates of *M. tuberculosis*, preserved sputum samples were directly inoculated into the MGIT after identification. The MGIT culture medium was collected by centrifugation at 4,000 rpm for 3 minutes. The harvested cultures were used to isolate genomic DNA and total RNA.

Genome Sequencing

Genomic DNA was isolated using a Quick-DNA Fungal/Bacterial Miniprep Kit (Zymo Research) as per the manufacturer's instructions. The TruSeq Nano DNA Kit (Illumina Inc.) was used to generate paired-end (2×150-bp) libraries. Whole-genome sequencing of the libraries was performed using an Illumina NovaSeq 6000 platform. Reads generated through sequencing were qualitatively validated and trimmed using Prinseq v0.20.4 [27]. Sequencing reads were aligned to the *M. tuberculosis* H37Rv reference genome (NC_000962.3) using CLC Genomics workbench 22.0 (Qiagen). This whole-genome sequencing project has been deposited in the National Center for Biotechnology Information (NCBI) Short Read Archive (SRA) and is accessible through the Bioproject accession number PRJNA887480.

RNA Sequencing

Total RNA was isolated using the RNeasy Plus Mini Kit (Qiagen) as per the manufacturer's instructions. RNA sequencing libraries were created using the TruSeq rapid SBS kit v4 (Illumina), and sequencing of the libraries was conducted using the HiSeq 2500 (Illumina) sequencing protocol. Quality validation and trimming of the reads were performed using FastQC v0.11.7 and Trimmomatic v0.38 [28], respectively. Paired-end reads (101 bp) were then mapped to the reference genome sequence of *M. tuberculosis* H37Rv (NC_000962.3) using CLC Genomics workbench 22.0 (Qiagen). The RNA sequencing data have been deposited in the NCBI SRA and are accessible through the Bioproject accession number PRJNA1010683.

Ethics Approval

This study was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (approval no: 2019-04-05-2C-A), and patients were recruited from a

Table 1. Clinical characteristics of DS-TB clinical isolates analyzed by genome and transcriptome sequencing

	Age (y)	Sex	TB treatment history	Pulmonary cavity	Chest X-ray	Initial AFB smear	TB RT-PCR	AFB smear at 2 mo	Treatment duration	Lineage	Categorization (mo)	Isolation time (W)	Analysis
CB030	73	Male	No	Negative	Positive	Positive	Positive	Positive	820	East-Asian	Treated > 6	0	RNA-Seq
CB050	38	Female	No	Negative	Negative	Positive	Positive	Negative	185	Euro-American	Treated 6	0	WGS, RNA-Seq
CB060	48	Male	Yes	Positive	Positive	Positive	Positive	Negative	336	East-Asian	Treated > 6	0, 2	WGS
CB131	32	Male	No	Negative	Positive	Positive	Positive	Positive	267	East-Asian	Treated > 6	0	WGS
CB213	83	Male	No	Negative	Negative	Positive	Positive	Positive	183	East-Asian	Treated 6	2	WGS, RNA-Seq
CN118	83	Male	Yes	Negative	Positive	Positive	Positive	Positive	246	East-Asian	Treated > 6	0	WGS
CN177	53	Male	Yes	Positive	Positive	Positive	Positive	Positive	607	East-Asian	Treated > 6	0, 2	WGS, RNA-seq
CN185	56	Male	No	Positive	Positive	Positive	Positive	Positive	197	Euro-American	Treated 6	0	RNA-Seq
CN272	55	Male	Yes	Positive	Positive	Positive	Positive	Positive	663	East-Asian	Treated > 6	0, 2	WGS, RNA-seq
IP004	70	Male	Yes	Positive	Positive	Positive	Positive	Negative	180	Euro-American	Treated 6	0	WGS, RNA-seq
IP006	81	Male	No	Positive	Positive	Positive	Positive	Negative	285	East-Asian	Treated > 6	0	WGS
IP016	22	Female	No	Negative	Positive	Positive	Positive	Negative	180	East-Asian	Treated 6	0	WGS, RNA-seq

DS-TB, drug-susceptible tuberculosis; TB, tuberculosis; AFB, acid-fast bacillus; RT-PCR, real-time polymerase chain reaction; RNA-Seq, RNA sequencing; WGS, whole-genome sequencing.

tuberculosis cohort from 2016 to 2018.

Results

Characteristics of DS-TB Patients

A total of 600 participants were screened from December 7, 2016, to October 8, 2019. Of these patients, 334 were excluded from the analysis because of NTM infection, TB without pulmonary involvement, death, transfer out, or withdrawal of consent (Figure 1). Among the remaining 266 patients, 132 were diagnosed with DR-TB and were excluded from the analysis. Of the 134 patients with DS-TB, 48 (35.8%) completed the standard 6-month treatment and 86 (64.2%) received >6 months of treatment. This indicates that the number of patients who received >6 months of treatment was almost twice the number of patients who completed the standard 6-month treatment.

Patient characteristics are described in Table 2. The mean age of patients treated with the 6-month regimen was 50.9 ± 19.9 years, and there were 26 females (54.2%) and 22 males (45.8%). In patients who were treated for >6 months, the mean patient age was 64.0 ± 19.5 years, with 37 females (43.0%) and 49 males (57.0%). In addition, 2 patients (4.2%) in the 6-month treatment group and 16 patients (18.6%) in the group treated for >6 months had a history of TB treatment. There were 24 patients (50.0%) with comorbidities in the 6-month treatment group and 55 patients (64.0%) in the group treated for >6 months. In the 6-month treatment group, 17 patients (35.4%) had pulmonary cavity positivity,

Table 2. Characteristics of enrolled patients with DS-TB

Characteristic	Treated with 6-mo regimen (*n* = 48)	Treated >6 mo (*n* = 86)
Median age (y)	49.5	71
Sex		
Female	26 (54.2)	37 (43.0)
Male	22 (45.8)	49 (57.0)
TB treatment history		
Yes	2 (4.2)	16 (18.6)
No	46 (95.8)	70 (81.4)
Comorbidities		
Yes	24 (50.0)	55 (64.0)
No	24 (50.0)	31 (36.0)
Pulmonary cavity		
Positive	17 (35.4)	37 (43.0)
Negative	31 (64.6)	49 (57.0)
Chest X-ray		
Positive	35 (72.9)	72 (83.7)
Negative	13 (27.1)	14 (16.3)
AFB smear at 2 months		
Positive	2 (4.2)	6 (7.0)
Negative	46 (95.8)	80 (93.0)

Data are presented as *n* (%).
DS-TB, drug-susceptible tuberculosis; TB, tuberculosis; AFB, acid-fast bacillus.

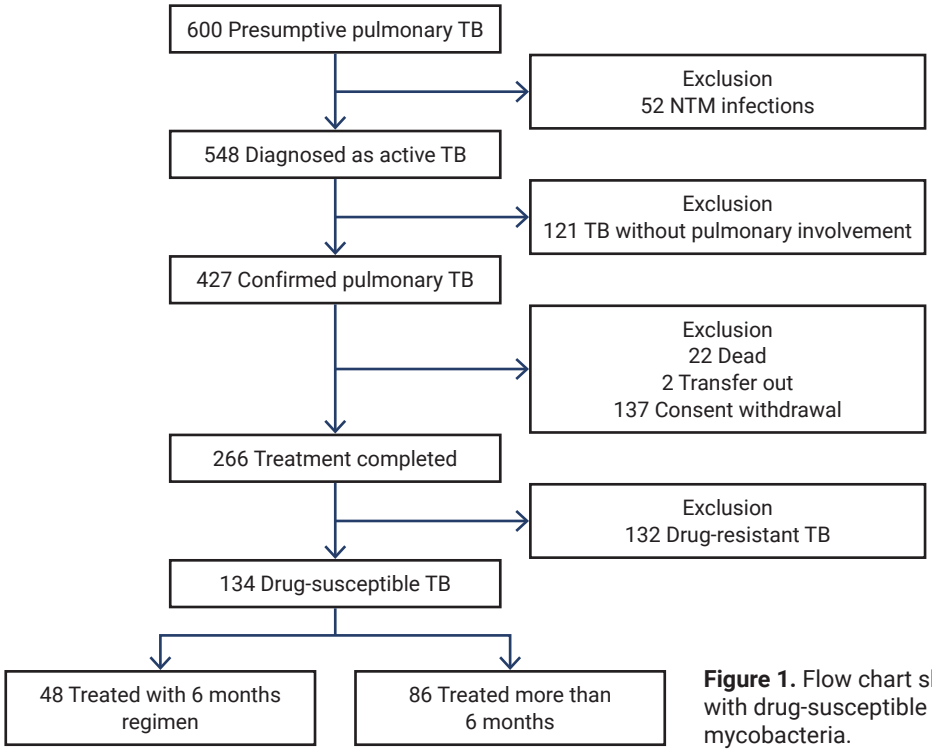

Figure 1. Flow chart showing the selection of participants with drug-susceptible tuberculosis (TB). NTM, nontuberculous mycobacteria.

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35 patients (72.9%) had chest X-ray positivity, and 2 patients (4.2%) had a positive AFB smear at 2 months. In the group treated for >6 months, 37 patients (43.0%) were positive for the pulmonary cavity, 72 patients (83.7%) were chest X-ray positive, and 6 patients (7.0%) had a positive AFB smear at 2 months.

Whole-Genome Sequencing Analysis of *M. tuberculosis* Isolated from Sputum Samples

We attempted to isolate *M. tuberculosis* from patient sputum samples collected 2 weeks after treatment for which bacterial culture was possible. *M. tuberculosis* could be isolated from the samples of 16 of the 134 DS-TB patients (data not shown). Analysis was conducted using samples from the 16 selected patients. Thirteen *M. tuberculosis* isolates from 10 patients were subjected to whole-genome sequencing (Table 1). Table 3 shows the total number of non-synonymous single-nucleotide polymorphisms (SNPs) between the clinical isolates and the *M. tuberculosis* H37Rv reference genome. The mean of the total number of non-synonymous SNPs was 676.5±264.9 and 875.6±28.3 in the 6-month and >6-month treatment groups, respectively (Figure 2). Interestingly, 2 isolates in the 6-month treatment group and all isolates in the group treated >6 months were identified as belonging to the East-Asian lineage. These isolates had larger numbers of non-synonymous SNPs than the Euro-American lineage isolates (CB050 and IP004). The large standard deviation of the 6-month treatment group implied that clinical isolates identified as East-Asian lineage are more genetically diverse than the Euro-American lineage isolates in our data.

Non-synonymous SNPs were analyzed to identify candidate genes that influenced treatment duration. We found 1 non-synonymous SNP in *pe_pgrs9* (*rv0746*) and *ppe34* (*rv1917c*) in the group treated for >6 months (Figure 3). The average frequencies of non-synonymous SNPs in *pe_pgrs9* and *ppe34* were 44.1%±4.4% and 40.0%±6.8%, respectively. This suggested that approximately 40% of the subpopulation had single non-synonymous SNP in *pe_pgrs9* and *ppe34*, but only in the group treated for >6 months.

Table 3. Total number of non-synonymous SNPs in the clinical isolates of patients with TB

Sample	No. of non-synonymous SNPs
CB050_0W	521
CB060_0W	878
CB060_2W	883
CB13_0W	834
CB213_2W	915
CN118_0W	849
CN177_0W	899
CN177_2W	923
CN272_0W	877
CN272_2W	846
IP004_0W	384
IP006_0W	891
IP016_0W	886

SNP, single-nucleotide polymorphisms; TB, tuberculosis.

Transcriptome Analysis of *M. tuberculosis* Isolated from Sputum Samples

Nine clinical isolates from 8 patients were used for transcriptome analysis (Table 1). The transcriptomes of the group treated for >6 months and the group treated for 6 months were compared using RNA deep sequencing. In the group treated for >6 months, 165 genes were differentially expressed ($p<0.05$; fold change ≥2) relative to the group treated for 6 months, of which 26 genes were induced and 139 were repressed (Figure 4A; Table S1).

To identify the function of differentially expressed genes (DEGs), functional categories of the DEGs were annotated by Mycobrowser (http://mycobrowser.epfl.ch/) and the database for annotation, visualization and integrated discovery (DAVID) (https://david.ncifcrf.gov/). Genes involved in virulence, detoxification, adaptation, cell wall formation, and cell processes were induced (Figure 4B). Gene ontology (GO)

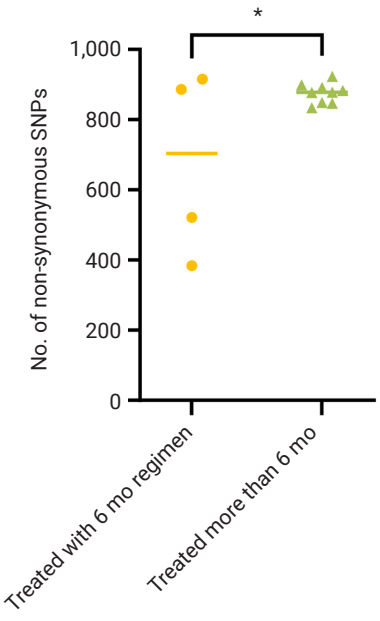

Figure 2. Mean number of non-synonymous single-nucleotide polymorphisms (SNPs) in the patient groups treated for 6 months or for >6 months. Statistical significance was determined by 2-tailed Student t-test. *$p<0.05$.

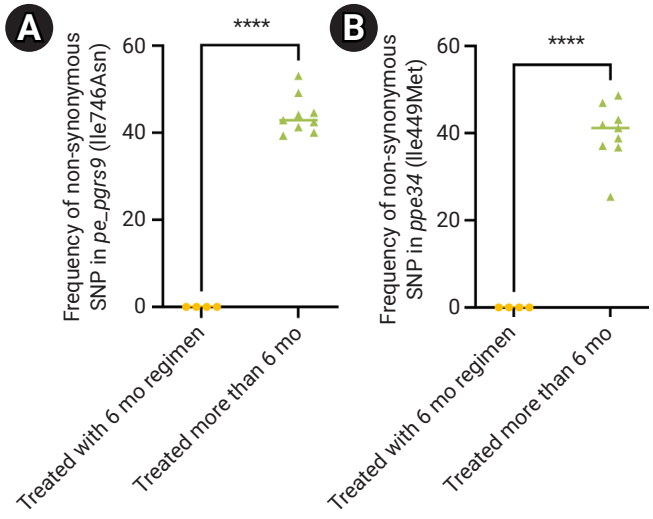

Figure 3. Frequency of non-synonymous single-nucleotide polymorphisms (SNPs) in *pe_pgrs9* (A) *and ppe34* (B). Statistical significance was determined by 2-tailed Student t-test. ****$p < 0.0001$.

analysis revealed that ribonuclease activity and magnesium ion binding were enriched in the induced genes (Figure 4C). Virulence, detoxification, and adaptation categories from Mycobrowser analysis, and the ribonuclease activity category from DAVID analysis included virulence-associated protein (Vap) family TA genes, such as *vapBC26*, *vapB38*, and *vapBC44*. Repressed DEGs were associated with cell wall formation and cell processes, intermediary metabolism and respiration, and information pathways (Figure 4B). In these categories, reductions in ribosomal protein genes and peptidoglycan biosynthesis involving *murE-X* genes were observed. According to GO analysis, the reduced genes were enriched in the structural constituent of the ribosome, the acyl carrier protein phosphopantetheine attachment site binding involved in the fatty acid biosynthetic process, acyl binding, hydrolase activity, and hydrolyzing N-glycosyl compound categories (Figure 4D). Based on the functional categorization results, the expression of TA module genes, rRNA and ribosomal protein genes, and proline-glutamate (PE)-proline-proline-glutamate (PPE) family genes are

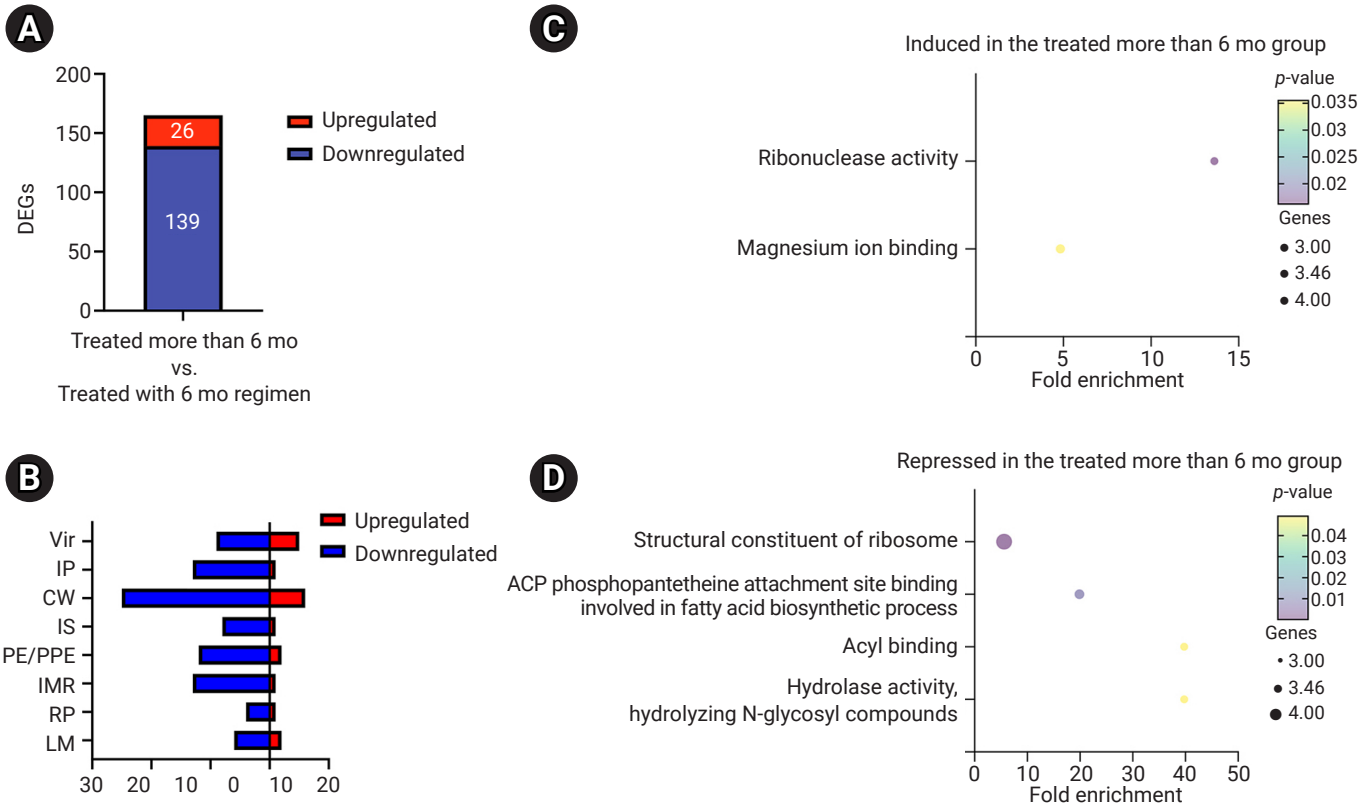

Figure 4. Enrichment analysis of differentially expressed genes (DEGs): (A) bar graph comparing the number of DEGs in the 2 groups. The red and blue bar indicate the number of genes whose expression was increased or decreased more than 2-fold in the group treated >6 months relative to the group treated for 6 months. (B) The number of induced and repressed DEGs categorized by functional category using Mycobrowser (http://mycobrowser.epfl.ch/) and (C, D) gene ontology analysis of the induced (C) and repressed (D) DEGs assessed by the database for annotation, visualization and integrated discovery (DAVID) functional annotation tool.
PE, proline-glutamate; PPE, proline-proline-glutamate; ACP, acyl carrier protein.

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shown as a heatmap (Figure 5). Among the TA module genes induced in the group treated for >6 months, Vap family genes were the most common, and various TA family genes were included in the reduced genes. The expression levels of rRNA genes (*rrs, rrl,* and *rrf*), 8 ribosomal protein genes (*rpmC, rpsQ, rpsN1, rplR, rpmD, rpmA, rplU*, and *rpmJ*), and 12 PE-PPE family protein genes (*pe_pgrs4, ppe29, ppe30, pe_pgrs32, ppe32, ppe38, ppe39, pe_pgrs42, pe29, lipY, ppe53*, and *pe_pgrs 61*) were reduced in the group treated for >6 months. This suggests that the TA module genes of several Vap families were upregulated in the group treated for >6 months, and peptidoglycan biosynthesis-involved rRNA and ribosomal protein genes were downregulated.

Discussion

The genetic diversity of *M. tuberculosis* influences its physiological outcomes. For example, TB is caused by *M. tuberculosis*, which includes 9 lineage classifications based on large sequence polymorphisms and SNPs. Genomic differences between lineages affect pathogenesis, host immune responses, and transmissibility [29–32]. In addition, the presence of *M. tuberculosis* subpopulations within the host affects cell growth, metabolic status, responses to environmental conditions, and drug use [9]. A subpopulation of drug-tolerant *M. tuberculosis* called persisters exhibits variable drug susceptibility. Persisters can avoid drug pressure through growth arrest and regrowth after the removal of bactericidal drugs [11,33]. These properties lead to long-term antibiotic treatment to eradicate persister cells [11]. Therefore, understanding the genetic diversity of *M. tuberculosis* is important for effective treatment.

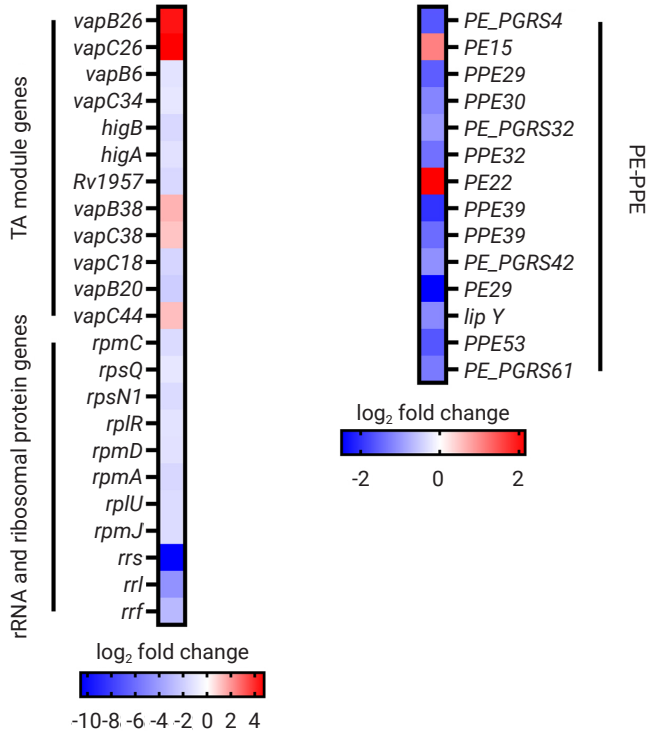

Figure 5. Heat map of the toxin-antitoxin (TA) module, rRNA and ribosomal protein, and proline-glutamate (PE)-proline-proline-glutamate (PPE) family genes identified as differentially expressed genes (DEGs), with expression of the genes indicated by color.

The involvement of TA modules and stringent response regulator A (RelA)-mediated stringent responses in persister formation has been well characterized in other bacteria [34–36]. Stringent response is a bacterial response to nutrient starvation and other stress conditions and is mediated by the accumulation of ppGpp, which is synthesized by RelA. Accumulated ppGpp stimulates protease Lon-dependent degradation of type II TA module antitoxins, resulting in endonuclease toxin-mediated translational inhibition and persister cell formation [35,37]. Under these stress conditions, expression of toxin genes is upregulated, and activated toxins inhibit important cellular processes, leading to growth arrest [38]. Several mechanisms have been proposed for the formation of mycobacterial persister cells. Like other bacteria, persister formation in *M. tuberculosis* is associated with TA modules and RelA [19,20,36,39,40]. In *M. tuberculosis*, the expression of *higAB*, *relFG*, *vapBC3*, and *vapBC31* TA module genes are upregulated in drug-tolerant subpopulations [19]. In addition, cholesterol-induced activation of the RNase toxin VapC12 inhibits translation, resulting in growth regulation and increased persister populations [41]. Three *relE* toxin homologs are involved in the formation of drug-tolerant persisters *in vitro* [20]. In *M. tuberculosis*, RelA is required for growth arrest and drug tolerance during nutrient deprivation [40]. Furthermore, RelA downregulates ribosomal protein genes and mediates the long-term persistence of *M. tuberculosis in vivo* [36]. Recent studies have shown that the expression of *vapC30* and *mazF* toxins and *relA* is induced in single-cell dormant persisters [39]. Our RNA sequencing results showed the upregulation of several Vap family TA module genes, especially *vapBC17*, *vapBC26*, and *vapBC44* in the group treated for >6 months (Figures 4 and 5). Moreover, VapC26 has ribonuclease activity targeting 23S rRNA, and overexpression of the *vapC26* gene strongly inhibits cell growth in *M. tuberculosis* [42,43]. The downregulated genes in our study included rRNA genes in the group treated for >6 months (Figure 5). The expression of genes encoding ribosomal proteins is downregulated in persisters [19,36]. Considering these data, it can be assumed that *M.*

tuberculosis isolated from the group treated for >6 months showed a higher persistence rate in the subpopulation than in the group treated for 6 months.

Genomic profiling of the 2 groups revealed a single non-synonymous SNP in *pe_pgrs9* and *ppe34* only in the group treated for >6 months (Figure 3). These 2 genes that encode PE-PPE family proteins account for approximately 10% of the *M. tuberculosis* genome [44]. The PE-PPE family is characterized by highly conserved N-terminal domains with PE and PPE motifs and is classified into PPE, PE, and PE Polymorphic GC-rich subfamilies (PGRS). Several studies have suggested that the PE-PPE family proteins function in mycobacterial pathogenesis, particularly in the modulation of host immune responses. For instance, the PE-PPE family of proteins binds to toll-like receptors (TLRs), which induces the maturation of dendritic cells (DCs) and macrophage activation, and modulate type 1 T helper (Th1) and type 2 T helper (Th2) responses [45–47]. Some PE-PPE family proteins induce immune evasion of intracellular *M. tuberculosis* by eliciting the Th2 response and inhibiting autophagic killing mediated by interferon-γ secreted from Th1 cells [48,49].

Proteomic analysis was performed to identify important proteins during *M. tuberculosis* infection in guinea pig lungs with PE_PGRS9 and PPE34; however, the functions of these 2 proteins have not been well studied [50]. Although the function of PE_PGRS9 remains inconclusive, it has been demonstrated that PPE34 is involved in immune evasion. Surface-exposed PPE34 induces DC maturation in a TLR2-dependent manner, and PPE34-matured DCs secrete interleukin (IL)-10, IL-4, and IL-5 to skew the Th1/Th2 balance toward Th2-preferred cellular immunity [45]. These PPE34-driven Th2 immune responses are induced by the Src homology 3-interacting domain of PPE34 (amino acids 348–824) [45]. Our genome sequencing data showed that approximately 40% of the subpopulation in the group treated for >6 months had a substitution of isoleucine for methionine at position 449, located in the SH3-interacting domain of PPE34. This suggested that there is an association between a single non-synonymous SNP in the *ppe34* gene and the duration of treatment; however, a detailed study is required. In addition, RNA sequencing data revealed a significantly decreased expression of the *ppe38* gene in the group treated for >6 months (Figure 5). In *M. tuberculosis*, it has been demonstrated that PPE38 mediates the secretion of the PE-PGRS proteins and deletion of the *ppe38* gene increases virulence [51]. In this respect, the decrease in *ppe38* gene expression in the group treated for >6 months appears to be responsible for the increased virulence of infected *M. tuberculosis*, thus affecting treatment duration.

Our data showed that non-synonymous SNP in *ppe34* and decreased *ppe38* expression were associated with long-term treatment. Transcriptome analysis revealed upregulation of the ribonuclease toxin *vapC26* gene and downregulation of rRNA and ribosomal protein-encoding genes in the prolonged treatment group. These characteristics of *M. tuberculosis* from the group treated for 6 months may affect treatment outcomes by modulating the host immune response and increasing the virulence and frequency of *M. tuberculosis* persister cells. However, our study demonstrated the molecular characteristics of drug-susceptible *M. tuberculosis* clinical isolates with extended treatment duration using a small number of samples. Further research is needed to determine whether the genetic variations and expression changes we identified influence the extended treatment.

Supplementary Material

Table S1. The genes that are differentially expressed in group treated more than >6 months relative to the group treated for 6 months. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0101.

Notes

Ethics Approval

We obtained approval from the Institutional Review Board of the Korea Disease Control and Prevention Agency (approval no: 2019-04-05-2C-A) and isolated *M. tuberculosis* from tuberculosis patients from 2016 to 2018. All clinical *M. tuberculosis* isolates were collected from the sputum of tuberculosis patients at Chungnam National University Hospital, Chungbuk National University Hospital, and Inje University Ilsan Paik Hospital in Korea.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

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Availability of Data

The datasets generated during the current study has been deposited in NCBI and accessible through the Bioproject accession number PRJNA887480 and PRJNA1010683.

Authors' Contributions

Conceptualization: EMK, JM, SL, SK; Data curation: EMK; Formal analysis: EMK; Funding acquisition: JAJ, SL, SK; Investigation: HK; Methodology: HK, EMK; Project administration: JAJ, SL, SK; Resources: JM, SL, SK; Software: EMK; Supervision: JM, SL, SK; Validation: EMK; Visualization: EMK; Writing–original draft: EMK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Methodology of comparative studies on the relative effectiveness of COVID-19 vaccines: a systematic review

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ABSTRACT

Objectives: This study aimed to comprehensively outline the methodological approaches used in published research comparing the vaccine effectiveness (VE) of coronavirus disease 2019 (COVID-19) vaccines.

Methods: A systematic search was conducted on June 13, 2024, to identify comparative studies evaluating the effectiveness of mRNA versus non-mRNA and monovalent versus bivalent COVID-19 vaccines. We screened titles, abstracts, and full texts, collecting data on publication year, country, sample size, study population composition, study design, VE estimates, outcomes, and covariates. Studies that reported relative VE (rVE) were analyzed separately from those that did not.

Results: We identified 25 articles comparing rVE between mRNA and non-mRNA COVID-19 vaccines, as well as between monovalent and bivalent formulations. Among the studies assessing VE by vaccine type, 126 did not provide rVE estimates. Comparative VE studies frequently employed retrospective cohort designs. Among the definitions of rVE used, the most common were hazard ratio and absolute VE, calculated as (1−odds ratio)×100. Studies were most frequently conducted in the United Kingdom and the United States, and the most common outcome was infection. Most targeted the general population and assessed the VE of mRNA vaccines using the AstraZeneca vaccine as a reference. A small proportion, 7.3% (n=11), did not adjust for any variables. Only 3 studies (2.0%) adjusted for all core confounding variables recommended by the World Health Organization.

Conclusion: Few comparative studies of COVID-19 vaccines have incorporated rVE methodologies. Reporting rVE and employing a consistent set of covariates can broaden our understanding of COVID-19 vaccines.

Keywords: Coronavirus; COVID-19; Systematic review; Vaccines

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The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to an unprecedented global health crisis. As of October 23, 2023, the world has seen 771,679,618 confirmed cases of COVID-19 and 6,977,023 deaths [1]. The development and distribution of vaccines to combat this viral threat have been crucial in mitigating the pandemic. A variety of COVID-19 vaccines with different mechanisms of action, formulations, and efficacy profiles have been developed and administered across the globe [2]. The urgent need to address this pandemic necessitated a rapid rollout of these vaccines. It is therefore vital to evaluate and compare their effectiveness in curbing the spread of the virus and reducing the severity of the disease.

Quantifying the real-world effectiveness of COVID-19 vaccines against specific viral variants and in diverse populations has emerged as a top research priority. Research on vaccine effectiveness (VE) has traditionally been focused on determining absolute VE (aVE), which compares outcomes between vaccinated and unvaccinated individuals. In contrast, relative VE (rVE) is often employed to assess the comparative risk reduction benefits provided by different vaccine products [3]. Systematic reviews of the methodologies used in comparative studies can be essential for synthesizing and critically appraising the available evidence. These reviews are instrumental in guiding policy decisions, shaping vaccination strategies, and improving our understanding of the real-world impacts of COVID-19 vaccines.

This study aimed to review the methodological approaches employed in research comparing the effectiveness of COVID-19 vaccines. We investigated the designs, study populations, methods for VE estimation, and outcomes of these studies. The primary objectives were to understand relevant trends, refine our comprehension of VE, and identify potential areas of improvement for VE assessment in various settings.

Materials and Methods

Eligibility Criteria

The search and review processes adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Only studies published in English were included. To encompass research on the relative effectiveness of COVID-19 vaccines that did not provide relative estimates, we also incorporated studies on VE.

HIGHLIGHTS

- Most comparative studies on coronavirus disease 2019 vaccines have not presented relative estimates.
- Comparative studies on vaccine effectiveness have focused on mRNA and non-mRNA vaccines, overlooking protein-based and bivalent vaccines.
- Advanced methodologies should be incorporated into comparative vaccine studies.

Information Sources

On June 13, 2024, we systematically searched several databases, including PubMed, Embase, and the Cochrane Library.

Search Strategy

The search terms used were:

1. "COVID" OR "COVID-19" OR "Coronavirus" OR "SARS-COV-2"
2. "vaccine" OR "vaccination"
3. "relative effectiveness" OR "relative efficacy"
4. #2 AND #3
5. "relative vaccine effectiveness" OR "relative vaccine efficacy" OR "relative VE"
6. "vaccine effectiveness" OR "VE"
7. #4 OR #5 OR #6
8. #1 AND #7

Selection Process

In accordance with the search strategy, articles were initially screened to identify and remove duplicates. Three researchers (E.B., J.S., and S.A.C.) independently screened the titles, abstracts, and full texts of the remaining studies. E.B. then verified the review results for consistency and accuracy. The inclusion criteria restricted the studies to interventional or observational research that provided COVID-19 VE estimates for 2 or more vaccine platforms. These studies were required to report outcomes of COVID-19 infection, symptomatic disease, severe disease, COVID-19–related hospitalization, intensive care unit (ICU) admission, and/or death. Given the scarcity of comparative studies on protein versus non–protein and monovalent versus bivalent vaccines, our review was focused on studies comparing mRNA and non-mRNA vaccines. We excluded studies evaluating the VE of a single COVID-19 vaccine type; those unrelated to COVID-19 VE; those concentrating on laboratory measurements of immunogenicity, determinants of vaccine uptake, or cost-effectiveness; simulation studies; and comparisons of vaccination schedules and doses.

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Additionally, we excluded preprints, systematic reviews, ongoing studies, Delphi studies, modeling studies, and articles without full-text availability.

Data Items

We extracted data on the publication year, country, study design, sample size, and composition of study participants, as well as the definition of VE, outcomes, and covariates. In the assessment of rVE studies, we collected information on the availability of aVE estimates and the criteria used to define aVE. Vaccine types were classified into 3 primary categories: mRNA versus non-mRNA, protein-based versus non–protein-based, and monovalent versus bivalent COVID-19 vaccines. Our analysis evaluated the effectiveness of COVID-19 vaccines in preventing infection, symptomatic disease, severe disease, hospitalization, ICU admission, and mortality, with results expressed in either relative or absolute terms. Additionally, 3 reviewers conducted the bias assessment. In accordance with the World Health Organization (WHO) interim guidance on evaluating COVID-19 VE [4], we assessed the extent to which studies adjusted for core covariates in 4 categories: time (such as date of illness onset or date of specimen collection), susceptibility to infection (namely previous COVID-19 infection), sociodemographic factors, and chronic medical conditions.

Assessment of Study Risk of Bias

The Risk of Bias in Non-randomized Studies (ROBINS-I) tool [5] was employed to assess the risk of bias, which was categorized as "low," "moderate," "serious," "critical," or "no information" across 7 domains for observational studies.

This research has been registered with PROSPERO (https://www.crd.york.ac.uk/prospero/), an international prospective register of systematic reviews, under the registration number CRD42023442560.

Results

Study Selection

The initial review of PubMed, Embase, and the Cochrane Library yielded a total of 2,921 articles. After 1,054 duplicates were removed and the inclusion criteria were applied, 151 articles remained for analysis (Figure 1).

Study Characteristics

rVE was estimated to compare mRNA vaccines (Pfizer, also known as BNT162b2 and Comirnaty, and Moderna, also known as mRNA-1273 and Spikevax) with non-mRNA vaccines (AstraZeneca, Janssen, Novavax, Sinovac-Coronavac, Sinopharm, Sputnik V, and Bharat-Biotech Covaxin [BBV152]). This comparison included 20 studies (13.2%), with 5 studies examining monovalent and bivalent mRNA COVID-19 vaccines (3.3%). In contrast, VE was estimated for mRNA versus non-mRNA vaccines in 118 studies (78.1%), monovalent versus bivalent mRNA vaccines in 5 studies (3.3%), and protein-based versus non–protein-based COVID-19 vaccines in 3 studies (2.0%). Most of these studies employed a retrospective cohort design (n=70, 46.4%), followed by test-negative (n=39, 25.8%), prospective cohort (n=18, 11.9%), case-control (n=12, 7.9%), and cross-sectional (n=3, 2.0%) designs. The most commonly used definitions of rVE were hazard ratio (HR; n=7, 35.0%), the formula (1–HR)×100 (n=6, 30%), and odds ratio (OR; n=4, 20.0%). For aVE, the definitions used were the formulas (1–OR)×100 (n=54, 42.9%), (1–HR)×100 (n=34, 27.0%), and (1–risk ratio [RR])×100 (n=10, 7.9%) (Figure 2).

Risk of Bias in Studies

We evaluated 25 studies assessing rVE for COVID-19 vaccines and 126 studies assessing only VE, using the ROBINS-I tool for quality assessment. Of the former, 20 studies were considered to have a low risk of bias. Two studies were categorized as having "no information" regarding risks, 1 study was identified as having a critical risk of bias, 1 presented a serious risk, and the remaining study displayed a moderate risk (Figure 3) [6]. For the study presenting critical risk, the potential bias stemmed from the lack of adjustment for confounding variables [7]. Outcome measurement was not specified in the databases of 2 studies [8,9], and 1 study did not mention the database source of exposure information [8]. Regarding the 2 studies identified as having serious or moderate selection bias risk, the cause was the limited sample size in 1 study [7] and the selection of volunteer participants in the other [10].

In studies assessing VE alone, the overall risk of bias was categorized as moderate in 51 studies (40.5%), low in 46 (36.5%), and indeterminate due to lack of information in 14 (11.1%). Additionally, 7 studies (5.6%) were classified as having a serious risk of bias, while 8 studies (6.3%) were deemed to be at critical risk (Figure 4) [6]. Regarding the confounding bias domain, 24 studies (19.0%) were found to have a moderate risk of bias, 4 (3.2%) [11–14] had serious risk, and 4 (3.2%) [15–18] had a critical risk. In terms of deviations from planned interventions and reporting of results, all studies were considered to have either a low or a moderate risk of bias. Participant selection bias was rated as serious in 3 studies [19–21] and as critical in 2 studies [22,23]. The risk of bias in intervention classification was moderate in 11 studies and critical in 3 studies [15,24,25]. Information on missing data was not provided in 39 (37.9%) studies, and 6 studies (5.8%) [26–31] were assessed as having a moderate

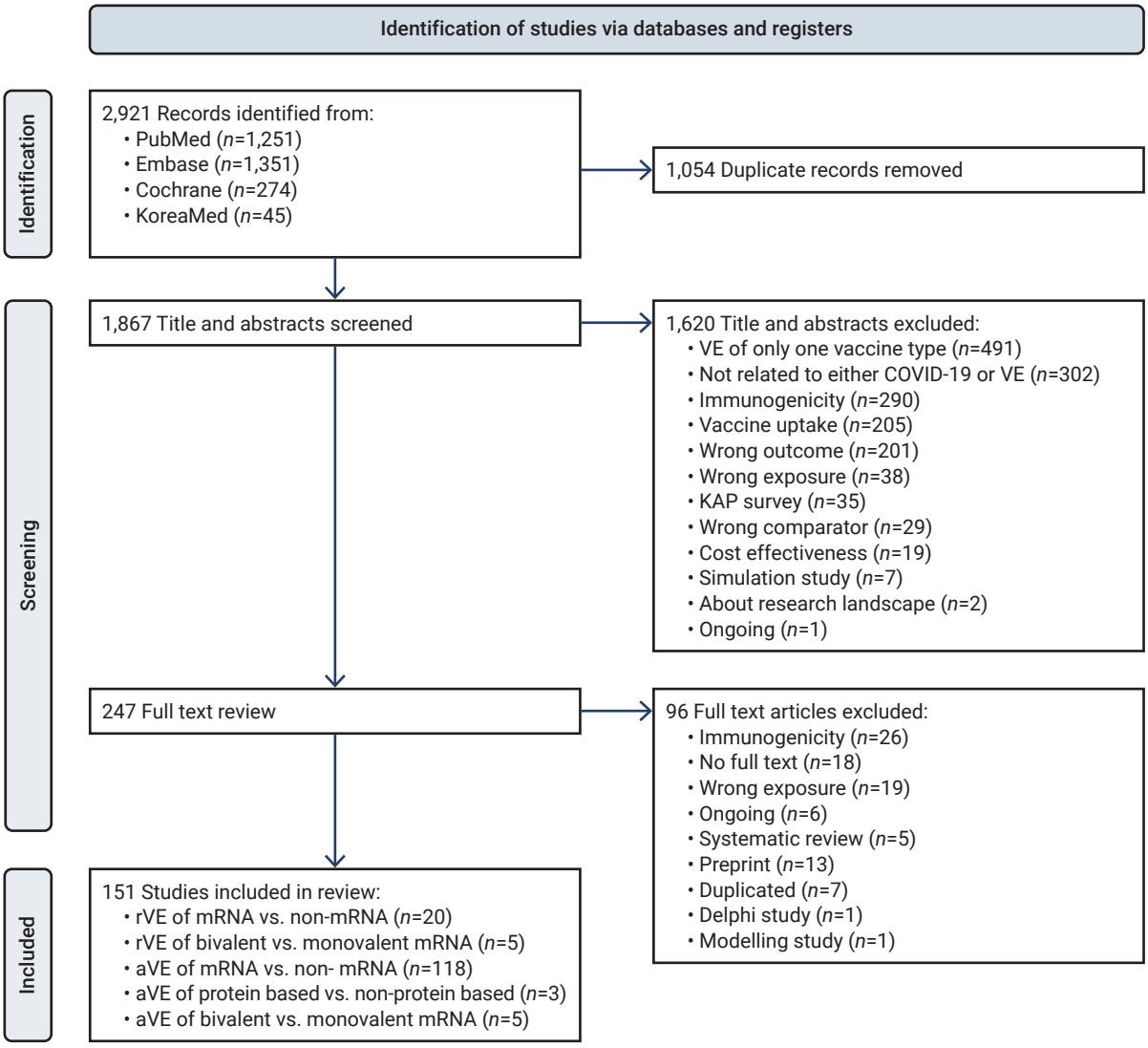

Figure 1. Flow diagram of studies identified through searches of the PubMed, Embase, Cochrane Library, and KoreaMed databases.
VE, vaccine effectiveness; COVID-19, coronavirus disease 2019; KAP, knowledge, attitude, practice; rVE, relative vaccine effectiveness; aVE, absolute vaccine effectiveness.

risk in this domain. Outcome measurement information was absent in 1 study [32], and a moderate risk of bias in outcome measurement was identified in 11 studies (10.7%).

Methodology of rVE Studies

Overall, 59,915,206 participants were included in 20 comprehensive studies that investigated the rVE of various mRNA and non-mRNA COVID-19 vaccines [7–10,33–48]. The studies were published between 2021 and 2024, with the research conducted from 2020 to 2022 (Table 1) [7–10,33–48]. The largest proportion of studies took place in the United States (*n*=6, 30.0%) [34,36,39,40,43,45], followed by the United Kingdom (*n*=5, 25.0%) [33,35,42,44]. Most studies targeted the general population (*n*=15, 75.0%), with some focusing on hospitalized patients (*n*=4, 20.0%) [10,39,41,43] and healthcare workers (*n*=1, 5.0%) [7]. Regarding study design, the evaluation of rVE among COVID-19 vaccine types utilized various methodologies, including retrospective cohort (*n*=11, 55.0%) [7,8,34–36,39–41,45,46,48], prospective cohort (*n*=6, 30.0%) [9,10,33,37,38,44], and case-control (*n*=3, 15.0%) designs [42,43,47]. The age distribution of participants varied, with 12 studies including individuals aged ≥18 years; 1 study each encompassing participants aged ≥12, ≥16, >20, >40, and >50 years; and 3 studies (15.0%) that did not provide age specifications.

The comparative analyses in these studies were primarily focused on the Pfizer and Moderna vaccines (*n*=9, 45.0%) [8,10,34,38–41,45,47], with other studies examining only the

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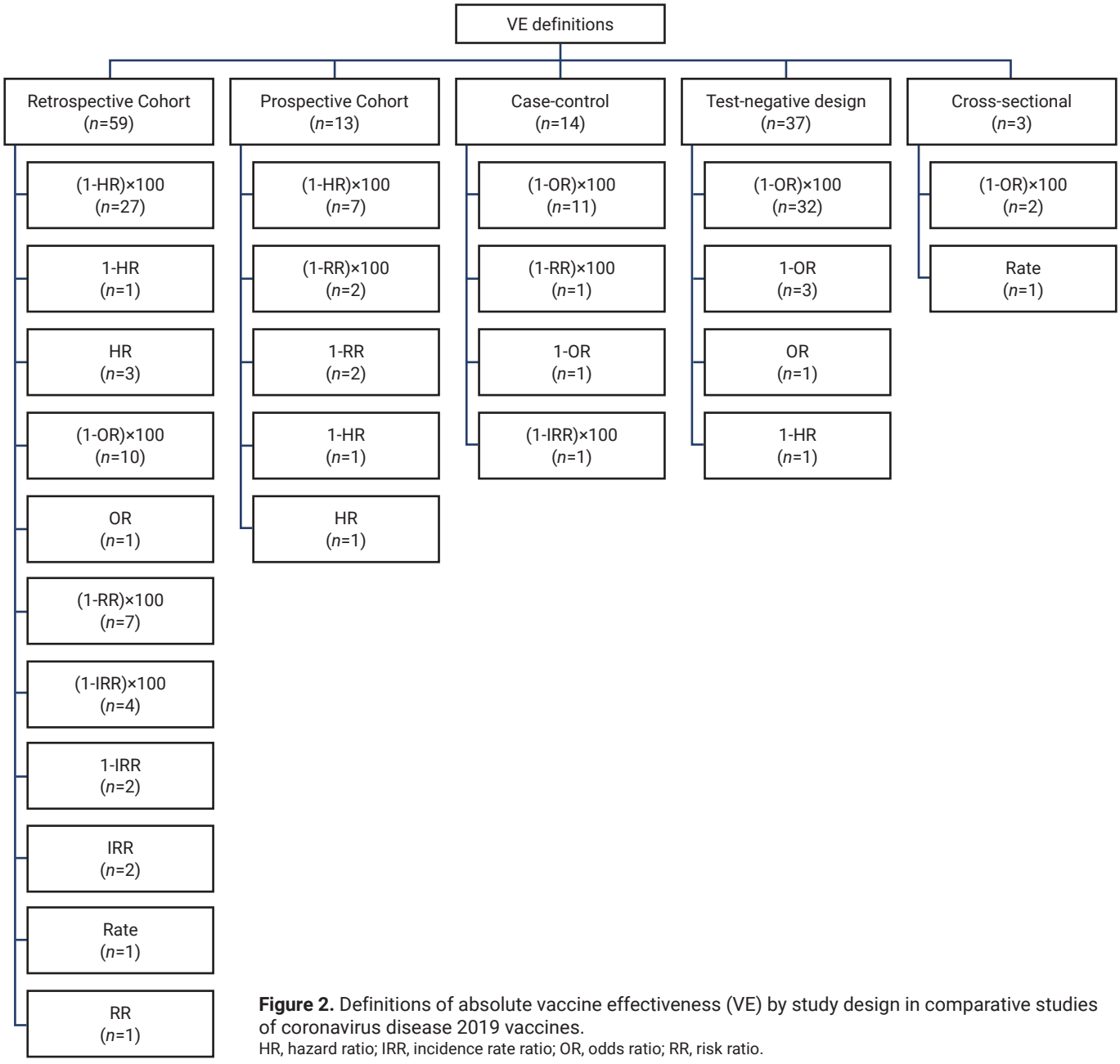

Figure 2. Definitions of absolute vaccine effectiveness (VE) by study design in comparative studies of coronavirus disease 2019 vaccines.
HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, risk ratio.

Pfizer vaccine (*n*=9, 45.0%) [7,9,33,35,37,42,44,46,48], only the Moderna vaccine (*n*=1, 5.0%) [43], or an unspecified mRNA vaccine (*n*=1, 5.9%) [36]. The comparator vaccines evaluated against mRNA vaccines included Janssen (*n*=10, 58.8%), AstraZeneca (*n*=9, 52.9%), and Sinovac-Coronavac (*n*=2, 11.8%). The most frequently reported outcomes across the studies were COVID-19–related infection (*n*=14, 70.0%), hospitalization (*n*=12, 60.0%), and mortality (*n*=6, 30.0%). The most common definitions of rVE were HR (*n*=7, 35.0%) [7,10,33,34,40,42,44], followed by the formula (1–HR)×100 (*n*=4, 20.0%) [36,37,39,45], OR (*n*=4, 20.0%) [9,41,43,47], incidence rate ratio (*n*=2, 10.0%) [8,35], the formula (1–RR)×100 (*n*=2, 10.0%) [38,48], and RR (*n*=1, 5.0%) [46]. Only 8 studies (40.0%) reported and defined both aVE and rVE [9,33,35,38,43,44,47,48].

Among the studies, the variables most commonly controlled for were age (*n*=18, 90.0%), sex (*n*=17, 85.0%), and comorbidities (*n*=15, 75.0%). Less frequently controlled variables included ethnicity (*n*=7, 35.0%), socioeconomic status (SES) (*n*=7, 35.0%), and body mass index (BMI; *n*=6, 30.0%), as well as geographic region and previous healthcare utilization (both *n*=4, 20.0%); calendar time, time of vaccination, and smoking

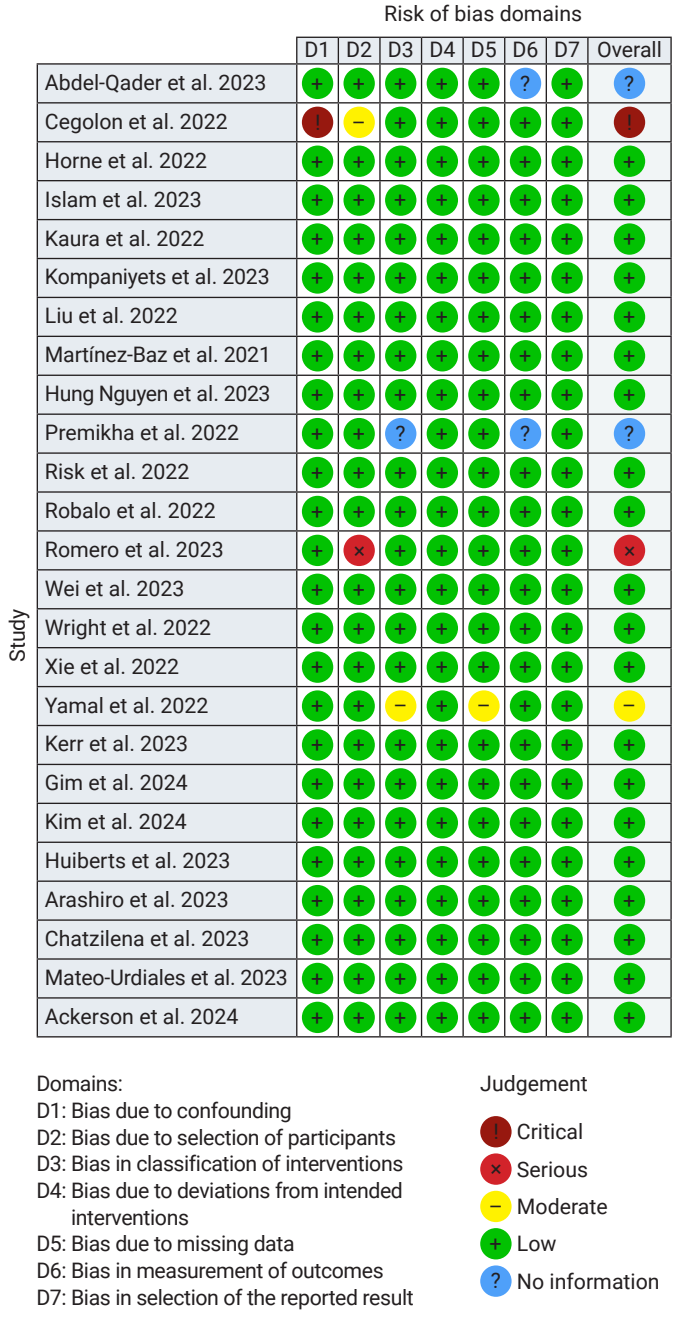

Figure 3. Risk-of-bias assessments for 25 relative vaccine effectiveness studies for coronavirus disease 2019, comparing mRNA vaccines to non-mRNA vaccines and bivalent to monovalent mRNA vaccines. These assessments were conducted using the Risk of Bias in Non-randomized Studies (ROBINS-I) tool and are visualized with the Robvis tool. Modified from McGuinness et al. Res Synth Methods 2021;12:55–61, according to the Creative Commons license [6].

status (each *n*=3, 15.0%); and care home residential status, influenza vaccine history, number of prior tests for COVID-19, COVID-19 infection history, immunocompromised status, and antibody levels (each *n*=2, 10.0%). Additional variables included learning disability, serious mental illness, current pregnancy, eligibility for first vaccine dose, clinical characteristics, electronic frailty index score, and alcohol consumption. Of the studies, 7 (35.0%) adjusted for the 3 WHO-recommended core sociodemographic covariates of age, sex, and SES; 15 (75.0%) adjusted for chronic medical conditions; 6 (30.0%) for time-related variables (date of illness, date of testing); and 3 (15.0%) for susceptibility to infection. Only 1 study accounted for all of the WHO-recommended core confounding variables, including age, sex, SES, chronic medical conditions, time-related variables, and susceptibility to infection [34]. One study did not make adjustments for any variables [7].

Only 5 studies investigated the rVE of bivalent versus monovalent mRNA vaccines (Table 2) [49–53]. These studies, conducted between 2022 and 2024 in the Netherlands, Japan, Italy, the United Kingdom, and the United States, encompassed a total of 2,253,040 individuals. The rVE assessment predominantly employed a test-negative design, using the definition (1–OR)×100. Among these 5 studies, 4 (80.0%) adjusted for the WHO-recommended core sociodemographic variables of age, sex, and SES along with chronic medical conditions, and 3 studies (60.0%) considered the core variables related to time and susceptibility to infection. Two of these studies adjusted for all WHO core confounding variables [49,50].

Methodology of aVE Studies

Across the 118 studies of VE for mRNA versus non-mRNA vaccine types, the cumulative sample size was 203,805,491 participants (Table S1). The greatest proportion of these studies took place in 2021 (*n*=50, 42.4%), followed by 2022 (*n*=28, 23.7%) and 2020–2021 (*n*=26, 22.0%). The United Kingdom was the most common study location (*n*=25, 21.2%), with the United States (*n*=17, 14.4%), Hong Kong (*n*=7, 5.9%), China and Spain (each *n*=6, 5.1%), Italy (*n*=5, 4.2%), and several other countries, including Canada, Brazil, Colombia, and France (each *n*=4, 3.4%), also contributing. The studies predominantly included participants from the general population (*n*=77, 65.3%). Hospitalized patients were the next largest group (*n*=24, 20.3%), followed by hospital workers (*n*=7, 5.9%), urgent care patients and long-term care residents (each *n*=2, 1.7%), patients in hospital wards and public sector healthcare users (each *n*=1, 0.8%), children (*n*=3, 2.5%), and military medical academy personnel (*n*=1, 0.8%). Among hospitalized

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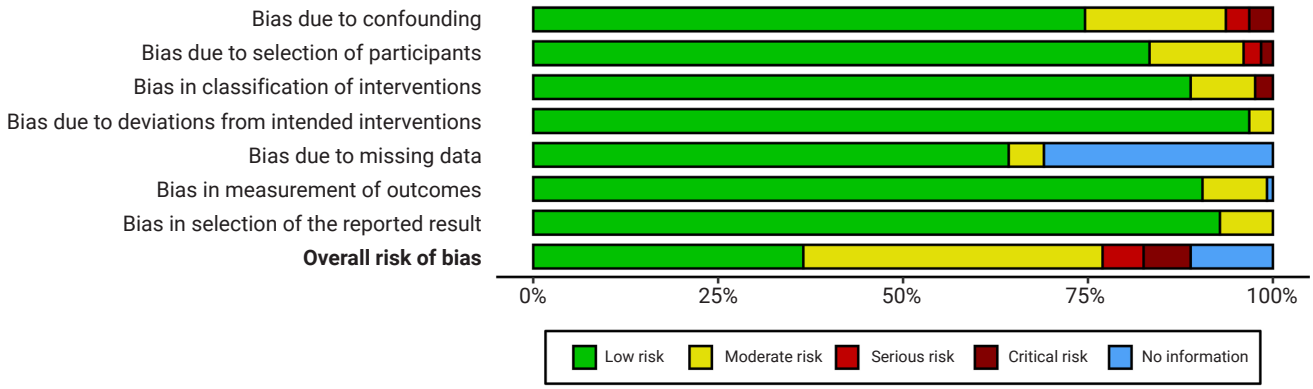

Figure 4. Risk-of-bias assessments for 126 vaccine effectiveness studies for coronavirus disease 2019, comparing mRNA to non-mRNA, bivalent to monovalent mRNA, and protein-based to non–protein-based vaccines. These assessments were conducted using the Risk of Bias in Non-randomized Studies (ROBINS-I) tool and are visualized with the Robvis tool. Modified from McGuinness et al. Res Synth Methods 2021;12:55–61, according to the Creative Commons license [6].

patients, specific subgroups were identified, including patients undergoing hemodialysis (*n*=3, 2.5%) [54–56], individuals with kidney disease (*n*=2, 1.7%) [57,58], solid organ transplant recipients (*n*=2, 1.7%) [59,60], patients using immunosuppressants (*n*=1, 0.8%) [61], and patients with cirrhosis (*n*=1, 0.8%) [62]. The studies involved participants with distinct attributes, such as US military personnel [63], attendees of a human immunodeficiency virus outpatient clinic [15], public emergency department patients [20], and those who underwent pharmacy-based testing for COVID-19 [64]. Concerning age, 68 studies (57.6%) involved adults aged 16 years and older, 18 studies (15.3%) included adults aged 50 years and older, and 9 studies (7.6%) did not specify participant ages. Seven studies (5.9%) encompassed participants of all ages. Three studies (2.5%) focused on children aged 3 to 17, 3 to 18, and 5 to 11 years, respectively. The remaining studies included age groups of ≥5, ≥10, ≥12, and ≥15 years.

The primary comparator among the mRNA vaccine groups was most frequently Moderna and Pfizer (*n*=60, 50.8%), followed by Pfizer alone (*n*=56, 47.5%), Moderna alone (*n*=1, 0.8%), and unspecified mRNA vaccine (*n*=2, 1.7%). Other comparator groups included AstraZeneca (*n*=75, 63.6%), Janssen (*n*=36, 30.5%), Sinovac-CoronaVac (*n*=32, 27.1%), Sputnik V (*n*=10, 8.5%), Sinopharm (*n*=9, 7.6%), a combination of Sinovac-CoronaVac and Sinopharm (*n*=3, 2.5%), Cansino (*n*=3, 2.5%), Bharat-Biotech BBV152 (*n*=1, 0.8%), and others (*n*=3, 2.5%). The studies primarily assessed the outcome of COVID-19 infection (*n*=76, 64.4%), followed by hospitalization (*n*=56, 47.5%), death (*n*=48, 40.7%), symptomatic disease (*n*=18, 15.3%), severe disease (*n*=18, 15.3%), ICU admission (*n*=4, 3.4%), all-cause mortality (*n*=4, 3.4%), reinfection (*n*=2, 1.7%), and breakthrough infection (*n*=1, 0.8%). The most common VE definitions were (1–OR)×100 (*n*=50, 42.4%), (1–HR)×100 (*n*=34, 28.8%), and (1– RR)×100 (*n*=10, 8.5%).

Age was the most frequently controlled variable across the studies (*n*=99, 83.9%), followed by sex (*n*=89, 75.4%), comorbidity (*n*=58, 49.2%), residential status (n=47, 40.0%), calendar time (*n*=32, 27.1%), SES (*n*=28, 23.7%), ethnicity (*n*=24, 20.3%), COVID-19 testing date (*n*=12, 10.2%), care home residential status (*n*=12, 10.2%), number of prior COVID-19 tests (*n*=15, 12.7%), previous healthcare utilization (*n*=16,13.6%), history of COVID-19 infection (*n*=10, 8.5%), clinical characteristics (*n*=8, 6.8%), BMI (*n*=7, 5.9%), influenza vaccine history (*n*=6, 5.1%), vaccination status (*n*=11, 9.3%), time of vaccination (*n*=8, 6.8%), and immunocompromised status (*n*=2, 1.7%). Additional confounding variables considered in these studies included incidence rate, the interval between COVID-19 onset and treatment initiation, cumulative person-days, time on dialysis, test type (antigen or genomic), local virus circulation, contact setting (household or other), travel history, and non-comorbid conditions. Of the 118 studies, 22 (18.6%) adjusted for the WHO-recommended core sociodemographic variables, including age, sex, and SES; 58 (49.2%) accounted for chronic medical conditions; 36 (30.5%) considered time-related factors; and 12 (10.2%) adjusted for susceptibility to infection. Nine studies did not incorporate adjustments for any variables.

Five studies compared the VE of bivalent versus monovalent mRNA vaccines (Table S2). These studies were conducted between 2023 and 2024 in Denmark, Finland, Norway, Sweden, the Republic of Korea, Canada, and the United States, including a total of 6,163,590 adults and 90,905 children. The VE assessments primarily utilized a prospective cohort design, employing 5 distinct definitions: 1–RR, 1–HR, (1– OR)×100, HR,

Table 1. Definitions of relative vaccine effectiveness in comparative studies of mRNA vs. non-mRNA COVID-19 vaccines

No.	Study	Country, year	Settings	Age (y)	Sample size	Study design	rVE definition	Vaccine type	Comparator vaccine type	Dependent/ outcome variable	aVE reported
1	Abdel-Qader et al. (2023) [9]	Jordan, 2021	General population	>18	1,200	Prospective cohort	OR	Pfizer	Sinopharm	Symptomatic disease	(1−RR)×100
2	Cegolon et al. (2022) [7]	Italy, 2021–2022	Healthcare workers	NS	1,994	Retrospective cohort	HR	Pfizer	AstraZeneca, Janssen, Novavax	Infection, reinfection	-
3	Horne et al. (2022) [33]	UK, 2021	General population	≥18	7,594,195	Prospective cohort	HR	Pfizer	AstraZeneca	Infection, hospitalization, death	HR
4	Islam et al. (2023) [34]	USA, 2021	General population	≥18	6,175,195	Retrospective cohort	HR	Pfizer, Moderna	Janssen	Infection, hospitalization/ ICU, death	-
5	Kaura et al. (2022) [35]	UK, 2021	General population	≥16	254,432	Retrospective cohort	IRR	Pfizer	AstraZeneca	Infection, hospitalization, death, all-cause mortality	IRR
6	Kompaniyets et al. (2023) [36]	USA, 2022	General population	≥18	18,912,378	Retrospective cohort	(1−HR) ×100	mRNA	Janssen	Infection, hospitalization/ ICU admission, outpatient claim	-
7	Liu et al. (2022) [37]	Australia, 2022	General population	>40	2,056,123	Prospective cohort	(1−HR) ×100	Pfizer	AstraZeneca	Infection, hospitalization, death	-
8	Martinez-Baz et al. (2021) [38]	Spain, 2021	General population	≥18	30,240	Prospective cohort	(1−RR) ×100	Pfizer, Moderna	AstraZeneca, Janssen	Symptomatic disease, hospitalization	(1−RR)×100
9	Hung Nguyen et al. (2023) [39]	USA, 2021–2022	Hospitalized patients	≥18	4,404,091	Retrospective cohort	(1−HR) ×100	Pfizer, Moderna	Janssen	Infection, hospitalization, outpatient claim	-
10	Premikha et al. (2022) [8]	Singapore, 2021	General population	≥20	2,709,899	Retrospective cohort	IRR	Pfizer, Moderna	Sinovac-CoronaVac, Sinopharm	Infection, severe disease, death	-
11	Risk et al. (2022) [40]	USA, 2021	General population	>18	159,055	Retrospective cohort	HR	Pfizer, Moderna	Janssen	Infection, hospitalization	-
12	Robalo et al. (2022) [41]	Belgium, 2021	Hospitalized patients	≥18	2,493	Retrospective cohort	OR	Pfizer, Moderna	AstraZeneca, Janssen	Severe disease, death	
13	Romero-Ibarguengoitia et al. (2023) [10]	Brazil and Mexico, 2021–2022	Hospitalized patients	NS	966	Prospective cohort	HR	Pfizer, Moderna	AstraZeneca, Janssen, Sinovac-CoronaVac, CanSino	Infection	-
14	Wei et al. (2023) [42]	UK, 2021	General population	≥18	1,311,075	Case-control	HR	Pfizer	AstraZeneca	Infection, hospitalization, death	-
15	Wright et al. (2022) [43]	USA, 2021	Hospitalized patients	≥18	48,335	Case-control	OR	Moderna	Janssen	Hospitalization	1−OR
16	Xie et al. (2022) [44]	UK, 2021	General population	>50	168,648	Prospective cohort	HR	Pfizer	AstraZeneca	Infection, hospitalization	HR

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Table 1. Continued

No.	Study	Country, year	Settings	Age (y)	Sample size	Study design	rVE definition	Vaccine type	Comparator vaccine type	Dependent/ outcome variable	aVE reported
17	Yamal et al. (2022) [45]	USA, 2020–2021	General population	≥12	146,731	Retrospective cohort	(1–HR) ×100	Pfizer, Moderna	Janssen	Infection	-
18	Kerr et al. (2023) [48]	UK, 2020-2021	General population	≥18	12,900,000	Retrospective cohort	1–RR	Pfizer	AstraZeneca	Hospitalization, death	1–RR
19	Gim et al. (2024) [47]	Republic of Korea, 2020–2022	General population	NS	23,034	Case-control	OR	Pfizer, Moderna	AstraZeneca, Novavax	Reinfection	1–OR
20	Kim et al. (2024) [46]	Republic of Korea, 2022	General population	≥18	15,122	Retrospective cohort	RR	Pfizer	Novavax	Infection	

COVID-19, coronavirus disease 2019; rVE, relative vaccine effectiveness; aVE, absolute vaccine effectiveness; OR, odds ratio; RR, risk ratio; NS, not specified; HR, hazard ratio; UK, United Kingdom; USA, United States of America; ICU, intensive care unit; IRR, incidence rate ratio; -, not reported.

Table 2. Definitions of relative vaccine effectiveness in comparative studies of monovalent vs. bivalent COVID-19 vaccines

No.	Study	Country, year	Setting	Age (y)	Sample size	Study design	rVE definition	Vaccine type	Comparator vaccine type	Dependent/ outcome variable	aVE reported
1	Huiberts et al. (2023) [51]	The Netherlands, 2022	General population	≥18	32,542	Prospective cohort	(1–HR)×100	Pfizer bivalent, Moderna bivalent	Monovalent	Infection	
2	Arashiro et al. (2023) [49]	Japan, 2022	Hospitalized patients	≥16	6191	Test-negative design	(1–OR)×100	Pfizer bivalent, Moderna bivalent	Monovalent	Infection	(1–OR) ×100
3	Chatzilena et al. (2023) [52]	UK, 2022–2023	Hospitalized patients	≥75	884	Test-negative design	(1–OR)×100	Pfizer bivalent, Moderna bivalent	Monovalent	Hospitalization	
4	Mateo-Urdiales et al. (2023) [53]	Italy, 2022–2023	General population	≥60	2,129,559	Retrospective cohort	(1–HR)×100	Pfizer bivalent, Moderna bivalent	Monovalent	Severe disease	
5	Ackerson et al. (2024) [50]	USA, 2022–2023	Hospitalized patients	NS	83,864	Test-negative design	(1-OR)×100, ([1/OR]-1) ×100	Pfizer bivalent, Moderna bivalent	Monovalent	Infection, severe disease, hospitalization, death, ICU admission	1–OR

COVID-19, coronavirus disease 2019; rVE, relative vaccine effectiveness; aVE, absolute vaccine effectiveness; HR, hazard ratio; OR, odds ratio; UK, United Kingdom; USA, United States of America; NS, not specified; ICU, intensive care unit.

and 1 –OR. Of the 5 studies, 1 (20.0%) adjusted for the 3 WHO-recommended core sociodemographic variables of age, sex, and SES. Three studies (60%) adjusted for chronic medical conditions, 2 (40%) considered core time-related covariates, and 1 (20%) accounted for susceptibility to infection.

Three studies assessed the VE of COVID-19 vaccines, differentiating between protein-based and non–protein-based vaccines. These studies were conducted in Russia, with a combined population of 327,997 individuals. Participants in the studies were adults aged 18 years and older. The methodologies employed were test-negative [65], retrospective cohort [18], and case-control [66] designs. To calculate effectiveness, all studies utilized the formula (1–OR)×100. In all 3 studies, a protein-based vaccine (EpiVacCorona) was compared with the non–protein-based vaccines Gam-COVID-Vac and CoviVac. The COVID-19–related outcomes evaluated included lung injury [18,65], death [65], and reinfection [66]. Of the 3 studies, 2 adjusted for the confounding variables of age and sex. One study adjusted for the region of the healthcare facility, while another adjusted for confirmed history of COVID-19. One study did not make adjustments for any variables.

Discussion

We examined the methodologies used to estimate VE in comparative studies of different COVID-19 vaccines. In this study, we observed results consistent with those recommended by the WHO guidelines for assessing vaccine efficacy. However, findings that reflected real-world conditions were also evident. Notably, only a small proportion of the studies (15%) focused on evaluating rVE when comparing various COVID-19 vaccine types; the majority concentrated on VE. Most comparative studies assessed the effectiveness of mRNA vaccines versus non-RNA vaccines, with only 3 studies comparing protein-based and non–protein-based options. This underscores the importance of considering methodologies that include both rVE and aVE in VE studies and emphasizes the need to explore vaccine types beyond mRNA, such as protein-based and bivalent vaccines. The rVE estimates alone did not provide information on the aVE of each vaccine. Consequently, a methodological approach that accounts for both rVE and aVE is crucial when making public health decisions and formulating policies related to VE.

This review employed a methodical and systematic approach to deepen our understanding of the challenges and opportunities in this critical research area. Our findings are poised to guide future research and inform public health initiatives. We aimed to enrich the current landscape of methodologies for comparing the recently introduced COVID-19 vaccines, thereby supporting future empirical studies. Our results lay the groundwork for informed decision-making about vaccine types and the optimization of the global response to the ongoing pandemic.

Across all the study designs, most VE estimators relied on ORs or HRs. These studies did not employ extensions of the standard methodological models. The prevalence of the retrospective cohort design highlighted the need to explore alternative designs, such as the test-negative design commonly used in influenza and rotavirus VE studies [67,68]. Retrospective cohort studies are susceptible to recall and misclassification biases during data collection, and it is difficult to eliminate the influence of unmeasured latent confounding factors. Measuring VE involves assessing the simple association between ongoing vaccine administration and disease risk, as well as evaluating the strength of causal effects. However, retrospective cohort studies are limited in their capacity to elucidate causal relationships. Test-negative designs could be more feasible for clinicians to conduct than case-control studies. Nonetheless, challenges exist, including the fact that rapid diagnostic testing may not be widely available in some countries, the potential underestimation of VE due to the tests' imperfect sensitivity and specificity, and the possibility of selection bias when enrolling participants in routine clinical settings [67].

The WHO has suggested that key covariates to be considered in COVID-19 VE studies include sociodemographic variables such as age, sex, a proxy for SES, pre-existing chronic conditions, the date of illness onset, the date of specimen collection, previous SARS-CoV-2 infection, and healthcare worker status [4]. In the reviewed studies, age and sex were adequately controlled. However, regarding other confounding factors, nearly half of the studies failed to consider comorbidities, more than one-third did not adjust for SES, and almost 90% neglected to account for the date of testing or prior SARS-CoV-2 infection. To mitigate outcome bias resulting from healthcare behaviors that are difficult to measure, several studies acknowledged limitations due to challenges in data collection, especially in adjusting for occupation and SES. As the pandemic has continued, the proportion of reinfections has approached half of all confirmed cases, with variations observed across countries. In terms of COVID-19 severity and mortality, outcome bias may arise from immunity gained through previous infections. Adjustment will be necessary to address this issue.

Despite the insights gleaned from the examined studies, the research has certain limitations. The emphasis on aVE over rVE, particularly when considering the diversity of COVID-19 vaccine types available, may have compromised

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the comprehensiveness of the findings. Furthermore, the disproportionate emphasis on comparing mRNA vaccines to their non-mRNA counterparts neglects the assessment of other vaccine categories, such as protein-based and bivalent vaccines. The methodological homogeneity, marked by the frequent use of ORs or HRs without considering more complex models, suggests a lack of innovation in statistical approaches [69,70]. The common reliance on a retrospective cohort design also prompts concerns about possible biases and the inherent limitations of this approach [71]. Furthermore, the lack of full adjustment for key confounding factors, including comorbidities, SES, and other essential variables recommended by the WHO, could have introduced bias and impacted validity [72]. Collectively, these limitations highlight the need for more diverse methodological approaches that include various vaccine types and robust adjustments for confounding factors, thereby improving the reliability and applicability of VE study findings across various settings.

The present review also has limitations. For instance, we did not assess VE across subgroups defined by vaccination status, number of doses received, vaccination regimen, booster status, or whether vaccination was homologous or heterologous. Furthermore, we did not incorporate meta-analyses of VE from other research or consider estimates of effectiveness that may vary over time. The periods characterized by the dominance of pre-Delta, Delta, and Omicron variants were not differentiated. Moreover, the effectiveness of other vaccine types, such as inactivated and viral vector vaccines, was not examined in this review.

Despite the identified limitations, a strength of this study is its comprehensive review and critical assessment of the methodologies used in COVID-19 VE research. The structured and systematic approach of this review improves our understanding of the challenges and opportunities in this field. By highlighting the prevailing methodological trends and emphasizing the need for more nuanced evaluation, this article serves as a valuable guide for future research and public health initiatives. Acknowledging the limitations demonstrates the study's commitment to transparency and contributes to the ongoing discourse on refining VE research methodologies, ultimately advancing our understanding of VE in diverse settings.

Conclusion

This study highlights the lack of focus on the potential of VE studies to report on rVE and aVE, as well as the scarcity of comparative studies of vaccine types that do not use mRNA technology. To obtain valid and reliable results, it is also crucial that the core confounding factors in COVID-19 VE studies be considered. Furthermore, it may be beneficial to include assessments of effectiveness within specific subgroups and the efficacy against certain variants, which are areas currently underrepresented in the evidence. These considerations should be incorporated into more thorough evaluations in future clinical trials.

Supplementary Material

Table S1. Definitions of vaccine effectiveness in comparative studies of mRNA versus non-mRNA COVID-19 vaccines; **Table S2.** Definitions of vaccine effectiveness in comparative studies of monovalent versus bivalent COVID-19 vaccines. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0063.

Notes

Ethics Approval
Not applicable.

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

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

Authors' Contributions
Conceptualization: YJC, SAC; Data curation: EB, SAC; Formal analysis: EB, JS, YSC, SAC; Funding acquisition: YJC; Investigation: SAC; Methodology: YJC, SAC; Project administration: YJC; Supervision: SAC; Validation: all authors; Visualization: EB, SAC; Writing–original draft: EB, SAC; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

BCED-Net: Breast Cancer Ensemble Diagnosis Network using transfer learning and the XGBoost classifier with mammography images

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ABSTRACT

Objectives: Breast cancer poses a significant global health challenge, characterized by complex origins and the potential for life-threatening metastasis. The critical need for early and accurate detection is underscored by the 685,000 lives claimed by the disease worldwide in 2020. Deep learning has made strides in advancing the prompt diagnosis of breast cancer. However, obstacles persist, such as dealing with high-dimensional data and the risk of overfitting, necessitating fresh approaches to improve accuracy and real-world applicability.
Methods: In response to these challenges, we propose BCED-Net, which stands for Breast Cancer Ensemble Diagnosis Network. This innovative framework leverages transfer learning and the extreme gradient boosting (XGBoost) classifier on the Breast Cancer RSNA dataset. Our methodology involved feature extraction using pre-trained models—namely, Resnet50, EfficientnetB3, VGG19, Densenet121, and ConvNeXtTiny—followed by the concatenation of the extracted features. Our most promising configuration combined features extracted from deep convolutional neural networks—namely Resnet50, EfficientnetB3, and ConvNeXtTiny—that were classified using the XGBoost classifier.
Results: The ensemble approach demonstrated strong overall performance with an accuracy of 0.89. The precision, recall, and F1-score values, which were all at 0.86, highlight a balanced trade-off between correctly identified positive instances and the ability to capture all actual positive samples.
Conclusion: BCED-Net represents a significant leap forward in addressing persistent issues such as the high dimensionality of features and the risk of overfitting.

Keywords: Breast cancer classification; Feature extraction and concatenation; Performance evaluation; XGBoost classifier

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Introduction

Breast cancer is increasingly recognized as a major global health concern, affecting a significant number of people worldwide. This type of cancer begins with the unchecked growth of abnormal breast cells, leading to the formation of tumors that can spread and become life-threatening if not addressed. The causes of breast cancer are multifaceted, encompassing genetics, environmental factors, reproductive complexities, and hormonal imbalances. Risk factors include age, hormone replacement therapy, family history, and lifestyle choices. The seriousness of breast cancer is underscored by stark statistics that emphasize its alarming prevalence and extensive impact, despite considerable advances in research and treatment. In 2020, breast cancer was responsible for approximately 685,000 deaths globally [1]. This statistic paints a somber tableau of the profound repercussions this malady imposes on individuals, families, and communities around the world. A poignant observation is that nearly half of all breast cancer cases occur in women who do not have obvious risk factors, underscoring the complex nature of this disease. Although it predominantly affects women, breast cancer also occurs in men, accounting for about 0.5% to 1% of cases. As we explore the origins, progression, and effects of breast cancer, it becomes clear that addressing this issue effectively requires more than medical expertise. A comprehensive approach involving public health education, early detection strategies, and improved access to treatment is essential for the effective management and mitigation of this global health challenge [2]. Figure 1 presents a choropleth map that visually depicts

HIGHLIGHTS

- The global responsibility to address breast cancer, with its complex etiology and potentially fatal metastases, necessitates increased accuracy in early identification. Deep learning for diagnosis has made progress, but enduring problems such as handling high-dimensional data and reducing overfitting persist.
- Our study proposes BCED-Net (Breast Cancer Ensemble Diagnosis Network), a framework using the XGBoost classifier and transfer learning on the Breast Cancer RSNA dataset, as a solution to these problems. Machine learning classifiers are used for classification, and pre-trained deep convolutional neural network models are used for feature extraction.
- BCED-Net robustly classified breast cancer; our most promising configuration, which combined ConvNeXtTiny, Resnet50, and EfficientnetB3, consistently outperformed the others. Combining these models' features into one ideal setup allowed the XGBoost classifier to classify the data with an impressive accuracy of 89.1%, along with high precision, recall, and F1-score.

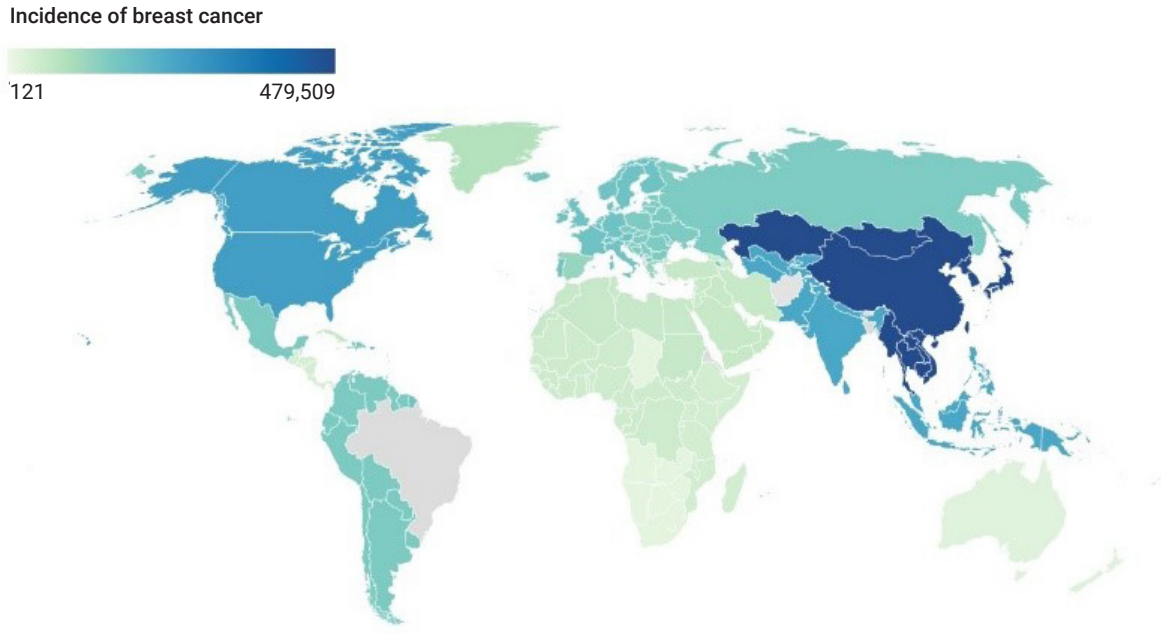

Figure 1. Choropleth map of the distribution and intensity of incident breast cancer cases.

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the distribution and intensity of breast cancer incidence, with Asia being the most affected continent.

The impetus for our research stems from the urgent need for precise and early breast cancer detection methods [3]. Current diagnostic techniques depend on the subjective visual assessments of medical professionals, which are prone to errors due to variations in interpretations and personal biases. To address these challenges, our study utilizes the intricate features extracted from deep convolutional neural network (CNN) models. These models enhance diagnostic accuracy by capturing complex patterns in medical images, providing more objective and reliable insights. The features are combined to create a comprehensive and informative feature set [4]. To increase the efficacy of our classification model, we have integrated an extreme gradient boosting (XGBoost)-based feature selection approach that identifies and retains the most influential features. Our methodology ultimately employs an XGBoost classifier that accurately distinguishes between cancerous and non-cancerous breast lesions. This tool is significant for aiding medical practitioners in their decision-making processes. Our multifaceted approach aims to deliver a dependable and automated system that supports oncologists in providing precise and timely assessments, potentially leading to improved patient outcomes and even life preservation [5]. Regular breast self-exams, clinical assessments, and mammography screenings are crucial in detecting breast cancer at manageable stages. Meanwhile, the incorporation of state-of-the-art technologies, particularly deep learning (DL), has opened promising avenues for enhancing detection accuracy. DL frameworks equipped with sophisticated algorithms can analyze extensive patient data and medical image datasets to detect complex patterns and anomalies that may indicate cancer. According to Murtaza et al. [6], radiologists can use these models to refine their image interpretations, which will reduce the likelihood of false positives and negatives and ultimately improve patient outcomes. This study has the potential to enhance the precision and effectiveness of automated diagnostic tools, benefiting oncologists and patients worldwide.

The structure of the remaining paper follows a systematic framework. Section 2 offers a concise overview of relevant prior research, critically analyzing and comparing various classification techniques used in diagnosing breast cancer. Section 3 details the dataset utilized in this research. Section 4 explores the methodology, highlighting key aspects such as the characteristics of the dataset, the pre-processing steps applied to the data, the details of feature extraction using deep CNNs (D-CNNs), and an examination of the classification methods being considered. Section 5 presents empirical results, providing a comprehensive analysis of how the classifiers performed across various evaluation metrics. Section 6 concludes the research and discusses the future scope of the work.

Literature Review

Breast cancer diagnosis and classification have been significantly advanced by machine learning (ML) and DL techniques. In this comprehensive literature survey, we explore various research efforts to understand their methodologies, performance, and potential impact on improving breast cancer classification [7]. These studies demonstrate the ongoing pursuit of more accurate and efficient diagnostic tools, which hold promise for timely detection. Bhardwaj and Tiwari [8] utilized the Wisconsin Breast Cancer database (WBCD) dataset and applied the Genetically Optimized Neural Network method, achieving high classification accuracy. Das et al. [9] employed a gene expression dataset from Mendeley to generate synthetic 2D datasets. Their innovative ensemble DL model included 3 CNNs as base classifiers, with a multilayer perceptron (MLP) used for the final classification. Their findings showed that the ensemble model surpassed the performance of single models. The GeneViT model featured a stacked autoencoder, Improved DeepInsight for image transformation, gene selection via t-SNE, and a channel expansion algorithm, all contributing to its superior performance on benchmark datasets. Adem [10] adopted a hybrid approach to analyze a microarray dataset for breast cancer, combining a stacked autoencoder with the Subspace k-nearest neighbors (KNNs) algorithm. On a smaller dataset from the Kent Ridge-2 database, this approach achieved an accuracy of 91.24%.

Alruwaili and Gouda [11] employed transfer learning to fine-tune pre-trained models such as ResNet50 and Nasnet-Mobile for evaluating their system on the Mammographic Image Analysis Society dataset. Their approach, which incorporated robustness augmentation techniques, achieved an accuracy of 89.5% with ResNet50 and 70% with Nasnet-Mobile. Mohammed et al. [12] utilized 184 ultrasound images to automate the characterization of breast lesions, achieving notable levels of specificity, sensitivity, and precision. Cai et al. [13] enhanced mammogram-based cancer diagnosis, achieving high accuracy through a comprehensive approach that included image quality improvement, segmentation, feature extraction, and an optimized CNN. Choudhury and Perumalla [14] combined CNNs with a vision transformer (ViT) for feature encoding to extract features from BUSI1311 and breast histopathological images. Their model's performance was further improved by a transfer learning strategy that incorporated BERT pre-training of Image Transformers. Additionally, Razavi et al. [15] achieved

strong mitosis detection and high segmentation accuracy using conditional generative adversarial networks across multiple datasets for mitosis and nuclei segmentation. These studies highlight the effectiveness of using various image modalities to address medical issues. In another study, Stephan et al. [16] introduced a highly accurate hybrid artificial bee colony with whale optimization algorithm, which was subsequently evaluated on multiple breast cancer datasets.

In a similar vein, Budak et al. [17] developed a model that combines a fully convolutional network for advanced feature extraction with a bidirectional long short-term memory to detect breast cancer using the BreaKHis database. Their model achieved a remarkable average accuracy of 91.90%. Additionally, Kadam et al. [18] proposed a feature ensemble learning approach that combines Sparse Autoencoders with Softmax Regression on the WBCD dataset, achieving an impressive accuracy of 98.60%. Togacar et al. [19] introduced the innovative BreastNet CNN model, which utilizes the BreaKHis dataset and demonstrated exceptional abilities in detecting breast cancer. Furthermore, Ayana and Choe [20] developed the BUViTNet model, employing a multistage transfer learning approach with visual information, using publicly available ultrasound breast image datasets. This framework achieved remarkable accuracies of 98.58% and 97.87% for binary and multi-class classification, respectively, utilizing INbreast mammograms.

Strelcenia and Prakoonwit [21] employed the WBCD without images and introduced the Kullback-Leibler Divergence Conditional GAN method to generate synthetic data. This method proved stable and accurately represented the original dataset. Dheeba et al. [22] developed an abnormality detection algorithm using a clinical database of 216 mammograms, achieving an area under the receiver operating characteristic curve score of 0.96853. Ferreira et al. [23] utilized RNA-sequencing (RNA-Seq) datasets along with image-derived features from blood smears and breast cell nuclei images, exploring various autoencoders and training approaches. Their research consistently outperformed baseline models, achieving notable F1 scores in RNA-Seq and image-derived data classification. Xiong et al. [24] used a micro-computed tomography dataset to predict breast cancer bone metastases, introducing a temporal variational autoencoder that demonstrated superior predictive accuracy compared to existing models. Tummala et al. [25] utilized the BreaKHis dataset and achieved exceptional performance with an ensemble of Swin transformers, recording average test accuracies of 96.0% for 8-class and 99.6% for binary classification. Wang et al. [26] introduced a model for recognizing colorectal cancer in pathological images through the use of semi-supervised DL. They utilized well-established CNN models, including VGG19, ResNet101, DenseNet201, and the ViT base model. Among these, ResNet101 demonstrated the highest accuracy (95.59) and F1 score (94.76). Qin et al. [27] explored breast cancer lesion segmentation in dynamic contrast-enhanced magnetic resonance imaging by employing the TR-IMUnet model. This 2-stage framework integrated the U-Net architecture with a transformer module to improve segmentation accuracy. Su et al. [28] developed the YOLO (You Only Look Once) and LOGO (Local-Global) model for detecting and segmenting masses in mammography, utilizing the CBIS-DDSM and INBreast datasets. This model surpassed the performance of baseline methods. Supriya and Deepa [29] introduced an optimized artificial neural network that incorporated data pre-processing, feature selection using the Modified Dragonfly algorithm, and optimization with the Gray Wolf Optimization algorithm. Their bit plane complexity segmentation showed superior performance compared to the Improved Weighted-Decision Tree classifier.

Abdar and Makarenkov [30] conducted a comprehensive analysis of the WBCD using the CWV-BANNSVM ensemble model, which achieved a 100% accuracy rate in depicting overfitting. Chiu et al. [31] analyzed a dataset from the University Hospital Centre of Coimbra, employing principal component analysis for dimension reduction and using an MLP for feature extraction. Their method achieved an impressive accuracy of 86.97% through 10-fold cross-validation. Wang [32] explored the use of microwave imaging combined with ML for breast cancer detection, showing promising results. The study involved a training dataset of 3-dimensional contrast-source inversion images and demonstrated exceptional performance on both synthetic and experimental data. Prinzi et al. [33] applied transfer learning to YoloV3, YoloV5, and YoloV5-Transformer using the CBIS-DDSM, INbreast, and a proprietary dataset. The smaller YoloV5 model exhibited superior performance with a mean average precision of 0.621, and the integration of YOLO predictions with Eigen-CAM-generated saliency maps effectively reduced false negatives in clinical settings.

In conclusion, the studies reviewed in this literature survey introduce innovative methods for diagnosing and classifying breast cancer. However, these studies also exhibit several limitations and drawbacks that must be taken into account when considering their implementation in clinical settings. These limitations include small and specific dataset sizes, limited diversity within datasets, difficulties in generalizing findings to clinical environments, challenges in interpreting complex models, potential biases in imbalanced datasets, a lack of sufficient external validation, ambiguous clinical relevance, and inadequate attention to ethical and privacy

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issues. In the following section, we introduce our solution designed to address these challenges-the Breast Cancer Ensemble Diagnosis Network (BCED-Net). Our model leverages the capabilities of transfer learning by integrating a range of pre-trained models for feature extraction. Additionally, we utilize ML classifiers to improve the accuracy of breast cancer classification. BCED-Net not only seeks to enhance the robustness, adaptability, and interpretability of breast cancer diagnosis models but also addresses ethical and privacy concerns by incorporating a diverse array of pre-trained models.

Materials and Methods

The RSNA Breast Cancer Detection dataset, publicly available on Kaggle, forms the basis of this research. It comprises over 60,000 mammograms from women, totaling more than 110,000 images, thus providing a substantial resource for analysis. Each mammogram is meticulously annotated to show whether a breast lesion is present or absent [34]. The dataset is divided into 3 subsets: 10% is allocated for validation, 10% for testing, and the remaining 80% for training purposes. Figure 2 presents 2 sample images from the RSNA dataset: one from a cancerous subject and one from a normal subject.

The primary objective of this study was to utilize the dataset to create a robust model that can accurately classify images into their respective categories. The main focus was on developing a model that can effectively differentiate between cancerous and normal cases using the provided images.

Methodology

The research's step-by-step methodology is graphically represented by the flowchart in Figure 3, which provides a clear and concise overview of the methodology used in this paper by elucidating the systematic procedures, techniques, and processes that were employed throughout the research process.

Data Pre-Processing

To enable essential model training and performance optimization, the first step of the process involved data pre-processing of the input images.

Resize

Images were scaled to a uniform size of 64×64 pixels. This standardization ensured that each image could be processed consistently in subsequent stages. As a result, the model benefited from learning from uniform image representations.

Scaling

Every image's pixel values were adjusted to fall between 0 and 1. This scaling was necessary for ML algorithms to process numbers effectively, as it standardized the intensity levels of the pixels.

These pre-processing stages, which converted the input images into a consistent and optimized format, enabled more effective and precise extraction of information from the data.

Feature Extraction

The scaled and resized images were input into various configurations of pre-trained CNNs to extract features. These D-CNNs were selected based on their diverse architectures and capabilities. The feature values were derived by removing the final convolutional layer from these networks. This removal exposed the activations from intermediate

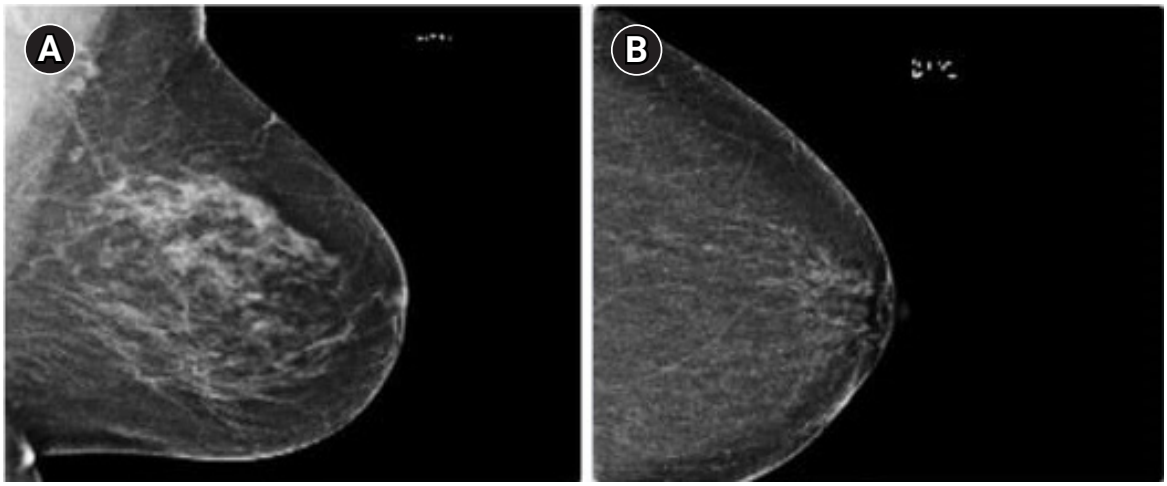

Figure 2. Two sample images from the RSNA dataset, (A) with cancer and (B) without cancer.

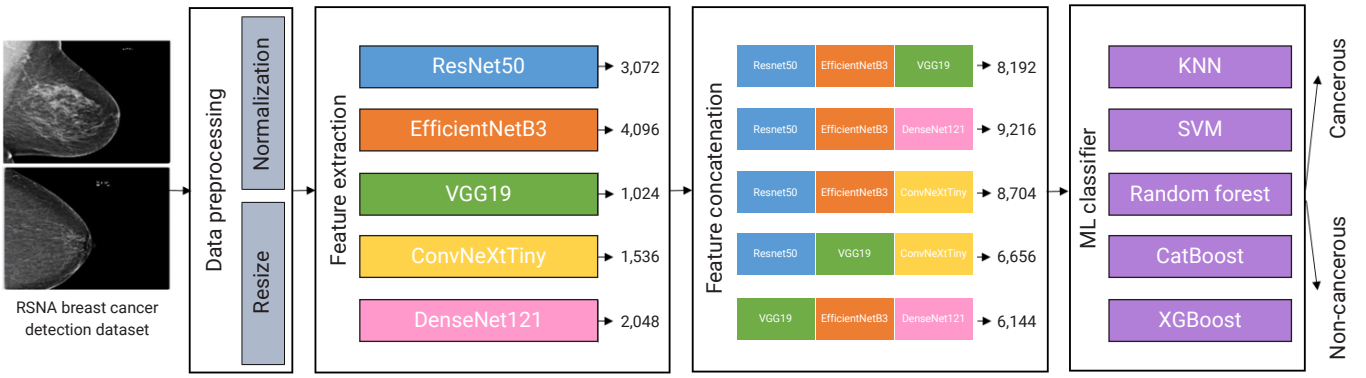

Figure 3. Methodology of the study.
KNN, k-nearest neighbor; ML, machine learning; SVM, support vector machine; XGBoost, extreme gradient boosting.

convolutional layers, after which the max pooling technique was applied to produce feature maps of the input images. The resulting feature vectors were then utilized for classification using ML algorithms. This approach involved examining a variety of pre-trained CNN models, each with a unique architecture, to capture a comprehensive range of image features [35].

Fusing Complex Deep Features

Considering the complex patterns found in breast lesion imagery, a standalone D-CNN may struggle to fully capture the intricate details present in mammographic images. To tackle this complexity, the current study introduces a method that integrates features from a variety of D-CNN models, thereby capturing the diverse patterns found in input dermoscopic images. We systematically explored different combinations of deep features, with a specific focus on those obtained from pre-trained models, including EfficientNetB3, ResNet50, VGG19, ConvNeXtTiny, and DenseNet121 [36–40].

The feature extraction process involves removing the fully connected layers from these models and directing the input through their final convolutional layers to global average pooling layers. The dimensionality of the features varies among these models, as shown in Figure 4.

The aggregation of these distinctive features results in a composite feature vector with a dimensionality of 11,776. Given the dimensionality of the synthesized feature vector, a careful evaluation is performed to identify features that may have limited informative value. Following this assessment, a streamlined feature vector is created, thereby improving the ML classifier's discriminatory capabilities and overall performance.

Feature Selection and XGBoost Classification

This section covers the strategic process of feature selection followed by the application of the XGBoost classifier for practical classification tasks. A variety of ML classifiers, such as support vector machine, random forest, KNN, XGBoost, and CatBoost, were assessed using a combined feature vector. The XGBoost classifier exhibited the best performance, leading to its selection as the preferred classifier by Chen and Guestrin [41].

To address the challenge of high-dimensional features, we employed a dimension reduction technique that assigns importance scores to individual features using the intrinsic evaluation mechanism of the XGBoost classifier. We then selected the top K-ranked features based on the validation accuracy achieved during classifier training. Subsequently, the XGBoost classifier was comprehensively trained using these selected features. In parallel, we constructed a combined feature set for the test set images, which was then used to evaluate the classifier's real-world performance.

Results and Discussion

The performance of various classifiers was evaluated using a dataset containing 64×64 images [42]. This assessment utilized different performance metrics, as presented in Table 1.

The feature extraction process involved experimenting with various combinations of pre-trained models. Different sets of features, derived from these model combinations, were used to train an XGBoost classifier. The performance of each set was assessed based on validation accuracy. Table 2 displays the combinations of pre-trained CNN models along with the number of concatenated features.

Table 3 presents the values of several evaluation metrics—accuracy, precision, recall, and F1-score—used to assess the performance of feature extraction from proposed combinations of pre-trained CNN models and classification using ML classifiers.

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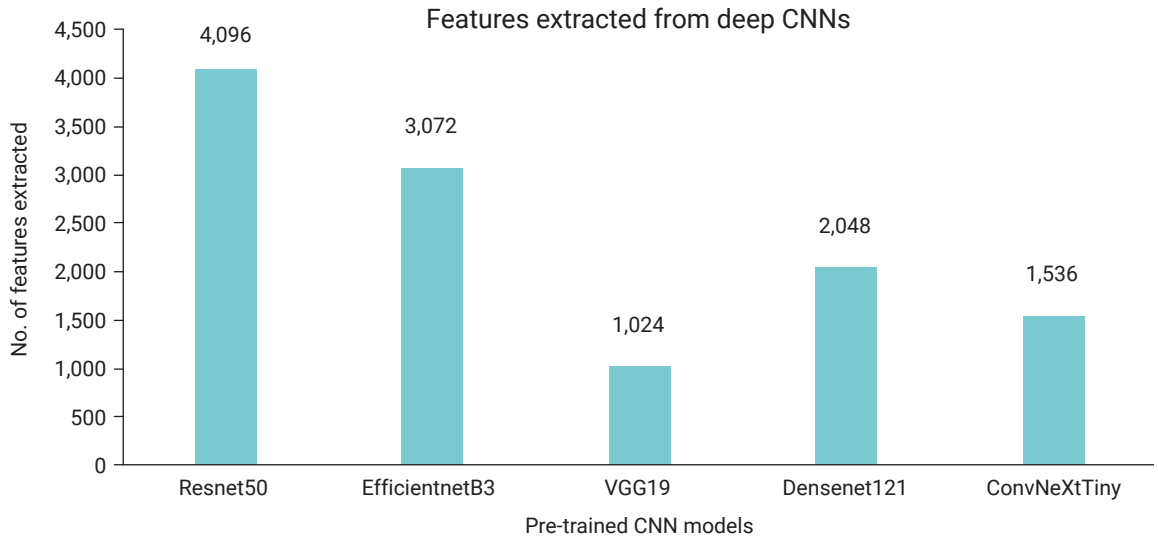

Figure 4. Number of features extracted from pre-trained models.
CNN, convolutional neural network.

Table 1. Performance metrics used in the present research

Performance metrics	Formula
Accuracy	$\text{Accuracy} = \frac{TP+TN}{TP+FP+TN+FN}$
Precision	$\text{Precision} = \frac{TP}{TP+FP}$
Recall	$\text{Recall} = \frac{FP}{FP+FN}$
F1-score	$\text{F1-score} = \frac{2*\text{Precision}*\text{recall}}{\text{Precision}+\text{recall}}$

TP, true positive; TN, true negative; FP, false positive; FN, false negative.

Table 2. Combinations of pre-trained models and numbers of concatenated features

Combination of pre-trained models	Concatenated features
Resnet50+EfficientnetB3+VGG19	8,192
Resnet50+EfficientnetB3+Densenet121	9,216
Resnet50+EfficientnetB3+ConvNeXtTiny	8,704
Resnet50+VGG19+ConvNeXtTiny	6,656
VGG19+EfficientnetB3+Densenet121	6,144

The confusion matrix shown in Figure 5 demonstrates the performance of a model that utilized feature extraction. This model combined ResNet50, EfficientNetB3, and ConvNeXtTiny, and integrates these with an XGBoost classifier.

Examining the values from the provided table, distinct performance trends emerged across various combinations of pre-trained models and classifiers. These variations in performance may have been due to potential overfitting or underfitting within the models, which could have impacted the complexity of the features extracted. Combinations that included Resnet50, EfficientnetB3, and ConvNeXtTiny appeared to capture more intricate patterns within the data, resulting in higher accuracy, precision, recall, and F1-score metrics. In contrast, combinations involving Densenet121 and VGG19 seemed to struggle with representing the necessary complexity within the dataset, adversely affecting the classifiers' predictive capabilities. The discrepancies observed in feature extraction and the alignment of complexity with classifier requirements might explain the varying performance metrics observed across the combinations of pre-trained models and classifiers. Improving the models' architectures and refining feature engineering techniques could potentially improve the representativeness and discriminative power of the extracted features, thereby boosting overall predictive capabilities.

Comparison with State-of-the-Art Algorithms

This section compares the proposed ensemble technique, which classifies breast lesions in mammography images as benign or malignant, with existing state-of-the-art algorithms.

Table 4 demonstrates that the proposed model surpasses existing techniques in classifying breast lesions. The use of transfer learning with pre-trained D-CNN, ResNet50, and Nasnet-Mobile resulted in low accuracy, primarily due to data mismatches and limited fine-tuning on a scarce training dataset. The subpar performance of MiNuGAN with cGAN and focal loss can be attributed to the introduction of noise by GANs, complicating the discrimination between real and synthetic images. ResNet-SCDA-50, enhanced with SCDA data augmentation, achieved an accuracy of 86.3% due to dataset variations caused by the data augmentation. In

Table 3. Accuracy of ML classifiers for concatenated features

Combination of pre-trained models	ML classifier	Accuracy	Precision	Recall	F1-score
Resnet50+EfficientnetB3+VGG19	KNN	0.69	0.66	0.63	0.64
	SVM	0.79	0.78	0.73	0.75
	Random forest	0.79	0.76	0.74	0.75
	CatBoost	0.81	0.79	0.75	0.77
	XGBoost	0.83	0.80	0.82	0.81
Resnet50+EfficientnetB3+Densenet121	KNN	0.64	0.61	0.62	0.61
	SVM	0.78	0.75	0.77	0.76
	Random forest	0.69	0.67	0.70	0.68
	CatBoost	0.78	0.74	0.75	0.74
	XGBoost	0.79	0.74	0.71	0.72
Resnet50+EfficientnetB3+ConvNeXtTiny	KNN	0.71	0.70	0.68	0.69
	SVM	0.84	0.82	0.83	0.82
	Random forest	0.81	0.79	0.81	0.80
	CatBoost	0.82	0.80	0.79	0.79
	XGBoost	0.89	0.86	0.86	0.86
Resnet50+VGG19+ConvNeXtTiny	KNN	0.67	0.64	0.61	0.62
	SVM	0.73	0.71	0.69	0.70
	Random forest	0.75	0.74	0.74	0.74
	CatBoost	0.75	0.71	0.75	0.73
	XGBoost	0.76	0.74	0.74	0.74
VGG19+EfficientnetB3+Densenet121	KNN	0.64	0.61	0.62	0.61
	SVM	0.63	0.62	0.61	0.61
	Random forest	0.65	0.63	0.63	0.63
	CatBoost	0.68	0.68	0.69	0.68
	XGBoost	0.70	0.68	0.70	0.69

ML, machine learning; KNN, k-nearest neighbor; SVM, support vector machine; XGBoost, extreme gradient boosting.

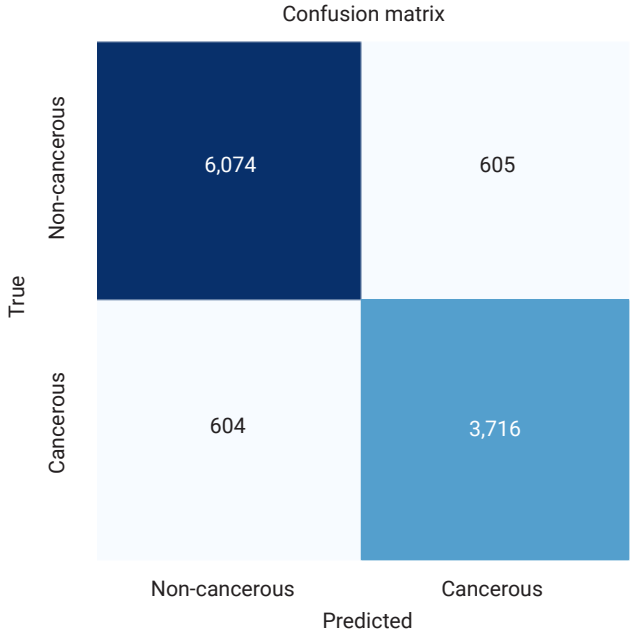

Figure 5. Confusion matrix for the proposed model.

Table 4. Comparison of the proposed model to state-of-the-art models

Algorithm	Accuracy
Transfer learning with ResNet50 and Nasnet-Mobile	87.5
MiNuGAN with cGAN and focal loss	72.1
ResNet-SCDA-50 with SCDA data augmentation	86.3
CNNs for feature extraction, ViT and transfer learning with BERT pre-training, and RNN-LSTM	80.6
Metaheuristics using Dunn index, 3D vectors	84.9
Proposed methodology (features extracted by Resnet50+EfficientnetB3+ConvNeXtTiny and XGBoost classifier)	89.0

CNN, convolutional neural network; ViT, vision transformer; RNN, recurrent neural network; LSTM, long short-term memory.

another approach that involved feature extraction through CNNs and ViT, coupled with transfer learning through BERT, the lower accuracy resulted from the combination of different neural networks, which led to suboptimal feature integration. The algorithm that utilized metaheuristics for classification was significantly affected by the choice of parameters, accounting for its lower accuracy. Finally, the proposed model attained an accuracy of 89% as it extracted intricate features from the input images using D-CNN models and then leveraged an ML classifier for effective

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decision boundary modeling.

Key Findings of the Research Work

Consistent high performers

Models such as Resnet50, EfficientnetB3, and ConvNeXtTiny consistently excelled in producing superior results across various classifiers. Their exceptional ability to effectively extract and represent complex data patterns is likely the key to their success.

Among these combinations, Resnet50+EfficientnetB3 +ConvNeXtTiny stood out with its impressive accuracy of 0.89, precision of 0.86, recall of 0.86, and F1-score of 0.86. These results demonstrate the model's robust predictive capabilities.

Underperforming combinations

Pairings involving Densenet121 or VGG19 tended to underperform, showing lower metrics across classifiers. This suggests that these models may have limitations in extracting highly representative and discriminative features, potentially leading to decreased predictive power.

One notable example is the impressive results achieved by combining Resnet50, EfficientnetB3, and Densenet121 with XGBoost. This powerful combination resulted in an accuracy of 0.79, precision of 0.74, recall of 0.71, and an F1-score of 0.72.

Influence of the selection of pre-trained models

The choice of pre-trained models had a profound impact on the success of feature extraction and directly affected the overall predictive ability of classifiers.

Conclusion

This study explored the synergy of combining and refining features extracted from various pre-trained CNN models on natural images, aiming to classify tumors as either cancerous or non-cancerous using different classifiers. Notably, the XGBoost classifier proved to be the most effective, particularly when trained with the amalgamated and refined features obtained through feature selection. The highest level of accuracy was attained by the XGBoost classifier, which excelled with the optimized combined features from feature selection.

There is significant potential for expanding this research in the future. Exploring a wider range of feature extraction techniques from various CNN architectures could further improve accuracy. Moreover, incorporating larger and more diverse datasets, along with advancements in neural network architectures, could lead to more robust and reliable systems for classifying breast tumors. Additionally, given the dynamic nature of the medical field, the integration of real-time diagnostic support tools into clinical settings offers a promising opportunity for the practical application of these methodologies. In conclusion, this study highlights the potential of using DL for feature extraction and selection and opens up exciting possibilities for future research aimed at increasing the accuracy and practicality of breast lesion classification methodologies.

Notes

Ethics Approval

All procedures were conducted in accordance with the ethical standards.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The data that support the findings of this study are openly available in Kaggle at https://www.kaggle.com/datasets/theoviel/rsna-breast-cancer-512-pngs.

Authors' Contributions

Conceptualization: DA, FA; Data curation: DA; Formal analysis: RG; Investigation: RG; Methodology: DA, FA; Project administration: RG; Software: DA; Supervision: RG; Validation: DA, FA; Visualization: DA, FA; Writing–original draft: DA, FA; Writing–review & editing: RG. All authors read and approved the final manuscript.

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Original Article

Performance of indicators used in regular risk assessments for COVID-19 in association with contextual factors

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ABSTRACT

Objectives: This study aimed to summarize the results of coronavirus disease 2019 (COVID-19) risk assessments and to examine the associations between risk levels and various indicators, including COVID-19 incidence, risk perception, community mobility, and government policy.

Methods: The results of the risk assessment and the indicators utilized were summarized. From November 2021 to May 2022, the COVID-19 risk level was evaluated on a weekly basis, and its correlation with these indicators was analyzed. Data were obtained from press releases by the Korea Disease Control and Prevention Agency, regular surveys conducted by Hankook Research, and information available on the Google and Oxford websites.

Results: Weekly risk assessments were conducted for 30 weeks, using different indices depending on the phases. Correlation analysis revealed the strongest positive correlation between risk level and risk perception ($r=0.841$). The risk level from "1-week lead" demonstrated a strong positive correlation with the time-varying reproduction number (Rt). Similarly, the risk level from "week lagged value" showed a strong positive correlation with the number of severe cases in the hospital.

Conclusion: At the time of risk assessment, the Rt precedes the risk level, while severe cases in hospitals follow. Therefore, the assessed risk level functioned as an early warning system. Risk perception demonstrated the strongest correlation with the risk level, suggesting consistency throughout the assessment period. Contextual indicators (e.g., risk perception) that consider time lags and implementation scales, could improve the evaluation of future risk assessment results, particularly when there are challenges in reflecting specific situations in coordinated emergency response.

Keywords: COVID-19; Emergency; Risk assessment

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Introduction

Risk assessments provide information essential for managing the adverse effects of public health risks [1] and must be completed promptly to enable actions such as prevention and response to disease outbreak. Some countries conducted risk assessments even during the coronavirus disease 2019 (COVID-19) pandemic [2,3]. In the Republic of Korea, rapid risk assessments (RRAs) were carried out to inform strategic responses [4]. In the early stages of the outbreak, when cases were primarily concentrated in China, public health authorities in various countries conducted RRAs to evaluate the potential threat of the outbreak spreading from China to other countries. These assessments were based on limited information about the virus's characteristics and transmission routes, aiming to control the spread and prevent new outbreaks [5].

During the COVID-19 public health emergency, which lasted from January 30, 2020, to May 5, 2023 [6], the pattern of the outbreak evolved due to the emergence of new variants. This change also affected risk assessment practices. For instance, the Robert Koch Institute developed risk levels and recommendations based on a qualitative evaluation of the latest global data, the epidemiological situation of COVID-19 in Germany, and the availability of preventive and treatment options [7]. Additionally, the United Kingdom Health Security Agency (UK HSA) employed impact indicators, such as the size and severity of outbreaks, to determine the alert levels for UK chief medical officers [8].

Owing to changes in outbreak patterns and ongoing outbreaks, the Republic of Korea gradually eased social distancing measures in November 2021, introducing a policy termed "Gradual Recovery to a New Normal." Additionally, weekly COVID-19 risk assessments were proposed to accurately monitor changes in COVID-19 outbreaks following the implementation of this new policy. These weekly COVID-19 risk assessments, which were conducted starting in November 2021, utilized different methods and indicators compared to the initial RRAs.

Some countries also modified their risk assessments to better reflect their specific needs. In the United States, indicators such as the number of newly confirmed cases per week, the number of newly hospitalized patients per week, and the percentage of hospital beds occupied by COVID-19 patients were used to inform community levels [9]. The UK HSA set the alert level by combining expert judgment and risk assessment with more quantifiable indicators and thresholds [8]. Utilizing available information to understand and communicate the situation is a crucial method in responding to COVID-19.

HIGHLIGHTS

- Risk assessments, which were developed using various indicators, and risk levels were released weekly to the public in the Republic of Korea, aiding in the implementation of preventive measures.
- Weekly coronavirus disease 2019 risk assessments were conducted to serve as an early warning system and to provide timely justification for government intervention policies.
- If risk assessments are tailored for target audience and incorporate contextual indicators, they could provide more useful and timely support for public health measures.

In this context, this study aimed to summarize the findings from the weekly COVID-19 risk assessments conducted by the Korea Disease Control and Prevention Agency (KDCA). It also sought to explore the relationship between the outcomes of these assessments and various factors, including incidence rates and contextual elements. Contextual factors encompass indicators that are considered in risk evaluations, taking into account all influences on risk, such as infrastructure, cultural practices, and beliefs [1].

Materials and Methods

The data analyzed in this study were sourced from KDCA press releases with information on the weekly risk assessments conducted from November 2021 to May 2022. Additionally, raw data and COVID-19 risk assessment indicator data were obtained from the National Infectious Disease Surveillance System website. Key indicators such as the "ratio of the incidence rate to maximum medical capacity" and the "availability of intensive care unit (ICU)" were crucial for evaluating changes in the COVID-19 risk assessments. Expert opinions were subsequently utilized to determine the derived risk levels. The weekly COVID-19 risk assessment was categorized into 5 levels: very low, low, moderate, high, and very high.

The weekly COVID-19 risk assessment incorporated 36 indicators across 4 categories: COVID-19 response capacity, incidence, vaccination, and diagnostic testing, as detailed in Table S1. The response capacity category included indicators such as ICU availability, hospitalization of severe cases, the ratio of incidence rate to medical capacity, and the availability of various treatment facilities for confirmed cases. Additional

indicators in this category were the percentage of patients treated at home, the daily average number of patients treated at home per week, and the percentage managed under quarantine. The incidence category comprised indicators including death cases, fatality rate, newly severe cases, severity rate, number of hospital admissions, daily average number of confirmed cases, newly confirmed cases, percentage of unvaccinated individuals (including those with only the first vaccination), the time-varying reproduction number (Rt) [10], and the weekly percentage of positive test results (Table 1). Indicators in the vaccination category encompassed the percentage of individuals fully vaccinated, the percentage receiving a booster shot, the percentage of those aged 60 years and older who are fully vaccinated, the percentage of those aged 60 years and older receiving a booster, the rate of fourth vaccinations in those aged 60 years and older, and the vaccination's effectiveness against infection, severity, and death. For the diagnostic testing category, indicators included the omicron variant detection rate and the BA.2 detection rate (Table S1).

Among the above indicators, the ratio of the incidence rate to medical capacity was used to assess medical capacity based on the number of hospital beds allocated for patients with severe diseases. This capacity was estimated by considering the number of patients that the available hospital beds (ICU and step-down unit) could accommodate, factoring in the proportion of cases that progress to severe disease and the average duration of hospital stays. The ratio of the incidence rate to medical capacity was determined by dividing the weekly average of daily confirmed cases by the estimated medical capacity (Table S1).

Community mobility, the risk perception rate, and the Oxford stringency index were analyzed alongside COVID-19 risk assessment indicators to explore the social and policy changes prompted by the COVID-19 pandemic [11].

The community mobility rate, as reported in the Google Community Mobility Report, reflects the percentage change in activity at retail and leisure facilities compared to baseline days. These baseline days were established by taking the median of data collected daily over a 5-week period from January 3 to February 6, 2020. Retail and leisure facilities include venues such as restaurants, cafes, shopping centers, amusement parks, museums, libraries, and movie theaters. The risk perception rate was derived from responses to the survey question regarding the "perception of the seriousness of COVID-19 spreading in South Korea," conducted by Hankook Research. This web-based survey was distributed biweekly via mobile phone or email to a sample of 1,000 male and female participants aged 18 years or older. The sample was proportionally allocated by region, sex, and age. Participants could choose from 5 responses: not serious, not so serious, mederate, serious, and very serious. The percentage of responses categorized as "very serious" was used to calculate the risk perception rate in this study. Additionally, to address gaps in the data due to the biweekly frequency of the survey, weeks without surveys were estimated using linear interpolation to fill in the missing data.

The Oxford stringency index was used as an indicator to evaluate the characteristics of policies. This index measures the strictness of each country's policy responses, including public health and social intervention measures, to combat the spread of COVID-19. It is calculated by taking a simple average of the converted values of 9 constituent indicators on a ranking scale, covering containment, closure, and health system policies, each scored out of 100 points. For this study, the index values reported on Saturdays during the COVID-19 risk assessment period were used.

Table 1. Definitions of the weekly COVID-19 risk assessment outcome indicators used in the analysis

Indicator	Definition
Newly confirmed cases	Patients diagnosed with COVID-19 during the corresponding week by PCR or RAT
Newly confirmed cases over 60 y	Patients aged ≥60 years diagnosed with COVID-19 during the corresponding week by PCR or RAT
Newly confirmed cases under 18 y	Patients aged ≤18 years diagnosed with COVID-19 during the corresponding week by PCR or RAT
Rt	The weekly mean Rt value was calculated using the Cori method [10]
Hospital admissions	No. of patients allocated to critical care and semi-critical care beds or infectious disease-dedicated hospitals during the corresponding week
Newly severe cases	No. of reported confirmed cases and assigned a treatment meeting the criteria for severe case during the corresponding week
Severe cases in hospitals	No. of reported confirmed cases receiving non-invasive ventilation, high-flow O_2, invasive ventilation, multi-organ failure, ECMO, or CRRT treatment during the corresponding week
Death	No. of reported confirmed cases that died during the corresponding week

COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; RAT, rapid antigen test; Rt, time-varying reproduction number; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

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To examine the distributions of the parameters analyzed in the weekly COVID-19 risk assessments in the Republic of Korea, the results for each indicator were presented as means and ranges. Linear graphs were utilized to compare the weekly COVID-19 risk levels with corresponding changes in COVID-19 incidence, public perception, and policy adjustments during the same timeframe. Additionally, correlation analysis was performed among various metrics: newly confirmed cases per week, the number of confirmed cases aged over 60 years per week, confirmed cases under 18 years per week, weekly hospitalizations, and weekly severe disease cases. Further correlation analyses included the daily average number of hospitalized patients with severe disease, weekly death counts, community mobility rates, risk perception rates, and the Oxford stringency index, categorized by weekly risk levels. The risk level was adjusted for each week to 1 week prior, 1 week subsequent, and 2 weeks subsequent to determine the effect of elapsed time. Correlations were assessed using Spearman correlation analysis.

Ethics Approval

This study was approved by the Institutional Review Board of the KDCA (No: 2023-02-05PE-A) and performed in accordance with the principles of the Declaration of Helsinki.

Results

The risk assessments analyzed in this study spanned 30 weeks, from November 2021 to May 2022. They encompassed data on national risk levels and risk levels in non-capital

Table 2. Distribution of weekly COVID-19 risk assessment outcome indicators used in the analysis

Indicators (case)	Mean ± SD (range)	Week used
Risk level	4 ± 1 (1–5)	30
Newly confirmed cases	1,068,357 ± 887,048 (129,337–2,832,230)	16
Newly confirmed cases over 60 y	105,533 ± 148,761 (3,124–504,070)	30
Newly confirmed cases under 18 y	192,569 ± 223,120 (6,121–710,417)	22
Rt	1.09 ± 0.27 (0.70–1.60)	30
Hospital admissions	6,434 ± 3,869 (1,176–13,387)	30
Newly severe cases	515 ± 286 (133–1,093)	30
Severe cases in hospitals	688 ± 317 (224–1,255)	30
Death	710 ± 721 (126–2,516)	30

COVID-19, coronavirus disease 2019; SD, standard deviation; Rt, time-varying reproduction number.

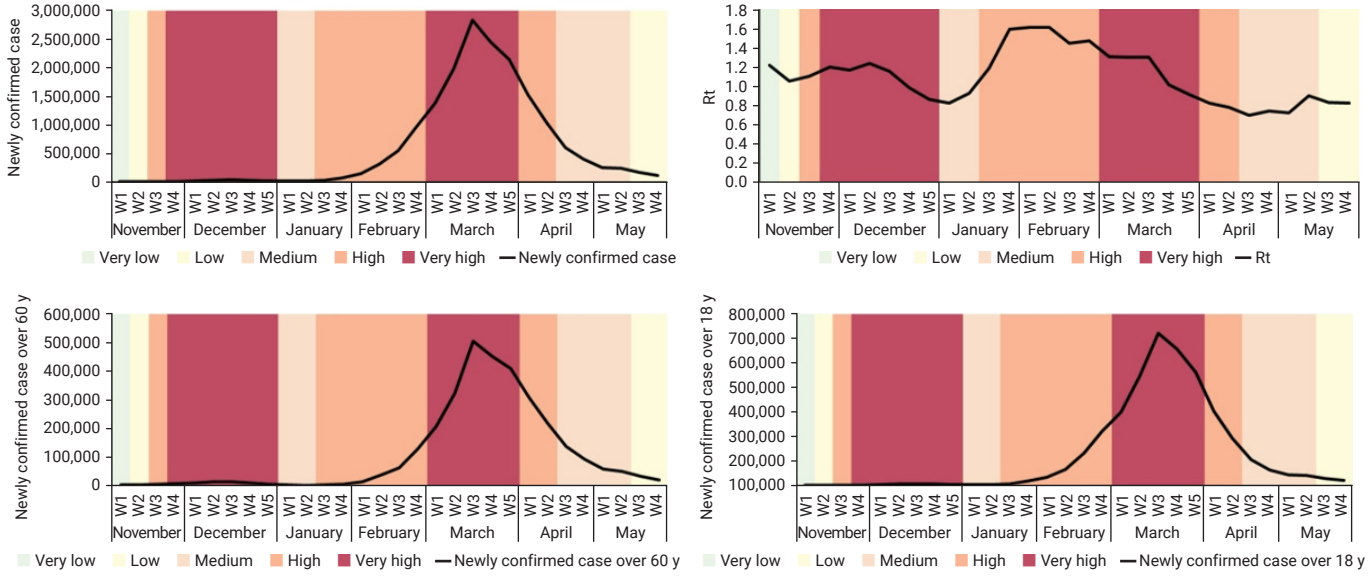

Figure 1. Weekly COVID-19 risk levels in the Republic of Korea and the number of confirmed COVID-19 cases (November 2021 to May 2022).
W1, week 1; W2, week 2; W, week 3; W4, week 4; W5, week 5; Rt, time-varying reproduction number.

areas, which varied from very low to very high. In capital areas, risks ranged from low to very high (Table 2). The review of risk assessment indicators primarily focused on the incidence rate and the countermeasures implemented during that period.

The weekly COVID-19 risk level escalated from "very low" in the first week of November 2021 to "very high" for 6 consecutive weeks, spanning from the fourth week of November to the fifth week of December. The risk level then consistently remained high before it began to decline gradually from the first to the fifth week of March 2022 (Figure 1). During the time when the delta and omicron variants were dominant, several indicators exhibited similar trends. These included the number of newly confirmed cases, the number of new cases in individuals aged over 60, the number of new cases in individuals under 18, the number of hospitalized patients, the number of patients hospitalized with severe disease, the number of newly confirmed severe cases, the number of deaths, and the risk perception rate. These indicators typically peaked between 2 and 5 weeks after the risk level reached "very high" (Figures 1–3). Additionally, when the risk assessment was "very high," the

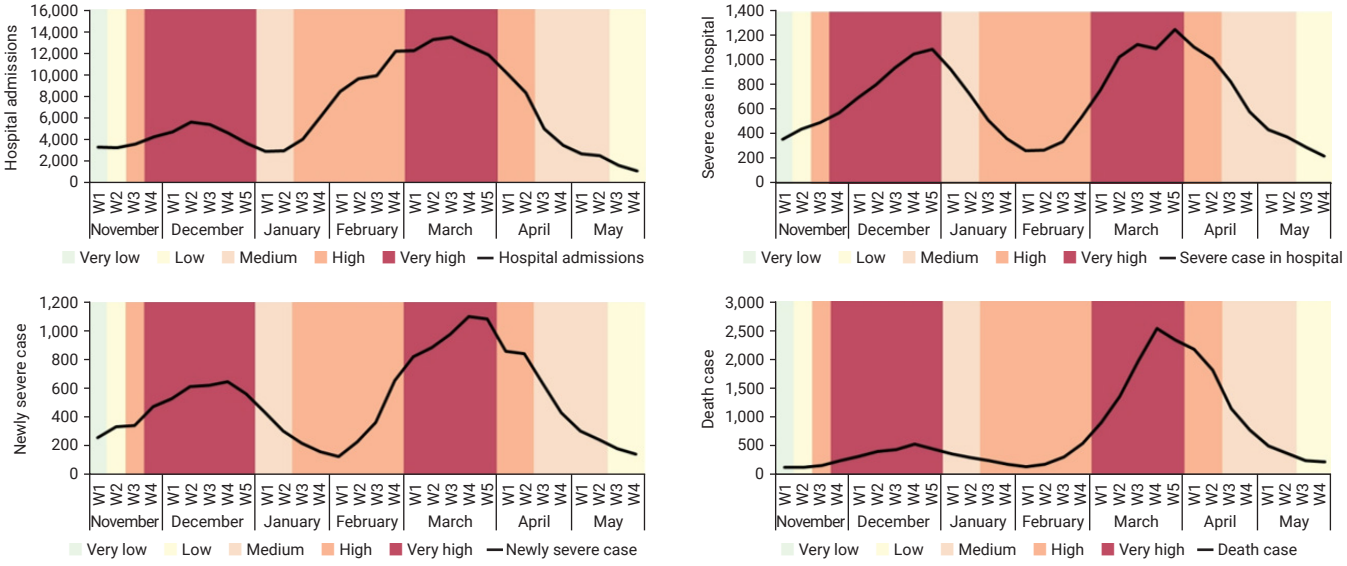

Figure 2. Weekly COVID-19 risk levels in the Republic of Korea and the number of severe COVID-19 cases (November 2021–May 2022).
W1, week 1; W2, week 2; W, week 3; W4, week 4; W5, week 5.

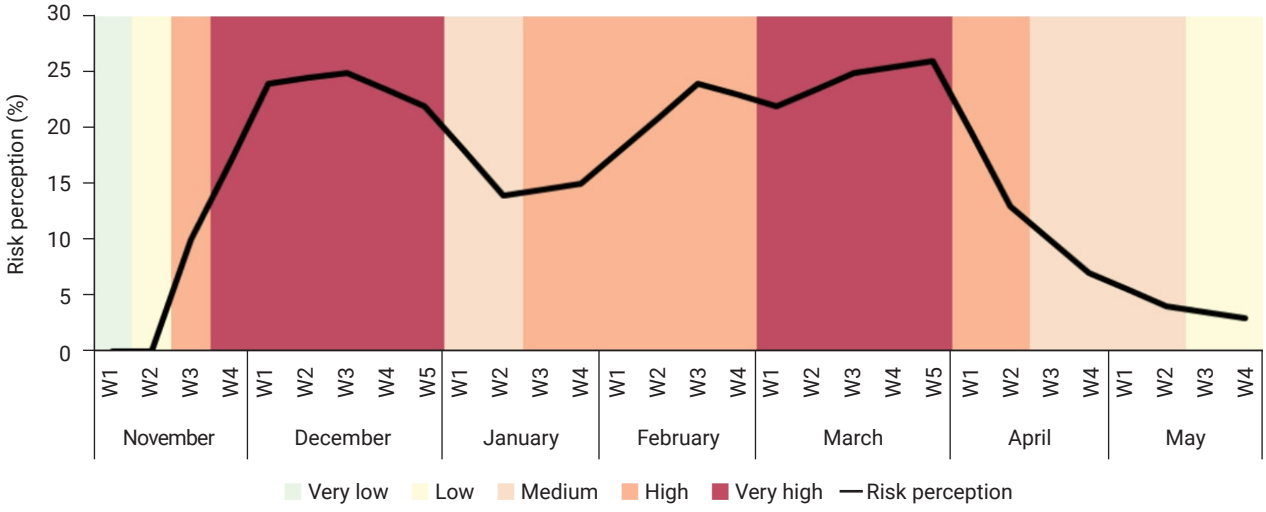

Figure 3. Weekly COVID-19 risk levels in the Republic of Korea and the risk perception rate (November 2021 to May 2022).
W1, week 1; W2, week 2; W, week 3; W4, week 4; W5, week 5.

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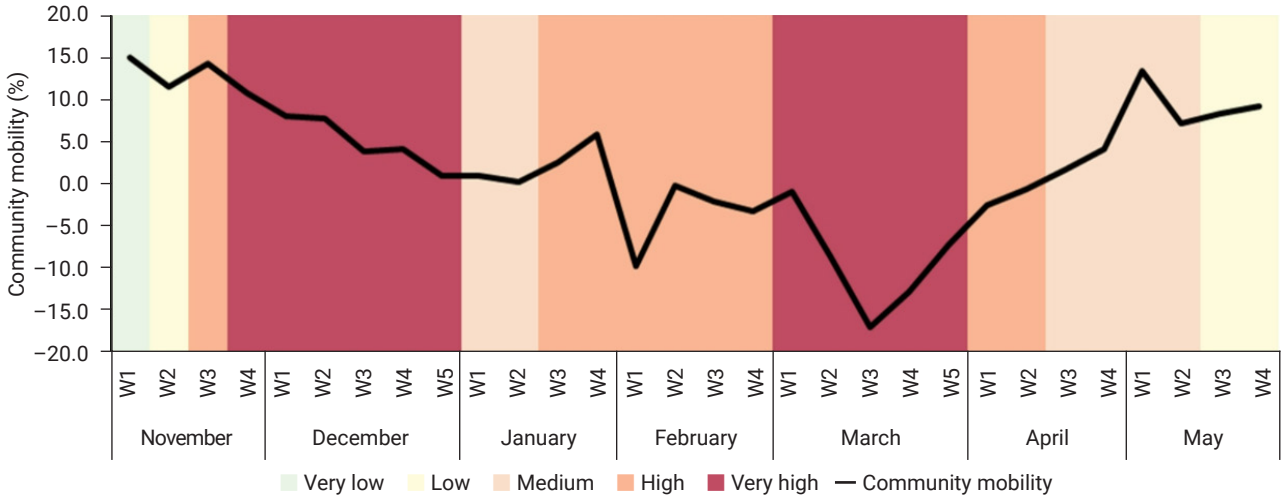

Figure 4. Weekly COVID-19 risk levels in the Republic of Korea and the community mobility rate (November 2021 to May 2022).
W1, week 1; W2, week 2; W, week 3; W4, week 4; W5, week 5.

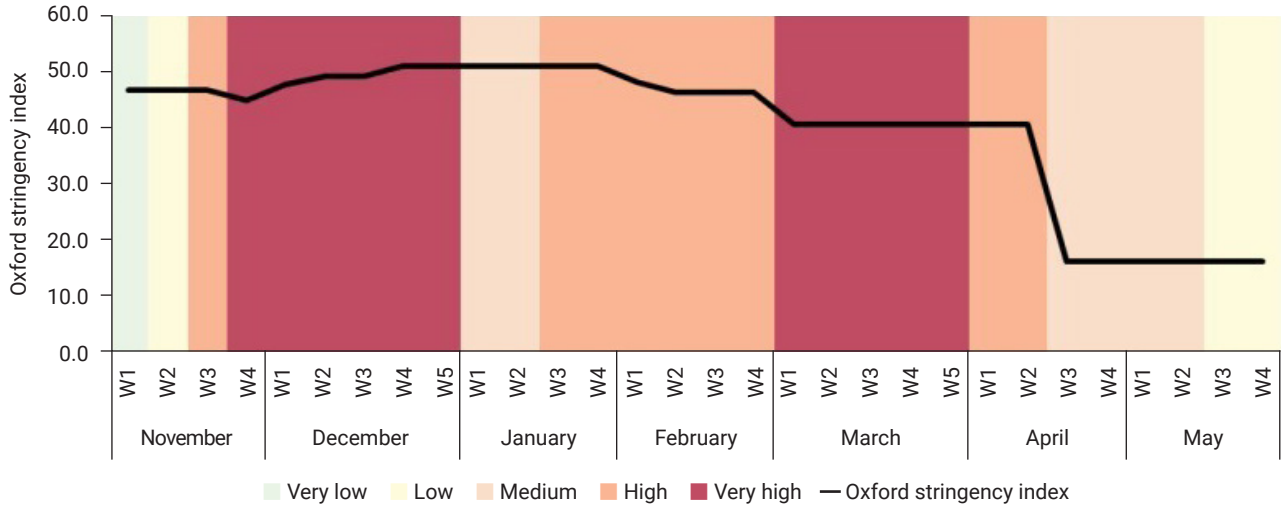

Figure 5. Weekly COVID-19 risk levels in the Republic of Korea and the Oxford stringency index (November 2021 to May 2022).
W1, week 1; W2, week 2; W, week 3; W4, week 4; W5, week 5.

community mobility rate decreased in March 2022, dropping to 0% in December 2021 when the delta variant was prevalent (Figure 4). The Oxford stringency index remained unchanged until the second week of April 2022, after which it decreased and stabilized (Figure 5).

An analysis of the weekly COVID-19 risk level showed correlations with several variables: the Rt, hospital admissions, newly confirmed severe cases, severe cases in hospitals, death cases, community mobility rate, and risk perception rate. The community mobility rate showed a negative correlation, while the Rt, hospital admissions, newly confirmed severe cases, severe cases in hospitals, death cases, and risk perception rate all exhibited positive correlations. Notably, the risk perception rate ($r = 0.841$) and hospital admissions ($r = 0.690$) were significantly positively correlated ($p < 0.05$) (Table 3).

The weekly COVID-19 risk level from "1-week lead" showed a significant positive correlation with the Rt, hospital admissions, newly severe cases, and risk perception. In addition, the risk perception rate showed a strong positive correlation ($r = 0.678$, $p < 0.05$) (Table 3).

The weekly COVID-19 risk level, based on the 1-week lagged value, demonstrated significant correlations with several indicators: hospital admissions, newly confirmed severe cases, severe cases in hospitals, death cases, community mobility

Table 3. Correlations between risk level and incidence, risk perception, community mobility, and government policy

Time period	1-wk lead	Original value	1-wk lagged value	2-wk lagged value
Newly confirmed cases	0.126	0.288	0.310	0.268
Newly confirmed cases over 60 y	0.166	0.308	0.318	0.254
Newly confirmed cases under 18 y	0.118	0.274	0.291	0.258
Rt	0.537*	0.386*	0.161	−0.114
Hospital admissions	0.601*	0.690*	0.602*	0.402*
Newly severe cases	0.474*	0.642*	0.693*	0.631*
Severe cases in hospitals	0.334	0.618*	0.740*	0.769*
Death	0.178	0.466*	0.575*	0.602*
Community mobility rate	−0.258	−0.449*	−0.537*	−0.586*
Risk perception rate	0.678*	0.841*	0.840*	0.627*
Oxford stringency index	0.252	0.256	0.270	0.285

Severe cases were defined as patients with multi-organ failure or those receiving treatment such as ventilation, high-flow O_2, extracorporeal membrane oxygenation, or continuous renal replacement therapy. Severe cases in hospitals were defined as those reported by admitted hospitals. Community mobility rate is defined as a 7-day moving average of the change of visitors and length of stay to retail and recreation compared to the baseline from Google. Risk perception rate was defined as "very serious" in the question of the severity of the spread of the COVID-19 outbreak from a biweekly survey conducted by Hankook Research and calculated as the percentage of people who answered "very serious." The Oxford stringency index is measured by containment and closure policy indicators, such as an indicator recording public information campaigns. It ranges from 0 to 100.
Rt, time-varying reproduction number.
*$p < 0.05$.

rate, and risk perception rate ($p < 0.05$). The community mobility rate was negatively correlated (r = −0.537), while the other significant indicators exhibited positive correlations. Specifically, the risk perception rate (r = 0.840), severe cases in hospitals (r = 0.740), and newly confirmed severe cases (r = 0.693) all showed strong positive correlations ($p < 0.05$) (Table 3).

The weekly COVID-19 risk level from the 2-week lagged value showed significant associations with the same indicators as those observed with the 1-week lagged value ($p < 0.05$). Notably, during this period, the strongest correlation occurred among severe cases in hospitals (r = 0.769, $p < 0.05$) (Table 3).

Discussion

Between November 2021 and May 2022, the Delta and Omicron-type BA.1 and BA.2 variants became prevalent in the Republic of Korea. The incidence of severe disease escalated with the prevalence of the Delta variant. Additionally, the prevalence of the Omicron variant led to a hundredfold increase in outbreak size and exhibited a distinct pattern [12,13]. During this period, the KDCA conducted weekly COVID-19 risk assessments, adjusting the indicators to account for the emergence of mutant viruses and shifts in national disease control policies. Consequently, the number of indicators expanded to 47.

Since November 2021, the KDCA has been conducting weekly COVID-19 risk assessments. The results, along with the 4-week values of the indicators used, are shared through briefings and regular press releases. These indicators objectively reflect the current situation, informing stakeholders of necessary measures and alerting the public to any changes in conditions. However, relying solely on the fluctuations of these indicators to determine the weekly COVID-19 risk level does not suffice for making accurate evaluations. Therefore, the "ratio of the incidence rate to medical capacity" and the "availability of hospital beds for severe patients" were incorporated as anchor indicators, following the assessment method that utilizes algorithms and a matrix similar to those used in general RRAs. The inclusion of various indicators and anchor indicators has enhanced the timeliness and appropriateness of evaluations. The United States Centers for Disease Control and Prevention categorizes community levels (low, medium, high) based on a scale that includes new cases, new admissions, and inpatient bed usage [9]. Similarly, the UK HSA sets the alert level by combining expert judgment and risk assessment with more quantifiable indicators and thresholds [8]. Information such as community levels and alert levels is communicated by establishing criteria for key indicators that are tailored to the specific conditions of each country. Effective and clear communication is crucial, as people are more likely to comply with government public safety advisories when they are well-informed about the risks they face and understand the preventative measures available [14,15].

The risk perception rate appeared to be strongly correlated with the COVID-19 risk level, suggesting that the perceived risk and the actual risk level were similar at the time of assessment. Public perception of risk plays a crucial role

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in shaping individual decisions related to COVID-19, where behavioral and policy support act as positive influences on quarantine measures [16,17]. Chatterjee et al. [15] highlighted that awareness and understanding of risk at the community level are essential for improving prevention efforts. Therefore, contextual information is vital in enhancing risk assessment. Additionally, policy adjustments are considered in light of the potential economic and social impacts that could result from a prolonged pandemic. In the Republic of Korea, the effectiveness and sustainability of infection prevention and control measures are experiencing diminishing returns due to cumulative effects, such as distress among micro-enterprises suffering significant sales losses, weakened support systems for vulnerable populations, and disruptions in student education [18]. Social factors, including education and income, along with infectious disease outbreaks, have also been observed to influence policy changes in the Republic of Korea. Consequently, in the face of an extended epidemic, further research is necessary to prioritize and understand how infectious disease outbreaks and social factors impact policy decision-making.

The significant correlation between the Rt and the weekly COVID-19 risk level, with a 1-week lead, indicated that this indicator responded rapidly to changes in the situation. The risk level from a 1-week lagged value showed the strongest correlation with the occurrence of newly confirmed severe cases. The highest correlation was observed between the risk level from the 2-week lagged value and the number of severe cases in hospitals, as well as between the risk level from the 2-week lagged value and the number of deaths. This suggests that the assessed risk level functioned as an early warning system.

This study compared the findings of COVID-19 risk assessments with subsequent national perceptions and policy changes. However, the Oxford stringency index, used as a representative measure of policy changes, did not accurately reflect the policy shifts in a single country. This index measures the extent of a country's response policies, such as public health and social intervention measures, in reaction to the spread of COVID-19. A more sensitive indicator that accurately represents the Republic of Korea's COVID-19 outbreak control policies would enable a more precise correlation. Currently, the Oxford stringency index is the primary indicator used to quantify and compare policies, and it was also employed in this study. Another limitation is that, although the same names for indicators are used, the methods of aggregating some indicators have changed. These adjustments were made in response to evolving circumstances, including the expansion of testing methods such as the rapid antigen test. As the criteria within the Republic of Korea were updated, this study incorporated these changes in aggregation methods (Table S1).

The KDCA conducted weekly risk assessments as part of its response to COVID-19. The results of these assessments were utilized in policymaking and influenced the adoption of evidence-based policies. The risk levels were communicated weekly through briefings and used for risk communication. In the context of COVID-19 becoming endemic, risk assessments in the Republic of Korea were conducted using methods different from the RRAs. These assessments were effectively implemented for early warning by incorporating useful indicators and reflecting expert opinions. However, it is anticipated that risk assessments tailored to specific targets could be even more effective for risk communication. The timing for raising alertness may vary depending on the target audience, such as the medical community or the general public. Global preparedness for, and response capacities to, emerging and re-emerging infectious diseases with epidemic potential can be enhanced with each outbreak [19].

In the next pandemic, it may be possible to conduct advanced risk assessments that are tailored to specific situations. Contextual indicators, which take into account time lags and scales of implementation [1], could enhance the evaluation of future risk assessment outcomes, particularly when there are challenges in reflecting specific situational factors in crisis management.

Supplementary Material

Table S1. Definitions of weekly COVID-19 risk assessment indicators. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0141.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of the KDCA (No: 2023-02-05PE-A) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

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

Authors' Contributions
Conceptualization: ST, SH; Data curation: SH, JO; Formal analysis: SH; Methodology: ST, SH, JL, YK, BIK; Resources: JO, MJL, HK; Visualization: SH, YK; Writing–original draft: SH; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Individual and contextual factors associated with measles infection in Malaysia: a multilevel analysis

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ABSTRACT

Objectives: Despite effective vaccination strategies, measles remains a global public health challenge. The study explored individual and contextual factors associated with measles infection in Malaysia from 2018 to 2022, informing the development of targeted public health interventions.

Methods: This cross-sectional study utilised data from the Ministry of Health, the Department of Statistics, and the Department of Environment Malaysia. Multilevel logistic regression analysis was employed to examine individual-level factors, including age, sex, ethnicity, nationality, contact history, travel history, and vaccination status. Concurrently, contextual factors were assessed, encompassing district-level determinants such as population density, median household income, urbanisation, the number of health and rural clinics, vaccination rates, fine particulate matter less than 2.5 μm ($PM_{2.5}$) levels, relative humidity, and temperature, to determine their impact on measles infection risk.

Results: Measles infection was significantly associated with various individual factors. These included age (adjusted odds ratio [aOR], 1.02; 95% confidence interval [CI], 1.02–1.03), ethnicity, non-Malaysian nationality (aOR, 34.53; 95% CI, 8.42– 141.51), prior contact with a measles case (aOR, 2.36; 95% CI, 2.07–2.69), travel history (aOR, 2.30; 95% CI, 1.13–4.70), and vaccination status (aOR, 0.76; 95% CI, 0.72–0.79). Among contextual factors, urbanisation (aOR, 1.56; 95% CI, 1.16–2.10) and the number of clinics (aOR, 0.98; 95% CI, 0.97–0.99) were significant determinants.

Conclusion: This multilevel logistic regression analysis illuminates the complexities of measles transmission, advocating public health interventions tailored to individual and contextual vulnerabilities. The findings highlight the need for a synergistic approach that combines vaccination campaigns, healthcare accessibility improvements, and socioeconomic interventions to effectively combat measles.

Keywords: Measles; Multilevel analysis; Risk factor

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Introduction

Measles, a highly infectious disease caused by the measles virus, represents a longstanding public health challenge worldwide. Despite the availability of an effective vaccine, global measles cases and related deaths remain a concern; outbreaks can affect millions, particularly in regions with low vaccination rates [1]. The World Health Organization has prioritised measles for elimination, but achieving this goal has been challenging due to factors such as vaccine hesitancy, accessibility issues, and global mobility [2]. In the wake of the coronavirus disease 2019 (COVID-19) pandemic, the year 2022 underscored the worsening global measles situation, with millions of children missing vaccinations. The resulting increases in cases and deaths highlighted the disease's persistent threat, especially in areas with low vaccination coverage [1]. In Malaysia, the healthcare system also faces obstacles, including vaccine hesitancy, which is partly fuelled by historical controversies and misinformation. For instance, unfounded fears linking the measles-mumps-rubella (MMR) vaccine to autism have periodically resulted in pockets of unvaccinated children, complicating efforts to achieve herd immunity [3].

Several individual factors have been previously identified as risk factors for measles infection. One outbreak study identified contact history with a measles case as a significant risk factor, with an adjusted odds ratio (aOR) of 1.15 and a 95% confidence interval (CI) of 1.12–3.70 [4]. A separate study in Japan revealed that individuals with a history of international travel had about 10 times higher odds of contracting measles compared to non-travellers (aOR, 10.2; 95% CI, 5.9–17.7) [5]. In Ethiopia, the risk of measles infection was reduced by 83% in individuals who had been vaccinated (aOR, 0.17; 95% CI, 0.05–0.53) [6]. Other individual factors include age, sex, and ethnicity [4,5,7–17]. Beyond biological susceptibility, broader contextual factors also influence measles transmission. Research in Italy demonstrated that areas with higher population densities experienced significantly more measles cases than less populated regions (incidence rate ratio, 1.70; 95% CI, 1.36–2.12) [18]. A study in Nigeria indicated that urban residence was a predictive factor for measles infection (aOR, 1.55; 95% CI, 1.02–2.34) [19]. Healthcare accessibility, vaccination coverage, and environmental factors such as fine particulate matter less than 2.5 μm ($PM_{2.5}$), relative humidity, and temperature have also been identified as significant factors in measles transmission [14,20–31].

In Malaysia, persistent measles outbreaks underscore the need to analyse the complex epidemiological landscape of the disease in this setting. A thorough assessment is necessary to overcome the obstacles impeding the country's progress toward eliminating this condition. Consequently, this study was designed to explore the individual and contextual factors associated with measles infection in Malaysia. By analysing secondary data from 2018 to 2022, we aimed to identify key determinants of measles infections, offering insights supporting the development of targeted public health strategies and interventions.

HIGHLIGHTS

- This study comprehensively examines individual and contextual factors contributing to measles infection in Malaysia, utilising multilevel logistic regression analysis.
- The results reveal that measles infection is significantly associated with individual factors including age, ethnicity, travel history, and vaccination status, alongside the contextual factors of urbanisation and healthcare facility density.
- These findings highlight the complexity of measles transmission and underscore the need for targeted public health strategies addressing both individual susceptibilities and environmental influences.
- This research offers valuable insights into the development of effective interventions and policies for the prevention and control of measles in Malaysia.

Materials and Methods

Study Design and Sample

This cross-sectional study utilised secondary data from the e-measles database of the Ministry of Health Malaysia, as well as data from the Department of Statistics Malaysia and the Department of Environment Malaysia. Two levels of variables were investigated: individual factors were analysed at the individual level, while contextual factors were evaluated at the district level. The dataset included all cases registered in the e-measles databases from January 1, 2018, to December 31, 2022. The exclusion criteria encompassed any duplicate entries or participants missing at least 30% of their data. Of the 31,468 individual records available in the e-measles database, 2,946 (9.36%) were excluded from the analysis due to incomplete data, leaving a final sample of 28,522 participant records.

Study Area

This study was conducted in Malaysia, a country in the Southeast Asian region with an approximate land area of

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329,847 km^2. Malaysia consists of 3 federal territories and 13 states, subdivided into a total of 160 districts. The nation is split into Peninsular Malaysia, bordering Thailand, and East Malaysia, located on the island of Borneo. Malaysia has a multiethnic and multicultural society, predominantly made up of Malays, Chinese, Indians, and indigenous groups, each contributing to the nation's rich cultural heritage and diversity [32]. The country experiences a tropical rainforest climate, with its environmental conditions and precipitation patterns impacted by 2 seasonal monsoons [33].

Dependent Variable

The dependent variable in this study was the measles status of participants, classified as either measles or non-measles. Measles was defined as including cases that were laboratory-confirmed, either by the presence of measles immunoglobulin M antibodies or through the detection of the virus in clinical samples using culture or molecular techniques, as well as any case that was epidemiologically linked to a laboratory-confirmed case. A non-measles case was defined as one with laboratory-confirmed negative results for measles in e-measles databases, including cases classified as discarded, laboratory-confirmed rubella, epidemiologically linked rubella, or vaccine-associated measles.

Independent Variables

The independent variables in this study included individual and contextual factors potentially relevant to measles infection in Malaysia. Individual-level factors comprised age, sex, ethnicity, nationality, contact history, travel history, and the number of vaccine doses received. Age was treated as a continuous variable, measured in years. Ethnicity was categorised into Malay, Chinese, Indian, Indigenous Sabah Sarawak, Indigenous Peninsular Malaysia, and other. Nationality was classified as either Malaysian or non-Malaysian. Contact history with a measles case was defined as any known contact with a person with measles within 7 to 21 days prior to the development of a rash [34]. Travel history included any travel to other countries within 7 to 21 days before rash onset. The total vaccine dosage was calculated based on the number of measles vaccine doses the individual had received [17,35].

Eight district-level contextual factors were analysed, including population density, median household income, urbanisation, the number of health and rural clinics, vaccination coverage, $PM_{2.5}$ levels, relative humidity, and temperature. Population density was calculated as the ratio of the district's population to its area in square kilometres. Median household income represented the middle value of the household incomes in a district when arranged in ascending order. The urbanisation status of the district of residence was classified as either rural or urban based on the local council designation, obtained from the Department of Statistics Malaysia [36]. The number of health and rural clinics referred to the total count of these facilities within the district where the participant resided. District vaccination coverage denoted the percentage of the district's population that had received MMR vaccination. For each person studied, data on relative humidity, temperature, and $PM_{2.5}$ levels correspond to the measurements taken in the district 14 days prior to the onset of rash symptoms. This period aligns with previous research indicating that the incubation period for measles ranges from 7 to 21 days, with around 14 days being the most common. Consequently, the environmental conditions, including relative humidity, temperature, and $PM_{2.5}$ levels from 14 days before rash appearance, were used to reflect the exposure conditions potentially influencing participants.

Data Sources

The data on measles status and all individual-level factors were obtained from the e-measles database of the Ministry of Health Malaysia. The e-measles system, developed by the Ministry of Health Malaysia and operational since 2007, provides a standardised platform for case investigation and case-based reporting at district, state, and national levels. This system is managed by the Disease Control Division of the Ministry of Health Malaysia.

The data on population density, median household income, urbanisation, and the number of health and rural clinics were sourced from the Department of Statistics Malaysia. Information on district vaccination coverage was obtained from the Health Informatics Centre of the Ministry of Health Malaysia. Environmental data on relative humidity, temperature, and $PM_{2.5}$ levels were obtained from the Department of Environment Malaysia.

Statistical Analysis

Descriptive analysis was performed to depict the distribution of individual- and district-level factors in relation to the dependent variables: measles and non-measles. Categorical variables were expressed as frequency and percentage, while continuous variables were summarised using the median and interquartile range (IQR). Initially, a series of univariable analyses were carried out using simple logistic regression. Factors with p-values less than 0.25 were then included in a multivariable analysis employing multilevel logistic regression to account for district-level clustering effects. The multilevel logistic regression model incorporated 2 levels: individual and district.

Four models were constructed for the multilevel logistic regression analysis. Model 1 represented a null model that did not incorporate any individual-level variables or district-level risk factors, establishing a baseline for comparison with the other models. The intraclass correlation coefficient (ICC) was estimated from this model, reflecting the proportion of total variance attributable to the districts. Model 2 included adjustments for individual-level variables. Model 3 accounted for contextual factors at the district level, while model 4 was fitted with both individual-level variables and district-level contextual factors. aORs with 95% CIs were determined, and *p*-values of less than 0.05 in the multivariable models were considered indicative of significant associations with measles infection.

The Akaike information criterion (AIC) and the area under the receiver operating characteristic curve (AUC) were utilised to evaluate the goodness of fit for the models in this study. A model with a lower AIC and a higher AUC value was considered to display a better fit. The absence of multicollinearity among the independent variables was confirmed by the presence of a variance inflation factor of less than 10 and a tolerance greater than one. Two-way interactions between the significant variables were also examined. Univariable and multilevel modelling was performed using R ver. 4.3.1 (The R Foundation) within RStudio ver. 2023.12.1+402, employing the *glm* and *glmer* functions, respectively.

Ethics Statement

The research was conducted in accordance with the Declaration of Helsinki guidelines and received ethical clearance from the Human Research Ethics Committee of Universiti Sains Malaysia, under the approval code USM/JEPeM/KK/23010094. Additionally, the Malaysia Medical Research and Ethics Committee granted approval under the code NMRR-23-00290-E4U.

Results

Descriptive Statistics

Table 1 summarises the individual factors within the registered data, consisting of confirmed measles and non-measles cases from 2018 to 2022. Regarding individual-level factors, the median participant age was 0.83 years (IQR, 1.42 years), or equivalently, 10 months (IQR, 17 months). The gender distribution was similar between groups. Among confirmed measles cases, the youngest participant was 1 day old, while the oldest was 64 years old. The majority (89.72%) were of Malay ethnicity, and nearly all (99.94%) were Malaysian. Over 90% of participants had no reported history of contact with measles cases and had not travelled abroad. The median number of measles vaccine doses received was one, with a range of no vaccination to a maximum of 4 doses.

Table 1. Descriptive statistics of individual factors associated with measles infection in Malaysia, 2018–2022 (*n* = 28,522)

Variable	Overall (*n* = 28,522)	Non-measles (*n* = 25,289)	Measles (*n* = 3,233)	*p*[a]
Age (y)	0.83 (0.58–2.00)	0.83 (0.58–2.00)	0.83 (0.58–3.00)	< 0.001
Sex				0.787
Male	15,317 (53.70)	13,588 (53.73)	1,729 (53.48)	
Female	13,205 (46.30)	11,701 (46.27)	1,504 (46.52)	
Ethnicity				< 0.001
Malay	25,591 (89.72)	22,956 (90.78)	2,635 (81.50)	
Chinese	937 (3.29)	852 (3.37)	85 (2.63)	
Indian	220 (0.77)	182 (0.72)	38 (1.18)	
Indigenous Sabah Sarawak	1,352 (4.74)	1,070 (4.23)	282 (8.72)	
Indigenous Peninsular	277 (0.97)	114 (0.45)	163 (5.04)	
Others	145 (0.51)	115 (0.45)	30 (0.93)	
Nationality				< 0.001
Malaysian	28,504 (99.94)	25,286 (99.99)	3,218 (99.54)	
Non-Malaysian	18 (0.06)	3 (0.01)	15 (0.46)	
Contact history				< 0.001
Yes	1,831 (6.42)	1,384 (5.47)	447 (13.83)	
No	26,691 (93.58)	23,905 (94.53)	2,786 (86.17)	
Travel history				< 0.001
Yes	51 (0.18)	37 (0.15)	14 (0.43)	
No	28,471 (99.82)	25,252 (99.85)	3,219 (99.57)	
Total vaccine dosage	1 (0.00–1.00)	1 (0.00–1.00)	0 (0.00–1.00)	< 0.001

Data are presented as median (interquartile range) or *n* (%).
[a]Simple logistic regression.

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Regarding district-level contextual factors, the median population density was 563.80 persons per km^2, and the median household income was 6,938.00 Malaysian ringgit (RM). Of the participants, 76.40% resided in urban areas, with a median of 27 health and rural clinics per district. The median vaccination coverage was 98.31%. The median $PM_{2.5}$ concentration recorded was 16.90 μg/m^3, along with a relative humidity of 80.75% and a median temperature of 27.5 °C. Details regarding these factors are displayed in Table 2.

Multilevel Logistic Regression

The final model, model 4, incorporates both individual and contextual-level factors. This model demonstrated that age, ethnicity, nationality status, history of contact with a measles case, history of travelling abroad, vaccine dosage, the number of health and rural clinics, and the degree of urbanisation were all significantly associated with measles infection (Table 3).

Measures of Association (Fixed Effects)

For individual-level factors, the risk of measles increased by 2% for 1 additional year of age (aOR, 1.02; 95% CI, 1.02–1.03). Ethnicity was also significantly associated with measles infection in Malaysia. Regarding nationality, non-Malaysians faced a risk of measles multiple times higher than that of Malaysians (aOR, 34.53; 95% CI, 8.42–141.51). Individuals with a history of contact with measles cases were 2.36 times more likely to become infected (aOR, 2.36; 95% CI, 2.07–2.69), while those reporting international travel 7 to 21 days prior had 2.3 times the odds of infection of those without such a travel history (aOR, 2.30; 95% CI, 1.13–4.70). An additional dose of the measles vaccine received by an individual was associated with a 24% reduction in the risk of infection (aOR, 0.76; 95% CI, 0.72–0.79) (Table 3).

Among contextual factors, urbanisation was significantly associated with measles infection, with urban residents displaying a higher risk of contracting measles compared to those in rural areas (aOR, 1.56; 95% CI, 1.16–2.10). Additionally, the presence of more health and rural clinics in a district was associated with a lower risk of measles infection among its residents (aOR, 0.98; 95% CI, 0.97–0.99), after adjusting for district clustering effects.

Measures of Variation (Random Effects) and Model Fit Statistics

Based on the multilevel logistic regression analysis, as depicted in Table 3, the null model (model 1) indicated an 18% variation in the odds of measles infection attributable to district-level factors (ICC, 0.18%). Model 4 emerged as the best-fitting model, as evidenced by its lowest log-likelihood (−9,207.73), highest AUC (0.70), lowest deviance (18,098.54) and lowest AIC (18,443.46). Multicollinearity was not observed in model 4.

Discussion

This study examined individual-level and contextual district-level factors in Malaysia that influence the risk of measles infection. The findings revealed that older age was associated with higher odds of contracting measles, contradicting the common perception that measles primarily affects children. Instead, older age groups are also at risk [37]. The identification of age as a risk factor for measles infection is supported by the concept that immunity to measles can vary across age groups. In many regions, individuals born before 1957 and older adults may have been exposed to measles in the pre-vaccination era, thereby acquiring natural immunity

Table 2. Descriptive statistics of district-level contextual factors associated with measles infection in Malaysia, 2018–2022 (*n* = 28,522)

Variable	Overall (*n* = 28,522)	Non-measles (*n* = 25,289)	Measles (*n* = 3,233)	*p*[a]
Population density	563.80 (173.18–1,636.61)	549.62 (173.18–1,636.61)	648.95 (137.03–1,636.61)	< 0.001
Median household income (RM)	6,938.00 (5,207.00–9,593.00)	6,938.00 (5,205.00–9,593.00)	7,125.00 (5,577.00–9,908.00)	< 0.001
Urbanisation				0.011
Rural	6,731 (23.60)	6,025 (23.82)	706 (21.84)	
Urban	21,791 (76.40)	19,264 (76.18)	2,527 (78.16)	
No. of health and rural clinics	27 (18–32)	27 (20–32)	26 (14–28)	< 0.001
Vaccination coverage (%)	98.31 (87.33–108.10)	99.07 (86.52–108.10)	97.34 (89.37–108.03)	0.925
$PM_{2.5}$ (μg/m^3)	16.90 (11.53–23.88)	16.80 (11.53–23.77)	17.62 (11.47–24.62)	0.738
Relative humidity (%)	80.75 (76.56–84.39)	80.75 (76.60–84.40)	80.74 (76.32–84.34)	0.313
Temperature (°C)	27.50 (26.60–28.43)	27.49 (26.59–28.43)	27.52 (26.69–28.38)	0.467

Data are presented as median (interquartile range) or *n* (%).
RM, Malaysian ringgit; $PM_{2.5}$, fine particulate matter less than 2.5 μm.
[a]Simple logistic regression.

Table 3. Individual and district-level factors associated with measles infection in Malaysia, 2018–2022 (*n* = 28,522)

Variable	Model 1	Model 2	Model 3	Model 4
Individual-level				
Age		1.02 (1.02–1.03)*		1.02 (1.02–1.03)*
Ethnicity				
Malay		1		1
Chinese		0.73 (0.58–0.93)*		0.72 (0.57–0.92)*
Indian		1.62 (1.12–2.34)*		1.61 (1.11–2.32)*
Indigenous Sabah Sarawak		1.19 (0.93–1.53)		1.16 (0.90–1.49)
Indigenous Peninsular		6.63 (4.76–9.23)*		6.80 (4.88–9.48)*
Others		1.60 (1.00–2.56)		1.55 (0.97–2.49)
Nationality				
Malaysian		1		1
Non-Malaysian		36.10 (8.73–149.37)*		34.53 (8.42–141.51)*
Contact history				
No		1		1
Yes		2.37 (2.08–2.70)*		2.36 (2.07–2.69)*
Travel history				
No		1		1
Yes		2.31 (1.13–4.72)*		2.30 (1.13–4.70)*
Total vaccine dosage		0.76 (0.72–0.79)*		0.76 (0.72–0.79)*
District-level				
Urbanisation				
Rural			1	1
Urban			1.57 (1.14–2.17)*	1.56 (1.16–2.10)*
No. of health and rural clinics			0.98 (0.97–0.99)*	0.98 (0.97–0.99)*
Random effects				
Variance	0.71	0.57	0.64	0.51
ICC	0.18	0.15	0.16	0.13
Model fit statistics				
Deviance	18,663.91	18,099.3	18,662.13	18,098.54
Log-likelihood	−9,510.20	−9,214.04	−9,503.77	−9,207.73
AIC	19,024.40	18,452.09	19,015.55	18,443.46
AUC	0.68	0.69	0.68	0.70

Data are presented as adjusted odd ratio (95% confidence interval) unless otherwise stated.
ICC, intraclass correlation coefficient; AIC, Akaike information criterion; AUC, area under the receiver operating characteristic curve.
*$p < 0.05$.

[14,38,39]. However, in populations with high vaccination coverage, younger cohorts are typically protected through vaccination [39]. Adults experience a slight increase in the odds of contracting measles, which could indicate a decline in immunity over time [39]. This underscores the importance of continued surveillance and the consideration of booster vaccination strategies for older groups. Measles vaccine-derived immunity is less robust and shorter-lived than natural immunity [38]. Although older adults and the elderly generally possess natural immunity against measles, this study indicates that these individuals are still susceptible to infection. Despite the median age of measles cases being less than 1 year, confirmed cases were reported in individuals up to 64 years old. The estimated decay rates of measles antibodies differ markedly between those with naturally acquired infections and those who have been vaccinated, with a mean duration of immunity of 25 years [40]. A study in Italy revealed that 15% of individuals vaccinated against measles did not exhibit a protective titre of immunoglobulin G antibodies 10 years after vaccination [41]. Similarly, a study among healthcare workers in Korea showed that 82.9% of participants tested negative for measles immunoglobulin G antibodies, with the seronegative status attributed to waning immunity [42]. The findings of this study highlight the importance of maintaining high vaccination coverage across all age groups, particularly young adults, as opposed to only children. Public health strategies may require revision to include booster doses for older age groups, especially in populations with evidence of diminishing immunity or relatively high exposure risk, such as healthcare workers. Additionally, the study highlights the need for ongoing surveillance of measles immunity levels.

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Ethnicity was identified as a significant risk factor for measles infection in this study. Malaysia, a multiethnic nation, is predominantly composed of the Malay ethnic group. The descriptive statistics of the overall sample reflect the demographic composition of Malaysia's population [43]. Indigenous populations in Peninsular Malaysia were found to face a higher risk of measles compared to the Malay population. This pattern may be attributed to lower vaccination rates among indigenous communities. For instance, during a large-scale measles outbreak among the Bateq tribe in Kuala Koh, Gua Musang, only 61.5% had received the first dose of the MMR vaccine, and just 30% had completed the second dose [44]. The nomadic lifestyle of the Bateq tribe poses a challenge for medical teams to provide consistent health services, such as vaccinations [44]. To reduce the risk of measles among all ethnic groups in Malaysia, it is crucial to improve vaccination coverage and address socioeconomic disparities.

This study highlights a significantly higher risk of measles infection among the non-Malaysian population living in Malaysia, primarily due to barriers in accessing preventive healthcare services. These challenges extend beyond legal limitations to include socioeconomic factors and language barriers [45,46]. Non-Malaysians, particularly undocumented immigrants, encounter difficulties such as legal restrictions and the fear of deportation, which may deter them from seeking healthcare services such as vaccinations [47]. Moreover, the substantial cost of immunization for non-Malaysians, which includes a clinic registration fee of RM 40 and an additional RM 40 per vaccine dose, poses meaningful challenges. In contrast, Malaysian citizens have access to government-subsidised vaccines at a nominal fee of RM 1, highlighting a pronounced disparity in healthcare access [48]. Language barriers profoundly impact the comprehension of vaccine importance and the ability to navigate healthcare systems effectively. Communication issues can result in misconceptions about vaccine significance, schedules, and follow-up protocols, decreasing uptake and completion rates within this demographic. The absence of health promotion materials in various languages means that non-Malaysian populations might not be informed of available vaccination programs or understand the need for vaccinations, resulting in lower immunization rates and heightened measles risk [49,50]. These factors collectively emphasise the critical need for improved healthcare accessibility and communication strategies tailored to the diverse linguistic and socioeconomic needs of non-Malaysian populations. Such improvements are essential to improve health outcomes and protect against diseases such as measles.

In this study, individuals with a history of exposure to measles were found to have a higher risk of contracting the disease compared to those without such exposure. An Indonesian study also highlighted this risk, revealing an OR of 2.31 (95% CI, 1.22–4.27) for individuals exposed to measles. These findings align with previous research from Yemen, Ethiopia, and the United Kingdom [6,12,51]. Given the basic reproduction number (R0) of measles, which ranges from 12 to 18, the likelihood of contracting the disease increases significantly upon exposure to the virus [52]. This elevated risk underscores the importance of effective quarantine measures and contact tracing in controlling the spread of measles. In 2015, Malaysia updated its guidelines for preparedness and response to measles cases and outbreaks. Previously, an outbreak required 2 confirmed cases to trigger a response, but under the updated guideline, a single confirmed case is now sufficient to initiate outbreak protocols [53]. This improved strategy emphasises the importance of prompt and effective public health measures—such as quarantine, contact tracing, and isolation of suspected cases, particularly in settings like schools—to minimise transmission. Furthermore, the provision of specific quarantine leave for parents and caregivers of children with measles, as well as other infectious diseases such as hand, foot, and mouth disease, dengue, chickenpox, diphtheria, malaria, or any medically certified infectious illness, assists in containing the spread of these diseases. Such a policy allows caregivers to take time off work to care for a sick child [54].

This study revealed that individuals with a history of international travel 7 to 21 days prior to the onset of a rash displayed a higher risk of contracting measles compared to those without such a travel history. Research conducted in Amhara indicated that people with a history of travel abroad were about 2.5 times more likely (95% CI, 1.31–7.24) to contract measles [9]. Similar results were reported in China [11]. Travelling internationally to areas where measles is endemic or where outbreaks are occurring can expose individuals to the virus. Travellers can easily become infected in crowded environments such as airports, public transportation, and tourist attractions. Since the incubation period for measles ranges from 7 to 21 days, individuals may appear healthy during their travels and only begin to show symptoms of the disease after returning home. A survey by a French insurance operator found that 69% of Malaysians planned to vacation abroad in 2023 [55]. This poses an increased risk of contracting and subsequently spreading infectious diseases like measles in Malaysia, potentially leading to imported cases. Thus, it is essential to ensure that travellers to endemic areas, especially young children, are fully vaccinated with the MMR vaccine before going abroad.

Older children and adults who have not received the 2 recommended doses of the measles vaccine should receive a vaccine dose before travel, as stated in the travel health advisory [56].

This study found that receipt of a second measles vaccine dose decreased the risk of measles infection by 24%. This finding aligns with research from Singapore and the United Kingdom [17,57]. The initial vaccine dose serves to prime the immune system by introducing an attenuated form of the virus, which triggers the production of antibodies and memory cells that target measles. However, the immune response to this vaccine varies among individuals; while the majority develop immunity, a small percentage do not achieve an adequate antibody level for protection. This underscores the importance of administering a second dose to ensure broader immunity within the population [58,59]. Furthermore, recent evidence suggests that immunity may wane over time, particularly among young adults, indicating a potential need for booster doses to strengthen the immune response [40–42]. The adoption of a 2-dose measles vaccination strategy not only maximises individual protection against the disease but also significantly boosts herd immunity. To maintain this immunity, at least 94% of the population must be immunized with a measles-containing vaccine [60]. Herd immunity is crucial for safeguarding vulnerable groups who cannot receive vaccinations, such as infants, individuals with certain health conditions, and those with allergies to vaccine components. The high coverage produced by the 2-dose vaccination schedule serves to protect against measles outbreaks.

Our research indicates that individuals living in urban areas faced a higher risk of contracting measles compared to their rural counterparts. This pattern is consistent with findings from studies conducted in Nigeria, which also reported higher rates of measles infection among urban residents [19,61]. The higher population density and close quarters typical of urban environments facilitate the rapid transmission of measles, particularly in crowded settings such as schools and public transportation systems. Furthermore, cities often serve as international travel hubs, featuring airports that receive visitors from all over the world. This continuous arrival of people from regions where measles may be more prevalent can introduce the virus into urban communities.

The COVID-19 pandemic has heightened the risk of measles outbreaks in urban areas by disrupting routine vaccination programs, including those targeting measles. As healthcare resources were reallocated to combat COVID-19, missed opportunities for measles vaccinations increased, leading to a larger pool of susceptible individuals and raising the potential for outbreaks. The recent pandemic highlights the vulnerability of public health systems and the critical importance of sustained immunization efforts to prevent vaccine-preventable diseases such as measles, especially in high-risk urban settings [62]. Consequently, the implementation of nationwide supplementary immunization activities may represent a vital step toward achieving herd immunity across Malaysia, particularly in the context of the COVID-19 pandemic.

Residents of districts with fewer health and rural clinics were found to face a higher risk of contracting measles. The number of these clinics within a district reflects the accessibility and effectiveness of healthcare delivery in Malaysia. The presence of more clinics improves diagnostic capabilities, enabling the swift isolation and treatment of measles cases. This quick response helps to mitigate both the severity of the disease and its spread within communities. Such prompt management meaningfully reduces the impact of measles, highlighting the critical role of accessible healthcare facilities in the control of infectious diseases [63]. Furthermore, these clinics play an essential role in improving vaccination coverage by facilitating immunization programs and improving vaccine accessibility, thus promoting equitable healthcare. The Ministry of Health Malaysia leverages health and rural clinics to implement various strategies—such as the child home-based book, the family doctor concept, home visits for defaulter tracing, and appointment reminders—to increase vaccine uptake, especially in remote regions [64].

Strengthening healthcare infrastructure, including the establishment of additional clinics, can improve health practices and education among the population. This may lead to increased public awareness of measles and a subsequent rise in vaccination rates. Health education initiatives carried out in these facilities can help disseminate information about measles and the importance of timely vaccination. Studies conducted in India and Pakistan have demonstrated the positive impact of intensive information and education campaigns on vaccination rates [65]. Thus, an increase in the number of health and rural clinics was associated with improved healthcare accessibility and more effective health education dissemination in Malaysia. Enhanced healthcare infrastructure not only makes measles vaccination more accessible but also ensures the widespread distribution of information regarding the importance of immunization.

Environmental factors such as relative humidity and temperature were not found to be significant factors in measles infection in Malaysia. This is largely because Malaysia is situated on the equator and experiences a tropical rainforest climate, which results in consistent temperatures ranging from 23 °C to 32 °C and high humidity throughout

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the year [33].

A notable strength of this study is its comprehensive approach to analysing both individual and district-level contextual factors through multilevel logistic regression analyses. This methodological strategy illuminated how various demographic, socioeconomic, and environmental factors contribute to the risk of measles, providing a solid foundation for targeted public health interventions. Additionally, the study's utilisation of a large, diverse dataset spanning several years enriched the robustness of its findings, offering a detailed snapshot of the measles landscape in Malaysia. Such a detailed analysis may be invaluable for policymakers and health practitioners aiming to design and implement effective measles control strategies tailored to the specific needs and challenges of certain communities. However, the study has certain limitations, which are inherent in its design and the nature of its data sources. The reliance on secondary data and the cross-sectional study design limit the ability to establish causality between the identified risk factors and measles infection.

Future research should aim to address several key areas. Longitudinal studies could provide deeper insights into the temporal relationships between risk factors and measles infection, helping to establish causality and clarify the dynamics of measles transmission over time. Additionally, further research into social determinants of health, such as access to healthcare and vaccine hesitancy, could illuminate underlying factors contributing to disparities in measles risk and vaccination coverage. Investigating these aspects could offer more targeted recommendations for improving vaccination strategies and healthcare access, particularly among vulnerable populations.

Conclusion

This study highlights the complexity of measles transmission and underscores the necessity for multifaceted public health strategies to address this persistent challenge. Targeted vaccination campaigns are key, especially in urban areas and among populations with lower vaccination coverage, such as non-Malaysians and certain ethnic groups. To progress toward the elimination of measles, Malaysia must implement comprehensive public health measures, improve surveillance, promote vaccination, and engage in international collaboration to effectively mitigate these multidimensional risk factors.

Notes

Ethics Approval

This study received approval from the Human Research Ethics Committee of University Sains Malaysia, under the approval code USM/JEPeM/KK/23010094, as well as from the Malaysia Medical Research and Ethics Committee, with the approval code NMRR-23-00290-E4U. The research was performed in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available but can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: MRHMD, NAY, WNA; Data curation: MRHMD, JAMS, WAHWI; Formal analysis: MRHMD, NAY, WNA; Methodology: MRHMD, NAY, WNA; Project administration: MRHMD, NAY; Visualization: MRHMD, NAY, WNA; Writing–original draft: MRHMD; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Rural-urban differences in common mental disorders among Indonesian youth: a cross-sectional national survey

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ABSTRACT

Objectives: The onset of common mental disorders (CMDs) is most prevalent among youth; thus, mental health management is crucial. We examined differences in risk and risk factor determinants regarding CMDs prevalence among youth in rural and urban Indonesia.
Methods: This cross-sectional study utilized data from the 2018 Indonesia National Health Survey. The population comprised 122,114 respondents, aged 15 to 24 years, who had completed the 20-item Self-Report Questionnaire along with providing demographic and health behavior data. Chi-square testing and logistic regression were employed for analysis.
Results: The CMDs risk was higher among urban than rural youth. Risk factors impacting both populations included being female, having a lower education level, consuming fewer than 7 portions of vegetables weekly, smoking, and drinking alcohol ($p < 0.05$). Consuming under 7 portions of fruit weekly and being in the highest or lowest wealth quintile were significant risk factors only in urban youth, while unemployment and divorce were significant only among rural respondents ($p < 0.05$). Marriage was protective against CMDs among rural participants.
Conclusion: Being male, possessing a college degree, consuming at least 7 portions of vegetables weekly, not smoking, and not consuming alcohol were associated with reduced CMDs risk in urban and rural youth. Among rural youth, marriage and employment were linked to decreased risk, whereas divorce displayed the opposite relationship. In urban populations, consuming at least 7 portions of fruit weekly and belonging to neither the highest nor the lowest economic quintile were protective factors. Management strategies for CMDs in young people must address these considerations.

Keywords: Common mental disorders; Indonesia; Rural; Urban; Youth

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Introduction

According to the World Health Organization (WHO), mental disorders account for 3 of the top

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10 causes of disability in individuals aged 15 to 44 years and are often associated with other factors [1,2]. A meta-analysis examining the onset of common mental disorders (CMDs) throughout the lifetime found that approximately 50% of CMDs cases began by age 14 and 75% by age 18 [3]. The prevalence of CMDs among young people varies across studies. One review spanning multiple countries indicated that about 25% of children and adolescents were affected by CMDs [1]. Additionally, a WHO international survey involving college students from 8 countries reported that 31% of respondents had experienced CMDs [4].

One theoretical framework concerning mental health status suggests that a combination of inherent factors (gender and age), demographic factors (education, employment, socioeconomic status, and place of residence), health, and behavioral factors collectively determine an individual's mental health status [5]. Previous studies have identified a range of behavior-related issues that can impact mental health, including sleep disturbances, poor dietary habits, smoking, and drinking [6,7], as well as early sexual activity and excessive screen time or internet use [8]. The mental health of adolescents is significantly influenced by social behavioral factors, such as peer interactions and community support [6]. Additionally, demographic characteristics [6,9] and area of residence—urban [10] or rural [11]—have been linked to the prevalence of mental health disorders, although the findings have been inconsistent.

Multiple studies have identified an elevated vulnerability to mental health issues in urban populations, as evidenced by research on mental illness and depression in Denmark, Canada, and Indonesia [12–14]. Conversely, some previous research has suggested a heightened risk of mental health problems in rural communities, as seen in a study conducted in West Java, Indonesia [15]. Research in Germany also reported that among residential settings, rural areas experienced the greatest increase in the prevalence of depression within adolescent and adult populations between 2009 and 2017 [16]. However, a study among university students in Bangladesh revealed no significant difference in the prevalence of depression or anxiety between urban and rural residents [17].

Previous research has explored the determinants of mental health in either rural [18,19] or urban settings [20]. However, these studies have typically focused on a single population and have not compared the determinants between urban and rural environments. Urban health hazards differ from those in rural areas. The rise in non-communicable diseases, including CMDs, is attributed to the unhealthy lifestyles prevalent in urban areas, which include physical inactivity, poor diet, tobacco use, and excessive alcohol consumption [21]. Conversely, in rural regions, challenges in managing mental health issues are generally due to lower mental health literacy, reduced access to care, and underutilization of mental health services [11]. Previous research employing a theoretical framework to assess mental health status, considering inherent, demographic, health, and behavioral factors [5], only accounted for health-related behaviors associated with the consumption of addictive substances, such as cigarettes and khat leaves, which are known for their stimulant and euphoric effects. This study omitted khat leaves from consideration, as they are not commonly used by Indonesian youth. Furthermore, it included indicators of vegetable, fruit, and alcohol consumption in the analysis of behavioral factors representing potential determinants of mental health issues.

CMDs affect health conditions and quality of life [18] and have emerged as a leading cause of disability [22]. This can lead to economic losses due to reduced productivity and increased medical expenses [23]. In low-resource communities, the prevalence of CMDs can present a challenge due to inadequate mental health services. As a result, individuals with CMDs may not be able to access or pursue the necessary treatment [24]. CMDs are also associated with a relatively high incidence of suicidal thoughts among adolescents with moderate to severe depressive symptoms [22]. Additionally, children with a depressed parent face an increased risk of developing depression themselves [25]. These impacts of CMDs underscore the urgency of addressing this issue. Understanding the different factors

HIGHLIGHTS

- The prevalence of common mental disorders (CMDs) was higher among urban than rural youth in Indonesia, with determinants also varying.
- Being male, possessing a college degree, consuming at least 7 portions of vegetables per week, not smoking, and not consuming alcohol were associated with lower CMDs risk in urban and rural youth.
- Among rural youth, marriage and employment were linked to lower CMDs risk, whereas divorced participants experienced higher risk.
- Among urban youth, consuming at least 7 portions of fruit weekly and having a socioeconomic status in neither the first nor the fifth quintile were associated with reduced CMDs risk.

influencing youth CMDs in urban and rural areas is crucial for designing effective strategies to prevent mental health problems among young people. This study aimed to identify the differences in risk and determinants of CMD prevalence among youth in rural and urban areas of Indonesia.

Materials and Methods

Study Design

This study utilized data from the 2018 Indonesia National Health Survey (INHS), a cross-sectional survey conducted by the National Institute of Health Research and Development (NIHRD) under the auspices of Indonesia's Ministry of Health [26].

Samples

A multistage systematic random sampling method was used for participant selection. The initial phase involved identifying census blocks (CBs) as the primary sampling units (PSUs). Within each PSU, CBs were chosen using a probability proportional to size approach, which was based on the master sampling framework of the Indonesia Central Bureau of Statistics. This selection process yielded 180,000 CBs from a total of 720,000. These CBs represented a mix of urban and rural areas across each sub-district at the district level. The INHS carried out the sampling procedure in partnership with the Indonesia Central Bureau of Statistics. Regions were classified as urban or rural according to definitions provided by the Indonesia Central Bureau of Statistics. Face-to-face interviews were conducted with all eligible household members who had lived there for at least 6 months and were part of the same food management unit. Our analysis was focused on individuals aged 15 to 24 years, of whom 123,201 took part in the survey. However, we excluded 1,087 participants from our analysis because they did not complete the 20-item Self-Report Questionnaire (SRQ-20). Consequently, our study included complete data from 122,114 individuals (Figure 1) [26].

Variables

The outcome variable in this study was the presence of CMDs, which was assessed using the SRQ-20. This instrument comprised 20 yes-or-no questions that inquired about the participants' feelings over the past month. The cut-off point for this study was set at 6; participants who answered "yes" to 6 or more questions were considered to be experiencing a mental-emotional disorder [27].

The study incorporated a variety of independent variables, which included inherent factors (gender and age), demographic elements (education, marital status, employment, socioeconomic status, and place of residence), and behavioral aspects (fruit and vegetable consumption, smoking status, and alcohol intake). Data on gender, age, education level, employment status, socioeconomic status, place of residence, and marital status were gathered using a validated questionnaire and through interviews with the study participants. Gender was categorized as either male or female. Age was classified into 2 groups: 15 to 18 years, representing early young adulthood, and 19 to 24 years, representing young adulthood [28]. Education level was segmented into 5 categories: none, elementary school, junior high school, senior high school, and university. Marital status was divided into 3 groups: unmarried, married, and divorced. Place of residence was distinguished between urban and rural settings.

Employment status was categorized as employed, unemployed, or student. Socioeconomic status was determined using the classifications from the Indonesia Central Bureau of Statistics, which consider household assets, average income, and expenditure. These factors are then used to assign placement within a wealth index that is divided into 5

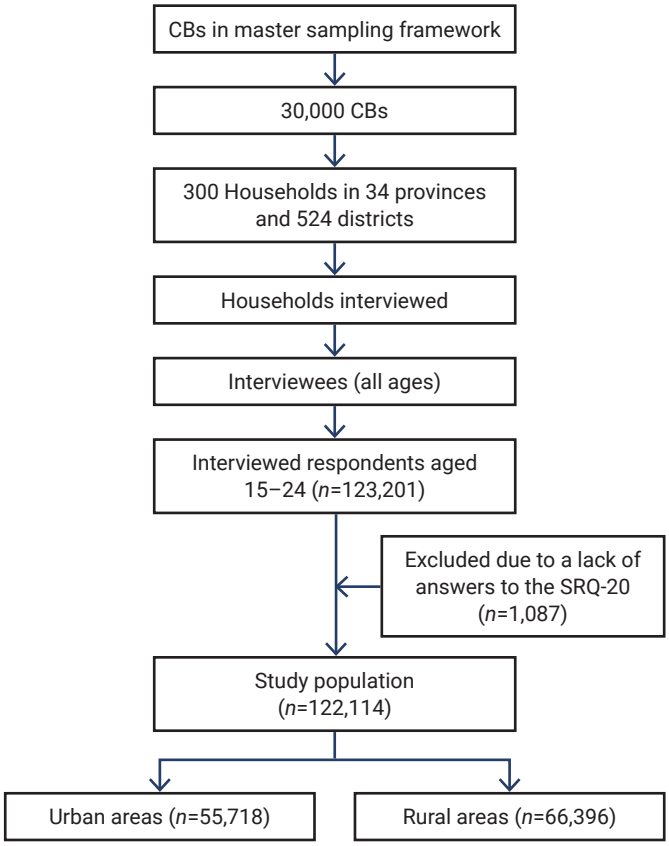

Figure 1. Flowchart of data selection, modified from the Indonesia National Health Survey 2018 report [26].
CBs, census blocks; SRQ-20, 20-item Self-Report Questionnaire.

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quintiles, with 1 representing the poorest and 5 constituting the richest [29].

Smoking status was categorized into 3 groups: non-smoker, occasional, and daily. Non-smokers were individuals who reported never having smoked. Occasional smokers were respondents who smoked from time to time, while daily smokers were those who smoked every day. Alcohol consumption was classified into 2 categories: "yes" for participants who consumed alcohol in the prior month and "no" for those who did not consume alcohol in the month preceding the interview.

Fruit consumption was categorized as "yes" for participants who consumed at least 7 portions of fruit per week and "no" for those who consumed fewer than 7 portions per week. Similarly, vegetable consumption was classified into 2 categories: "yes" for consuming at least 7 portions of vegetables per week and "no" for consuming less than this amount [30].

Data Analysis

The research variables were analyzed using descriptive, bivariate, and multivariate analyses. Descriptive statistics were utilized to characterize respondent demographics. In bivariate analysis, the chi-square test was used to explore the relationship between the independent and the dependent variables. Logistic regression analysis was conducted to determine the adjusted associations between CMDs and various independent variables. To ensure an accurate assessment of the risk difference associated with urban or rural residence in youth mental health, while accounting for other variables in comprehensive multivariate models, adjustments were made for demographic variables (education, marital status, employment, and socioeconomic status), inherent variables (gender and age), and behavioral variables (smoking status and consumption of alcohol, fruits, and vegetables). Statistical analyses were performed using IBM SPSS for Windows ver. 21.0 (IBM Corp.).

Ethics Statement

Ethical approval for this study was granted by the Ethical Committee of Health Research at the NIHRD, Ministry of Health, Republic of Indonesia, under the approval number LB.02.01/2/KE.267/2017.

Results

Table 1 displays the characteristics of the study sample. Among the 122,114 participants, the prevalence of CMDs was higher in urban environments (10.4%) compared to rural areas (8.9%). The distribution of male and female participants was approximately equal in both settings. In urban areas, more participants were aged 19 to 24 years (52.6%) than 15 to 18 years (47.4%). Conversely, in rural areas, participants aged 15 to 18 constituted a higher percentage (51.4%) than those aged 19 to 24 (48.6%). Regarding education level, a substantial proportion of urban youth achieved higher education, most frequently senior high school (42.4%) but in some cases university (6.0%). In rural areas, the largest proportion of participants had completed up to junior high school (39.6%), while the smallest had attained a university-level education (2.8%). A greater proportion of youth in rural areas were married (21.9%) relative to urban areas (13.3%). In terms of employment status, students represented the largest group of participants in both rural (36.6%) and urban (41.5%) areas. The greatest number of respondents in urban areas fell into the wealthiest socioeconomic quintile (31.4%), nearly 3 times the proportion found in rural areas (11.7%). The largest socioeconomic category in rural areas was the poorest quintile (23.5%). Most participants consumed fewer than 7 portions of fruits and vegetables per week in both urban (fruits, 86.3%; vegetables, 51.1%) and rural (fruits, 91.9%; vegetables, 50.6%) areas. Fruit consumption of 7 or more portions per week was more common in urban areas (13.7%), while higher vegetable consumption (≥ 7 portions per week) was more frequent in rural areas (49.4%). Most participants in both urban (73.4%) and rural (72.6%) areas were non-smokers. Similarly, a high percentage of participants did not consume alcoholic beverages in both urban (95.0%) and rural (94.2%) settings.

The results presented in Table 2 delineate the risk factors associated with CMDs in urban and rural settings. No significant association was observed between age and CMDs in either urban or rural populations ($p > 0.05$). In terms of the adjusted odds ratio, in urban areas, female respondents were 2.993 times more likely than male participants to have CMDs (95% confidence interval [CI], 2.664–3.363). Individuals with only an elementary school education had a 2.093 times higher risk of CMDs than those with a university education (95% CI, 1.639–2.674). Regarding economic status, individuals in the fourth quintile ("rich") and those in the second quintile ("poor") had a lower likelihood of experiencing CMDs, by 0.868 times (95% CI, 0.760–0.991) and 0.869 (95% CI, 0.756–0.998) times respectively, compared to those in the fifth quintile ("richest").

Regarding fruit consumption, respondents who consumed fewer than 7 portions per week were 1.168 times more likely to have CMDs than those who consumed 7 or more portions per week (95% CI, 1.022–1.335). In terms of weekly vegetable intake, individuals consuming fewer than 7 portions per week were 1.346 times more likely to have CMDs compared

Table 1. Characteristics of rural and urban respondents (n = 122,114)

Variable	Urban (n = 55,718)	Rural (n = 66,396)	p
CMDs			< 0.001
Yes	5,774 (10.4)	5,903 (8.9)	
No	49,944 (89.6)	60,493 (91.1)	
Gender			< 0.001
Male	26,819 (48.1)	33,182 (50.0)	
Female	28,899 (51.9)	33,214 (50.0)	
Age group (y)			< 0.001
15–18	26,417 (47.4)	34,150 (51.4)	
19–24	29,301 (52.6)	32,246 (48.6)	
Education level			< 0.001
University	3,353 (6.0)	1,830 (2.8)	
Senior high school	23,619 (42.4)	19,486 (29.3)	
Junior high school	19,941 (35.8)	26,294 (39.6)	
Elementary school	6,846 (12.3)	13,673 (20.6)	
No education	1,959 (3.5)	5,113 (7.7)	
Marital status			< 0.001
Unmarried	47,998 (86.1)	51,397 (77.4)	
Married	7,399 (13.3)	14,539 (21.9)	
Divorced	321 (0.6)	460 (0.7)	
Employment status			< 0.001
Employed	17,327 (31.1)	20,420 (30.8)	
Unemployed	15,276 (27.4)	21,663 (32.6)	
Student	23,115 (41.5)	24,313 (36.6)	
Economic status			< 0.001
Richest	17,522 (31.4)	7,790 (11.7)	
Rich	11,446 (20.5)	13,652 (20.6)	
Middle	10,867 (19.5)	14,359 (21.6)	
Poor	9,180 (16.5)	14,985 (22.6)	
Poorest	6,703 (12.0)	15,610 (23.5)	
Weekly fruit consumption			< 0.001
Yes (≥ 7 portions)	7,613 (13.7)	5,409 (8.1)	
No (< 7 portions)	48,105 (86.3)	60,987 (91.9)	
Weekly vegetable consumption			0.105
Yes (≥ 7 portions)	27,254 (48.9)	32,786 (49.4)	
No (< 7 portions)	28,464 (51.1)	33,610 (50.6)	
Smoking status			< 0.001
Non-smoker	40,895 (73.4)	48,211 (72.6)	
Occasionally	5,450 (9.8)	5,767 (8.7)	
Daily	9,373 (16.8)	12,418 (18.7)	
Alcoholic beverage consumption			< 0.001
No	52,926 (95.0)	62,560 (94.2)	
Yes	2,792 (5.0)	3,836 (5.8)	

Data are presented as n (%).

to those eating 7 or more portions per week (95% CI, 1.231–1.472).

The findings revealed that urban residents who smoked, either occasionally or daily, were at a 2.119-fold (95% CI, 1.812– 2.478) or 2.020-fold (95% CI, 1.734–2.354) increased risk of developing CMDs, respectively, compared to non-smokers. Urban respondents who consumed alcohol were found to be 2.283 times more likely to experience CMDs than those who abstained (95% CI, 1.916–2.721). In urban settings, neither marital status nor employment status was significantly linked to the likelihood of CMDs (p > 0.05). Similarly, no significant association was found between CMDs incidence and being in the middle or poorest economic quintile (p > 0.05).

In rural areas, female participants were 2.889 times more likely to experience CMDs than male respondents (95% CI, 2.557–3.267). Respondents with no education were 1.906 times more likely to experience CMDs compared to those

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Table 2. Factors associated with CMDs among youth in rural and urban areas of Indonesia

Variable	Total (*n* = 122,114)	*p*	Urban (*n* = 55,718)	*p*	Rural (*n* = 66,396)	*p*
Area of residence						
Urban	Ref.		NA		NA	
Rural	0.780 (0.727–0.836)	0.000*	NA		NA	
Sex						
Male	Ref.		Ref.		Ref.	
Female	2.956 (2.712–3.221)	0.000*	2.993 (2.664–3.363)	0.000*	2.889 (2.557–3.267)	0.000*
Age group (y)						
15–18	Ref.		Ref.		Ref.	
19–24	1.042 (0.959–1.133)	0.325	1.029 (0.909–1.165)	0.647	1.072 (0.967–1.189)	0.186
Highest education attained						
University	Ref.		Ref.		Ref.	
Senior high school	1.491 (1.272–1.747)	0.000*	1.571 (1.296–1.904)	0.000*	1.254 (0.963–01.634)	0.093
Junior high school	1.621 (1.359–1.933)	0.000*	1.696 (1.351–2.129)	0.000*	1.376 (1.047–1.809)	0.022**
Elementary school	1.846 (1.534–2.223)	0.000*	2.093 (1.639–2.674)	0.000*	1.452 (1.096–1.925)	0.009**
No education	2.075 (1.691–2.546)	0.000*	1.959 (1.445–2.656)	0.000*	1.906 (1.415–2.567)	0.000*
Marital status						
Unmarried	Ref.		Ref.		Ref.	
Married	0.901 (0.820–0.991)	0.032**	0.966 (0.839–1.113)	0.636	0.842 (0.751–0.945)	0.004**
Divorced	1.304 (0.983–1.732)	0.066	1.008 (0.627–1.621)	0.972	1.722 (1.245–2.381)	0.001**
Employment status						
Employed	Ref.		Ref.		Ref.	
Unemployed	1.172 (1.083–1.268)	0.000*	1.117 (0.998–1.249)	0.054	1.265 (1.139–1.404)	0.000*
Student	1.090 (0.993–1.196)	0.068	1.038 (0.916–1.177)	0.559	1.198 (1.055–1.359)	0.005**
Economic status						
Richest	Ref.		Ref.		Ref.	
Rich	0.934 (0.845–1.032)	0.178	0.868 (0.760–0.991)	0.036**	1.059 (0.916–1.226)	0.437
Middle	0.934 (0.842–1.038)	0.205	0.913 (0.796–1.047)	0.194	0.994 (0.849–1.164)	0.941
Poor	0.904 (0.816–1.003)	0.057	0.869 (0.756–0.998)	0.048**	0.982 (0.839–1.148)	0.815
Poorest	0.979 (0.879–1.093)	0.715	1.019 (0.876–1.184)	0.809	0.989 (0.844–1.159)	0.893
Weekly fruit consumption						
Yes (≥7 portions)	Ref.		Ref.		Ref.	
No (<7 portions)	1.108 (1.002–1.226)	0.046**	1.168 (1.022–1.335)	0.023**	0.991 (0.862–1.138)	0.899
Weekly vegetable consumption						
Yes (≥7 portions)	Ref.		Ref.		Ref.	
No (<7 portions)	1.277 (1.199–1.359)	0.000*	1.346 (1.231–1.472)	0.000*	1.179 (1.088–1.278)	0.000*
Smoking status						
Non-smoker	Ref.		Ref.		Ref.	
Occasionally	2.170 (1.932–2.437)	0.000*	2.119 (1.812–2.478)	0.000*	2.250 (1.917–2.642)	0.000*
Daily	2.061 (1.846–2.301)	0.000*	2.020 (1.734–2.354)	0.000*	2.117 (1.818–2.466)	0.000*
Alcoholic beverage consumption						
No	Ref.		Ref.		Ref.	
Yes	2.344 (2.079–2.642)	0.000*	2.283 (1.916–2.721)	0.000*	2.420 (2.077–2.821)	0.000*

Data are presented as adjusted odds ratio (95% confidence interval).
CMDs, common mental disorders; ref., reference; NA, not applicable.
*$p < 0.001$, **$p < 0.05$.

with a university-level education (95% CI, 1.415–2.567). Divorced respondents exhibited a 1.772 times higher risk of experiencing CMDs than those who were unmarried (95% CI, 1.245–2.381). In turn, being married appeared to represent a protective factor against CMDs in rural areas, with married respondents having a 0.842 times lower risk of CMDs than their unmarried counterparts (95% CI, 0.751–0.945).

Unemployed respondents were 1.265 times more likely to experience CMDs than their employed counterparts (95% CI, 1.139–1.404). Those who consumed fewer than 7 portions of vegetables per week were at a 1.179 times greater risk of CMDs compared to individuals who consumed 7 or more portions per week (95% CI, 1.088–1.278). However, weekly fruit consumption, socioeconomic status, and possession of a senior high school education did not significantly

influence the incidence of CMDs in rural areas ($p > 0.05$).

Individuals who smoked, whether occasionally or daily, were found to have a 2.250-fold (95% CI, 1.917–2.642) or 2.117-fold (95% CI, 1.818–2.466) increased risk of CMDs, respectively, compared to non-smokers. Similarly, those who consumed alcoholic beverages were 2.420 times more likely to experience CMDs than those who abstained from alcohol (95% CI, 2.077–2.821).

Discussion

The results indicated that the prevalence of CMDs among youth was higher in urban than in rural areas. Similar findings were reported in a study conducted in Bangladesh and in a meta-analysis [20,31]. Various factors contribute to the incidence of mental disorders in urban settings, including the social environment, neighborhood characteristics, population density, and personal space [32]. The increased prevalence of CMDs in urban areas may be attributed to the stress associated with urban living and the diminished social support experienced by individuals who have migrated from rural areas [33]. Several demographic factors were found to be associated with elevated risk of CMDs, with differences observed between rural and urban youth. Being male and possessing a college education appear to reduce the risk of CMDs for both demographics. However, the impact of socioeconomic status, marital status, and employment varied between urban and rural populations.

This study revealed a significant relationship between CMDs and education level among both rural and urban youth. The risk of CMDs varied across educational attainment levels, with less educated individuals being more susceptible to CMDs than those with the highest attainment in both urban and rural contexts. Education is widely recognized as a strong determinant of mental health, improving mental health outcomes by increasing an individual's literacy and ability to manage psychological stressors [34]. Additionally, advanced education contributes to economic stability, expanded social networks, and improved employment prospects, all of which support better mental health outcomes [35]. These findings are consistent with previous research conducted in Finland, Denmark, Poland, and Spain, which demonstrated a positive association between lower educational attainment and the prevalence of mental disorders [36,37].

The present research determined that age did not significantly impact CMDs in either urban or rural settings. We divided age into 2 categories: 15 to 18 years (early young adulthood) and 19 to 24 years (young adulthood) [28]. Consequently, the lack of significant age-related influence may stem from similarities in these developmental stages. These periods signify the transition from childhood to adulthood, marked by a shift from reliance on family to autonomy and a progression toward independent living [38].

Female participants exhibited a higher likelihood of experiencing CMDs than male respondents, regardless of their residence in urban or rural areas. These findings align with previous research conducted in Indonesia and Australia [39,40]. The underlying causes are likely a combination of social and biological factors. From a biological perspective, the differing sex chromosomes of men and women have been implicated as a contributing factor to the higher prevalence of mental disorders among women [41]. Additionally, during puberty, female adolescents are particularly susceptible to the effects of sex hormones. Fluctuations in hormones during puberty and other hormone-related transitional periods have been associated with an increased risk of mental illness in girls and women [42]. Social factors also play a significant role. Female individuals often face unique life experiences, including continuous exposure to social and cultural expectations and constraints that can adversely affect their mental health. For example, girls and young women may place a high value on physical attractiveness, largely because societal norms encourage this focus. Indonesian culture, in particular, expects women to marry by the age of 25. Those who do not meet this expectation may be stigmatized as "leftover" or undesirable [43]. Women may strive to embody these societal ideals to gain acceptance or respect, but this can lead to chronic stress and contribute to mental health problems [44].

This study determined that the association between marital status and CMDs was significant exclusively in rural regions. Divorced young people in these areas were more likely to experience CMDs compared to their unmarried counterparts. Conversely, marriage appeared to act as a protective factor against CMDs in rural settings. These findings align with previous research conducted in the United States, which found that individuals who married between the ages of 22 and 26 years reported greater life satisfaction than those who remained single or were in non-marriage relationships [45]. The substantial contribution of social support, including that provided by a spouse, was identified as a key factor in the protective influence of marriage against depression [46].

In contrast, the results of the present study indicated that marital status was not significantly associated with CMDs in urban areas. Several factors may account for this finding. Urban residents often prioritize personal choices, such as deciding when to marry. Conversely, in rural communities, family and community members frequently play a key role in shaping individual life choices and may

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exert social pressure [47]. Additionally, urban environments might exhibit less stigma toward unmarried, divorced, or widowed individuals, contributing to a culture of acceptance and support regardless of marital status. Being divorced or widowed in rural areas can be particularly difficult due to the associated stigma. In tight-knit communities where collective norms are strong, people often are deeply involved in one another's personal affairs. Widowed individuals, particularly women, may face social marginalization and sexual objectification, which can intensify their stress and sense of vulnerability [48]. Similarly, divorced individuals face an increased risk of mental health problems, stemming from reduced social support and feelings of loneliness [49].

The relationship between CMDs and socioeconomic status was not significant in rural youth; however, a significant association was observed among urban respondents. Research conducted in rural Canada indicates that depression rates are lower in rural regions compared to urban settings, perhaps due to a stronger sense of community belonging and social support. The incidence of depression does not decrease in correlation with socioeconomic advantage. Instead, the reduced risk of depression in rural areas is strongly linked to the level of community attachment and the availability of social support [13].

Compared to those in the highest ("richest") economic quintile, urban residents in the second ("poor") and fourth ("rich") quintiles were less likely to experience CMDs. This disparity may be attributed to the greater expectations placed on the wealthiest by their families and social circles. The pressure to attain the highest level of education at prestigious schools and to secure employment could increase the vulnerability of the wealthiest individuals to CMDs, with the most severe symptoms often observed in students from higher socioeconomic backgrounds [50]. The findings of this study align with research conducted in Mozambique, which indicates that, compared to those in the highest wealth quintile, individuals in the lowest quintile exhibited a lower prevalence of depressive symptoms [24]. However, these results contrast with other studies that have identified a strong link between poverty and CMDs [51], suggesting that wealthier people are less prone to mental health issues [52].

The present study identified a significant link between unemployment among young people and CMD in rural, but not urban, areas. A systematic review in a Nordic country found that unemployed young individuals are more prone to mental health issues than their employed counterparts, which can be attributed to financial hardship and a lack of social support [53]. In India, research suggests that unemployed young people are at a greater risk of mental health problems compared to those who are employed. They are more likely to experience anxiety, depression, and challenges in regulating their emotions and behaviors. Unlike their employed peers, unemployed young people often report dissatisfaction with their lives, which contributes to reduced psychological well-being [54]. Additionally, a Swedish study indicated that unemployment is associated with an increased risk of mental health disorders among young people [55].

In terms of healthy diet, this study revealed an association between a lack of vegetable intake (fewer than 7 portions per week) and youth CMDs in both urban and rural settings. Previous research has demonstrated that individuals with mental health issues often consume greater amounts of high-fat and high-sugar foods and lower quantities of nutrient-dense options [56]. Additionally, research indicates that obesity may influence depression symptoms [57]. A study conducted in the Philippines reported that social-environmental and socioeconomic factors, along with proper nutrition education and accessibility, are key determinants of vegetable consumption in both urban and rural communities [58]. Research from Scotland indicated that rural youths tend to have healthier eating habits than their urban counterparts [59]. The cost and consumption of food also appear to be influenced by geographic location, with traditional foods being more prevalent in rural areas, while Western foods are more common in urban settings [60].

In turn, a lack of fruit consumption, defined as fewer than 7 portions per week, was associated with youth CMDs exclusively in urban areas. Research conducted in urban regions of India has also indicated an increasing trend in the inadequate consumption of fruits, as well as heightened intake of fast food, sweets, and snacks [61]. A meta-analysis examining dietary patterns and depression revealed that a higher intake of fruits and vegetables was associated with a lower incidence of mood disorders [62]. The provision of unsaturated fatty acids and antioxidant vitamins—found in abundance in fruits—along with zinc and selenium, and the concurrent restriction of saturated and trans fatty acids, appear to exert a synergistic effect in diminishing the inflammation linked to depression [57].

Smoking status and alcohol consumption were significantly associated with CMDs among youth in both urban and rural areas, although the prevalence rates varied slightly. Young people who smoked, whether occasionally or daily, were at a higher risk of CMDs compared to their non-smoking counterparts. Similarly, youths who consumed alcoholic beverages were more likely to face CMDs than those who abstained from alcohol. In Indonesia, alcohol consumption and smoking have been identified as risk

factors for depression [25]. Multiple studies have highlighted the adverse effects of alcohol consumption on adult mental health [7,63]. A Brazilian investigation found associations between mental disorders in adolescents and smoking, alcohol use, and exposure to cigarette smoke [7]. In a study of several developing countries, 44.4% of young people who drank alcohol reported experiencing depression, while 82.1% described experiencing anxiety-related sleeplessness [63].

This study carries substantial implications. Its findings highlight the urgent need for comprehensive mental health policies tailored to the needs of Indonesian youth. It illuminates the prevalence of CMDs in this demographic, revealing that the determinants of CMDs vary between urban and rural settings. By identifying factors such as gender, education level, diet, smoking, alcohol consumption, employment status, and marital status as being associated with CMDs, the research offers vital information for policymakers. These insights can guide the development of targeted interventions and public health programs. The study underscores the necessity of recognizing the diverse determinants of mental health status among youth from different demographic backgrounds, establishing distinctions between urban and rural areas. Looking ahead, it is essential to explore how the determinants of mental health issues differ across various demographic characteristics, including socioeconomic status, parental education level, cultural background, and geographic location of residence. Such understanding is crucial for supporting mental health policies and interventions for youth on a global scale. The insights gained from this study should inform worldwide efforts aimed at addressing mental health issues among young people, informing the creation of more effective strategies and interventions across the globe.

Conclusion

A higher prevalence of CMDs was observed among urban than rural youth in Indonesia. Furthermore, the factors influencing CMDs in young people varied between urban and rural settings. For both populations, being male, holding a college degree, consuming at least 7 portions of vegetables per week, abstaining from smoking, and not drinking alcohol were associated with a reduced risk of CMDs. In rural areas, being married and employed were additional protective factors, whereas being divorced was linked to an increased risk of CMDs. In urban settings, consuming at least 7 portions of fruit per week and not being in the highest socioeconomic bracket were associated with lower risk. The findings underscore the importance of designing interventions that address specific risk factors tailored to regional differences to effectively reduce CMDs among Indonesian youth. Policymakers, healthcare providers, and community leaders should collaborate to promote healthy lifestyles and target vulnerable segments of the population to decrease the prevalence of CMDs within this demographic.

Strengths and Limitations

This study has contributed to our understanding of the determinants of CMDs among youth in Indonesia. It utilized secondary data from the 2018 INHS, a nationwide survey that offers a substantial dataset representative of the Indonesian population. The research encompassed a broad range of variables, including demographic and socioeconomic factors, as well as several health behavior indicators pertinent to the youth demographic. Nonetheless, the study is not without its limitations regarding the data variables. Notably, the analysis was confined to the variables made available by the INHS. Consequently, certain potential determinants of youth CMDs were not included in the analysis, such as sleep disturbances, early sexual activity, excessive screen time or internet use, peer interactions, community support, and neurological disorders [5,6,8].

Notes

Ethics Approval

Ethical approval for this study was granted by the Ethical Committee of Health Research at the National Institute of Health Research and Development (NIHRD), Ministry of Health, Republic of Indonesia, under the approval number LB.02.01/2/KE. 267/2017.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

All data generated or analyzed during this study are included in this published article. The data can be obtained by submitting a written request to the Data Management Laboratory of the National Institute of Health Research and Development (NIHRD) at datin.bkpk@kemkes.go.id.

Authors' Contributions

Conceptualization: MK, LL; Data curation: all authors; Formal analysis: YF, SH, HDK; Investigation: all authors; Methodology: DY, DEE; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Associations of type and intensity of social participation with depression, self-rated health, and life satisfaction among community-dwelling older adults in the Republic of Korea: a nationwide cross-sectional study

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ABSTRACT

Objectives: Social activities are important and influential factors for healthy aging. However, limited information is available regarding the associations of the type and intensity of social participation with health and well-being. This study aimed to investigate how various types of social activities are associated with several dimensions of health outcomes.

Methods: This cross-sectional study utilized data from the Seventh Korean Longitudinal Study of Aging, which included 5,526 adults aged 60 years and older. Multivariate linear regression analysis was employed to analyze the associations of social activities with depression, self-rated health, and life satisfaction. Additionally, subgroup analyses by sex and age were performed.

Results: Among the participants, 73.5% reported involvement in at least 1 of the 4 types of social engagement. After adjustment for all covariates, individuals who participated in any social activity reported better self-rated health and higher life satisfaction compared to those who did not participate. However, the intensity of engagement in different social activities had varying impacts on subjective health outcomes. An increased level of participation was associated with a lower rate of depression and improved self-rated health. However, no significant differences were observed in the relationship between the intensity of participation in activities (with the exception of alumni societies or family councils) and life satisfaction.

Conclusion: This study suggests that to improve their health, older adults in the Republic of Korea should not only engage in social activities but also do so actively and regularly.

Keywords: Depression; Health status; Older adults; Personal satisfaction; Social participation

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Introduction

In 2022, the Republic of Korea became an aged society, with individuals aged 65 years and

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older comprising 17.5% of its total population. The nation is expected to transition to a super-aged society by 2025, when this proportion is projected to exceed 20% [1]. The life expectancy in the Republic of Korea has risen to 82.7 years, placing it 10th among Organization for Economic Cooperation and Development countries [2]. However, 89.5% of those aged 65 years or older are physically ill and receive treatment in hospitals [3].

Social participation is considered one of the most important and influential factors in promoting healthy aging [4]. Among older people, social participation is associated with increased life expectancy, as it extends the duration of good health and promotes appropriate social integration [5]. Thus, the World Health Organization has recommended the implementation of active aging policies to improve the health, participation, and security of older adults [6].

According to the activity theory of aging, engaging in physical and mental activities is crucial for the psychological well-being of older adults [7]. Involvement in a variety of social practices, such as sports and cultural pastimes, has been linked to greater life satisfaction and mental health among this demographic. Active involvement in social activities not only has a beneficial impact on mental health by reducing depression and increasing happiness, but also improves subjective physical health and is associated with lower mortality [2,8–13]. However, any potential detrimental effects of older adults' participation in various social activities are unclear. Furthermore, research has not yet definitively indicated whether a directly proportional relationship exists between the intensity of participation in social activities and the health of older adults.

Studies of the relationship between social activities and the health of older people in the Republic of Korea have focused on their involvement in religious and leisure activities [14–17]. However, few studies have explored the relationships between health and social activities by type, such as religious, volunteer, and leisure activities [18–20]. Consequently, it is necessary to examine the specific aspects of health influenced by each type of activity and to understand the differences in their effects, considering the type and nature of social participation, before the Republic of Korea becomes an aging society.

Several studies of East Asian elderly populations have explored the relationship between instrumental activities of daily living (IADLs), depression, and life satisfaction. The findings suggest that several factors positively influence IADLs; furthermore, depression and life satisfaction are associated with political and religious activities but are not significantly linked to civil activities, arts, sports, or leisure pursuits [21–23]. While research on the effects of social activities on the physical health, mental health, and cognitive function of older adults has generally not been differentiated by sex or age group, the role and impact of social participation may vary based on these factors. Therefore, multiple explanations and interpretations could be necessary. Addressing this gap in knowledge, the present study investigates how different types and levels of social activity participation relate to 3 key health and well-being indicators in older adults: self-rated health, depressive symptoms, and life satisfaction.

HIGHLIGHTS

- Social participation is considered one of the most important and influential factors in the healthy aging of older adults.
- Engagement in specific social activities, such as sports and cultural pursuits, has also been associated with life satisfaction and mental health within this demographic.
- Increased intensity of participation in a variety of social activities was significantly related to depression and self-rated health, but not life satisfaction.

Materials and Methods

Data and Participants

The present study utilized data from the Korean Longitudinal Study of Aging (KLoSA), which is administered by the Korea Employment Information Service (KEIS). The KLoSA is a nationally representative panel survey of the household-dwelling population of the Republic of Korea aged 45 years and older, employing a multistage, stratified probability sampling method [24]. The baseline survey, conducted in 2006, included interviews with 10,254 individuals across 6,171 households. Subsequent interviews were carried out biennially through 2018, encompassing a total of 7 survey waves. Of the 6,940 participants in the seventh KLoSA in 2018, our analysis incorporated data from 5,526 respondents.

Variables and Measurements

Depression was assessed using the 10-item short form of the Center for Epidemiological Studies Depression Scale, a tool commonly employed to identify depression in non-psychiatric community settings [25,26]. Participants responded to the 10 items using a 4-point Likert scale. The

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scoring for each item ranged from 0 to 3, with the following designations: 0 for "very rarely or less than once a day"; 1 for "sometimes (1–2 days in the past week)"; 2 for "often (3–4 days in the past week)"; and 3 for "almost always (5–7 days in the past week)". The total score varied from 0 to 30, with higher scores reflecting greater severity of depression.

Self-rated health was assessed with the question, "Would you say your health is very good, good, fair, poor, or very poor?" For analytical purposes, continuous variables were generated by assigning point values to the responses, with 1 representing "very poor" and 5 indicating "very good".

Life satisfaction was evaluated using 5 questions. These items covered overall quality of life, economic status, health, and relationships with one's children and spouse, selected to offer a thorough assessment of quality of life. The measurement instrument employed was an 11-point scale with 10-unit intervals, ranging from 0 to 100 units, with higher scores signifying greater well-being.

Social participation was defined as involvement in social groups beyond one's home. For the purposes of this study, social participation was divided into 4 categories: religious activities, activities at senior centers, leisure/cultural/sports activities, and participation in alumni societies or family councils. Participants were asked to rate the frequency of their involvement in each type of activity using a 10-point scale, where 0 indicated "never," 1 "almost never," 2 "less than once a year," 3 "1–2 times a year," 4 "3–4 times a year," 5 "5–6 times a year," 6 "once a month," 7 "twice a month," 8 "once a week," 9 "2–3 times a week," and 10 "every day or almost every day."

In this study, 2 types of social activity variables were utilized. As the frequency of participation in formal social activities did not follow a normal distribution, the first variable was categorized dichotomously as either participation or non-participation. We then aggregated the total number of formal social activities for each respondent to quantify the extent of social participation.

Sociodemographic covariates included sex (male or female), age, educational status (middle school or less, high school or more), marital status (married, widowed/divorced/never married), and residential area (urban or rural). Health-related behavior covariates encompassed regular exercise (yes or no). The number of chronic diseases was determined based on self-reported clinical diagnoses of 9 health conditions: hypertension, diabetes, cancer, chronic lung disease, chronic hepatitis, cardiovascular disease, cerebrovascular disease, mental illness, and arthritis. The number of these conditions was categorized as 0, 1, or 2 or more. Living arrangements were classified into 2 groups: living alone or living with family, which could include a spouse. Household income was calculated by dividing the total household income by the square root of the number of household members, with the resulting values segmented into quartiles. Economic activity was ascertained using the question, "Are you currently employed?" In this context, employment referred to working for an employer, being self-employed, or working for a family or relative's business, with potential responses of "yes" or "no".

Statistical Analysis

The general characteristics of the samples were summarized using frequencies, percentages, and means (with standard deviations) for demographic factors, socioeconomic status, health indicators, and types of social participation, categorized by sex and age group. F-tests and t-tests were employed to compare mean differences in depression, self-rated health, and life satisfaction across these variables. Multivariate linear regression modeling was employed to examine the relationship between social participation and the outcome variables, adjusting for all covariates. Additionally, multivariate linear regression analysis was conducted separately for subgroups defined by age and sex. Statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc.). All tests were 2-tailed, with an alpha threshold of 0.05.

Ethical Consideration

This study was exempt from Institutional Review Board of Chung-Ang University (IRB No. 1044396-202203-HR-073-01) as all data are publicly available. Informed consent to participate in the survey was obtained from all respondents during the data collection by the KEIS. Formal consent was not required for this study because it was retrospective and utilized secondary data that were analyzed anonymously.

Results

The characteristics of the study population are summarized in Table 1. Among the participants, 58.1% were between 60 and 74 years old, 57.4% were female, 47.0% had received a primary school education or less, and 30.7% belonged to the lowest quartile in terms of annual household income.

More than three-quarters of the participants engaged in at least 1 social activity. The most common form of participation occurred at senior centers, with 60.6% of participants reporting engagement. The 60 to 74 age group displayed a higher rate of involvement in senior center activities (69.4%) and alumni society or family council activities (17.8%) than those 75 years old or above, who participated at rates of 48.4% and 5.6%, respectively. Women's participation in religious

Table 1. Descriptive statistics of sample

Variable	Sample distribution (*n* = 5,527)	60–74 y (*n* = 3,211)	≥75 y (*n* = 2,316)	Male (*n* = 2,353)	Female (*n* = 3,174)
Age (y)					
60–74	3,211 (58.1)			1,447 (61.5)	1,764 (55.6)
≥75	2,316 (41.9)			906 (38.5)	1,410 (44.4)
Sex					
Male	2,353 (42.6)	1,447 (45.1)	906 (39.1)		
Female	3,174 (57.4)	1,764 (54.9)	1,410 (60.9)		
Educational level					
Elementary school or under	2,596 (47.0)	1,007 (31.4)	1,589 (68.6)	668 (28.4)	1,928 (60.7)
Middle school graduate	973 (17.6)	697 (21.7)	276 (11.9)	441 (18.7)	532 (16.8)
High school graduate	1,452 (26.3)	1,139 (35.5)	313 (13.5)	851 (36.2)	601 (18.9)
College and above	506 (9.2)	368 (11.5)	138 (6.0)	393 (16.7)	113 (3.6)
Marital status					
Married	3,972 (71.9)	2,674 (83.3)	1,298 (56.0)	2,124 (90.3)	1,848 (58.2)
Widowed/unmarried/divorced	1,555 (28.1)	537 (16.7)	1,018 (44.0)	229 (9.7)	1,326 (41.8)
Household income					
Q1 (lowest)	1,699 (30.7)	553 (17.2)	1,146 (49.5)	565 (24.0)	1,134 (35.7)
Q2	1,652 (29.9)	1,001 (31.2)	651 (28.1)	722 (30.7)	930 (29.3)
Q3	1,275 (23.1)	967 (30.1)	308 (13.3)	604 (25.7)	671 (21.1)
Q4 (highest)	901 (16.3)	690 (21.5)	211 (9.1)	462 (19.6)	439 (13.8)
Living arrangement					
Alone	1,011 (18.3)	366 (11.4)	645 (27.8)	179 (7.6)	832 (26.2)
With someone	4,516 (81.7)	2,845 (88.6)	1,671 (72.2)	2,174 (92.4)	2,342 (73.8)
Economic activity (paid labor)					
Yes	1,620 (29.3)	1,333 (41.5)	287 (12.4)	986 (41.9)	634 (20.0)
No	3,907 (70.7)	1,878 (58.5)	2,029 (87.6)	1,367 (58.1)	2,540 (80.0)
Residential area					
Urban	4,020 (72.7)	2,452 (76.4)	1,568 (67.7)	1,729 (73.5)	2,291 (72.2)
Rural	1,507 (27.3)	759 (23.6)	748 (32.3)	624 (26.5)	883 (27.8)
Regular exercise					
Yes	1,800 (32.6)	1,178 (36.7)	622 (26.9)	888 (37.7)	912 (28.7)
No	3,727 (67.4)	2,033 (63.3)	1,694 (73.1)	1,465 (62.3)	2,262 (71.3)
No. of chronic diseases					
2 or more	2,610 (47.2)	1,172 (36.5)	1,438 (62.1)	1,034 (43.9)	1,576 (49.7)
0 or 1	2,917 (52.8)	2,039 (63.5)	878 (37.9)	1,319 (56.1)	1,598 (50.3)
Participation in any social activity					
No	1,464 (26.5)	533 (16.6)	931 (40.2)	550 (23.4)	914 (28.8)
Yes	4,063 (73.5)	2,678 (83.4)	1,385 (59.8)	1,803 (76.6)	2,260 (71.2)
Participation in religious activity	1.04 ± 2.68	1.11 ± 2.78	0.94 ± 2.59	0.75 ± 2.32	1.25 ± 2.90
No	4,770 (86.3)	2,736 (85.2)	2,034 (87.8)	2,119 (90.1)	2,651 (83.5)
Yes	757 (13.7)	475 (14.8)	282 (12.2)	234 (9.9)	523 (16.5)
Participation in senior center activity	4.17 ± 3.63	4.48 ± 3.22	3.75 ± 4.08	4.28 ± 3.44	4.09 ± 3.75
No	2,176 (39.4)	982 (30.6)	1,194 (51.6)	840 (35.7)	1,336 (42.1)
Yes	3,351 (60.6)	2,229 (69.4)	1,122 (48.4)	1,513 (64.3)	1,838 (57.9)
Participation in in leisure/cultural/sports activity	0.43 ± 1.84	0.49 ± 1.93	0.35 ± 1.70	0.43 ± 1.78	0.43 ± 1.88
No	5,215 (94.4)	3,001 (93.5)	2,214 (95.6)	2,214 (94.1)	3,001 (94.5)
Yes	312 (5.6)	210 (6.5)	102 (4.4)	139 (5.9)	173 (5.5)
Participation in alumni societies or family councils	0.63 ± 1.76	0.89 ± 2.03	0.27 ± 1.21	1.00 ± 2.12	0.36 ± 1.38
No	4,828 (87.4)	2,641 (82.2)	2,187 (94.4)	1,878 (79.8)	2,950 (92.9)
Yes	699 (12.6)	570 (17.8)	129 (5.6)	475 (20.2)	224 (7.1)
Depression (0–30)	6.26 ± 5.29	5.40 ± 4.87	7.45 ± 5.60	5.77 ± 5.16	6.62 ± 5.35
Self-rated health (1–5)	2.85 ± 0.87	3.08 ± 0.81	2.53 ± 0.86	2.97 ± 0.87	2.76 ± 0.87
Satisfaction (0–100)	59.99 ± 14.8	63.23 ± 13.44	55.49 ± 15.49	61.86 ± 14.35	58.59 ± 15.03

Data are presented as *n* (%) or mean ± standard deviation.
Q, quartile.

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activities (16.5%) was more prevalent higher than men's (9.9%). Conversely, men were more active in social pastimes such as senior center activities (64.3%) and alumni society activities (20.2%), compared to women's participation rates of 57.9% and 7.1%, respectively.

Mental health (as indicated by depressive symptoms), self-rated health, and life satisfaction were relatively poor among respondents who were widowed, unmarried, or divorced; had lower levels of education; fell within the lower income quartiles; had a greater number of comorbidities; and exercised infrequently. Regarding employment status, employed participants reported higher levels of depression and significantly lower self-rated health and life satisfaction compared to those who were not employed (Table 2).

A multivariate linear regression model was used to explore the relationship between social participation and health and well-being. In contrast to the results for self-rated health and life satisfaction, as the intensity of participation in any type of social activity increased, the risk of depression significantly decreased. Self-rated health appeared to improve with greater involvement in social activities, with the exception of religious activities. However, a positive association with the intensity of involvement in alumni societies and family councils was observed only for life satisfaction. When examining the association between social participation and each health outcome, life satisfaction and self-rated health were significantly higher in participants compared to nonparticipants, a trend that was not significant in the cases of depression (Table 3).

In the age group analysis, the intensity of social engagement was a highly significant predictor of depression. Furthermore, engaging in at least 1 social activity had a positive impact on self-rated health and satisfaction in both age groups, unlike increasing the level of participation in certain types of activities. This pattern aligned with the findings from the sex group analysis (Table 4). Specifically, greater involvement in an alumni society significantly impacted the health indicators, while participation in senior center activities positively influenced depression and self-rated health. In contrast, neither involvement nor heightened participation in religious activities significantly affected health outcomes.

Discussion

This cross-sectional study examined the associations between the types and intensities of participation in social activities and self-rated health, depression, and life satisfaction among community-dwelling older adults in the Republic of Korea.

For all types of activities studied, a dose-response relationship was observed with levels of depressive symptoms and self-rated health, although this pattern did not extend to life satisfaction. Specifically, an increase in the frequency of social activities was associated with a decrease in negative depressive symptoms and an improvement in self-rated health. These results align with prior studies that have identified a strong association between engaging in a variety of social activities in later life and better self-rated health, greater life satisfaction, and fewer depressive symptoms [2,4,9,11]. However, the significance and strength of these associations varied depending on the type of social activity, suggesting that the mechanisms by which social participation influences subjective well-being and mental health in older adults may differ across activities [27].

In terms of social engagement, depression decreased with increasing intensity of participation in all types of activities. This finding aligns with previous research indicating that, in older adults with chronic diseases, active engagement in social activities and higher levels of social support are associated with reduced depression. In other words, diminished social support and loneliness are risk factors for depression among older adults [22,28,29].

Regarding depression, the study revealed no significant sex differences. A higher intensity of social engagement was associated with a decrease in depressive feelings, which partially supports previous findings that the intensity of social engagement is inversely (albeit non-significantly) related to the frequency of negative affect, including depression [11]. Consequently, when addressing the high rates of depression and suicide among older adults, it is important to recognize that participation in social activities during old age can increase the likelihood of receiving social support through interactions with others, which reduces depression.

Unlike the results for depression, the findings for self-rated health and life satisfaction differed according to the type of social participation. Furthermore, the study revealed differences in sex and age groups regarding the associations of social activities with these outcomes.

First, participation in community-based leisure, culture, and sports group activities was associated with a lower rate of depression [4,9]. However, the positive impacts of these activities on life satisfaction and self-rated health appear to be limited [8].

Second, activities at senior centers were positively associated with self-rated health and inversely related to depressive symptoms in both older men and women, regardless of age group. However, with respect to life satisfaction, these activities demonstrated a positive association only for men and those

Table 2. Bivariate analysis of dependent variables

Variable	Depression			Self-rated health			Satisfaction		
	Mean±SD	*t* or F	*p*	Mean±SD	*t* or F	*p*	Mean±SD	*t* or F	*p*
Age (y)									
60–74	5.41±4.88	14.49	<0.001	3.09±0.81	24.26	<0.001	63.23±13.44	19.33	<0.001
≥75	7.46±5.61			2.53±0.87			55.50±15.50		
Sex									
Male	5.78±5.16	5.93	<0.001	2.97±0.87	8.7	<0.001	61.87±14.35	8.21	<0.001
Female	6.63±5.36			2.77±0.88			58.60±15.04		
Educational level									
Elementary school or under	7.16±5.46	49.73	<0.001	2.61±0.86	157.03	<0.001	55.73±15.18	163.42	<0.001
Middle school graduate	5.77±5.09			2.95±0.84			61.72±13.81		
High school graduate	5.34±4.94			3.10±0.82			63.89±13.20		
College and above	5.28±5.03			3.25±0.84			67.32±12.67		
Marital status									
Married	5.77±5.10	10.88	<0.001	2.96±0.85	14.36	<0.001	62.10±13.98	16.51	<0.001
Widowed/unmarried/divorced	7.54±5.55			2.59±0.89			54.61±15.60		
Household income									
Q1 (lowest)	7.52±5.67	55.88	<0.001	2.56±0.89	121.92	<0.001	54.20±15.73	168.96	<0.001
Q2	6.15±5.00			2.86±0.84			60.08±13.94		
Q3	5.61±5.17			3.05±0.82			63.62±13.18		
Q4 (highest)	5.05±4.76			3.13±0.83			65.62±13.01		
Living arrangement									
Alone	7.56±5.49	8.68	<0.001	2.64±0.90	8.86	<0.001	54.94±15.87	11.38	<0.001
With someone	5.98±5.20			2.90±0.87			61.12±14.36		
Economic activity (paid labor)									
Yes	4.56±4.31	17.41	<0.001	3.19±0.72	20.82	<0.001	64.96±12.23	18.0	<0.001
No	6.97±5.50			2.71±0.90			57.93±15.33		
Residential area									
Urban	6.31±5.41	1.04	0.299	2.88±0.89	4.11	<0.001	60.11±14.91	0.93	0.350
Rural	6.15±4.96			2.78±0.86			59.69±14.63		
Regular exercise									
Yes	5.17±4.67	11.43	<0.001	3.08±0.79	13.88	<0.001	63.46±13.14	12.9	<0.001
No	6.80±5.49			2.75±0.90			58.32±15.32		
No. of chronic diseases									
2 or more	7.32±5.71	14.04	<0.001	2.51±0.87	29.08	<0.001	56.45±15.34	17.1	<0.001
0 or 1	5.33±4.69			3.16±0.77			63.16±13.62		
Participation in any social activity									
No	8.66±6.05	18.63	<0.001	2.35±0.93	25.2	<0.001	52.55±16.32	21.31	<0.001
Yes	5.41±4.70			3.04±0.79			62.67±13.28		
Participation in religious activity									
No	6.42±5.32	5.55	<0.001	2.84±0.88	2.71	0.006	59.89±14.95	1.32	0.187
Yes	5.28±5.01			2.94±0.85			60.65±14.13		
Participation in senior center activity									
No	7.91±5.88	18.17	<0.001	2.53±0.94	22.13	<0.001	55.04±15.99	19.89	<0.001
Yes	5.20±4.57			3.07±0.76			63.21±13.07		
Participation in leisure/cultural/sports activity									
No	6.42±5.31	10.95	<0.001	2.84±0.88	6.87	<0.001	59.67±14.88	7.39	<0.001
Yes	3.65±4.28			3.19±0.80			65.32±12.99		
Participation in alumni societies or family councils									
No	6.57±5.31	12.46	<0.001	2.79±0.88	18.04	<0.001	58.92±14.91	16.92	<0.001
Yes	4.17±4.66			3.33±0.73			67.39±11.96		

SD, standard deviation; Q, quartile.

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Table 3. Multivariate regression analysis (n = 5,526)

Variable	Depression				Self-rated health				Satisfaction			
	Estimate	SE	*t*	*p*	Estimate	SE	*t*	*p*	Estimate	SE	*t*	*p*
Age (y)												
60–74	Ref.				Ref.				Ref.			
≥75	0.49	0.161	3.04	0.002	−0.17	0.025	−6.9	<0.001	−1.06	0.436	−2.44	0.015
Sex												
Female	Ref.				Ref.				Ref.			
Male	0.01	0.155	0.06	0.953	0.00	0.024	−0.04	0.968	−1.19	0.418	−2.85	0.004
Educational level												
College and above	Ref.					Ref.			Ref.			
Elementary school or under	−0.21	0.275	−0.78	0.436	−0.17	0.042	−4.11	<0.001	−5.02	0.744	−6.74	<0.001
Middle school graduate	−0.45	0.282	−1.58	0.114	−0.12	0.043	−2.76	0.006	−2.76	0.764	−3.62	<0.001
High school graduate	−0.36	0.258	−1.38	0.168	−0.08	0.039	−1.96	0.050	−2.21	0.697	−3.17	0.002
Marital status (ref: married)												
Widowed/unmarried/ divorced	0.38	0.225	1.69	0.091	−0.09	0.034	−2.74	0.006	−3.59	0.608	−5.9	<0.001
Household income												
Q4	Ref.				Ref.				Ref.			
Q1(lowest)	0.55	0.235	2.35	0.019	−0.12	0.036	−3.27	0.001	−5.39	0.635	−8.49	<0.001
Q2	0.23	0.214	1.06	0.288	−0.04	0.033	−1.35	0.178	−2.62	0.579	−4.52	<0.001
Q3	0.27	0.215	1.27	0.204	−0.01	0.033	−0.22	0.829	−1.03	0.582	−1.76	0.078
Living arrangement												
With someone	Ref.				Ref.				Ref.			
Alone	0.27	0.255	1.04	0.297	0.10	0.039	2.6	0.010	1.59	0.689	2.3	0.021
Economic activity												
Yes	Ref.				Ref.				Ref.			
No	1.61	0.163	9.85	<0.001	−0.23	0.025	−9.14	<0.001	−3.12	0.442	−7.05	<0.001
Residential area												
Urban	Ref.				Ref.				Ref.			
Rural	−0.32	0.156	−2.04	0.042	−0.05	0.024	−2.03	0.042	1.17	0.421	2.78	0.005
Regular exercise												
Yes												
No	0.92	0.151	6.1	<0.001	−0.16	0.023	−7.08	<0.001	−2.66	0.407	−6.53	<0.001
No. of chronic diseases												
0 or 1	Ref.				Ref.				Ref.			
2 or more	1.07	0.139	7.73	<0.001	−0.44	0.021	−20.95	<0.001	−3.08	0.375	−8.2	<0.001
Participation in any social activity												
No	Ref.				Ref.				Ref.			
Yes	−0.26	0.255	1.04	0.298	0.27	0.039	−6.89	<0.001	4.90	0.689	−7.11	<0.001
Level of participation in religious activity	−0.17	0.028	−6	<0.001	0.00	0.004	0.06	0.951	−0.18	0.077	−2.32	0.021
Level of participation in senior center activity	−0.25	0.029	−8.85	<0.001	0.02	0.004	4.52	<0.001	0.13	0.078	1.69	0.091
Level of participation in leisure/cultural/ sports activity	−0.25	0.037	−6.73	<0.001	0.01	0.006	2.03	0.042	0.12	0.100	1.19	0.233
Level of participation in alumni societies or family councils	−0.22	0.041	−5.37	<0.001	0.04	0.006	6.13	<0.001	0.53	0.110	4.86	<0.001
Intercept	5.11	0.376	13.61	<0.001	3.56	0.057	62.05	<0.001	73.44	1.016	72.27	<0.001

SE, standard error; ref., reference; Q, quartile.

Table 4. Result of subgroup analysis

	Depression				Self-rated health				Satisfaction			
	Estimate	SE	*t*	*p*	Estimate	SE	*t*	*p*	Estimate	SE	*t*	*p*
60–74 y (*n* = 3,211)												
Participation in any social activity												
No	Ref.				Ref.				Ref.			
Yes	0.16	0.318	−0.51	0.608	0.22	0.050	−4.35	< 0.001	3.83	0.847	−4.52	< 0.001
Level of participation in religious activity	−0.19	0.033	−5.88	< 0.001	0.00	0.005	0.7	0.484	−0.09	0.088	−1.08	0.282
Level of participation in senior center activity	−0.29	0.036	−8.19	< 0.001	0.02	0.006	3.42	0.001	0.25	0.095	2.66	0.008
Level of participation in leisure/cultural/sports activity	−0.23	0.043	−5.3	< 0.001	0.01	0.007	0.88	0.377	0.00	0.115	0.03	0.978
Level of participation in alumni societies or family councils	−0.22	0.043	−5.07	< 0.001	0.04	0.007	5.6	< 0.001	0.44	0.115	3.84	< 0.001
≥ 75 y (*n* = 2,316)												
Participation in any social activity												
No	Ref.				Ref.				Ref.			
Yes	−0.82	0.435	1.89	0.059	0.32	0.065	−4.9	< 0.001	5.98	1.196	−5	< 0.001
Level of participation in religious activity	−0.12	0.052	−2.39	0.017	0.00	0.008	−0.64	0.520	−0.31	0.143	−2.17	0.030
Level of participation in senior center activity	−0.19	0.049	−3.95	< 0.001	0.02	0.007	2.42	0.016	−0.02	0.133	−0.15	0.883
Level of participation in leisure/cultural/sports activity	−0.26	0.067	−3.85	< 0.001	0.02	0.010	1.92	0.055	0.28	0.184	1.52	0.130
Level of participation in alumni societies or family councils	−0.27	0.097	−2.79	0.005	0.05	0.014	3.33	0.001	1.14	0.266	4.29	< 0.001
Male (*n* = 2,353)												
Participation in any social activity												
No	Ref.				Ref.				Ref.			
Yes	−0.13	0.387	0.34	0.737	0.35	0.059	−5.87	< 0.001	5.24	1.030	−5.09	< 0.001
Level of participation in religious activity	−0.18	0.046	−3.82	< 0.001	0.00	0.007	0.25	0.802	−0.27	0.122	−2.22	0.026
Level of participation in senior center activity	−0.29	0.044	−6.6	< 0.001	0.02	0.007	2.93	0.003	0.29	0.116	2.48	0.013
Level of participation in leisure/cultural/sports activity	−0.23	0.057	−3.96	< 0.001	0.00	0.009	0.34	0.736	0.12	0.153	0.76	0.446
Level of participation in alumni societies or family councils	−0.21	0.052	−4.12	< 0.001	0.03	0.008	4.1	< 0.001	0.45	0.137	3.28	0.001
Female (*n* = 3,174)												
Participation in any social activity												
No	Ref.				Ref.				Ref.			
Yes	−0.38	0.343	1.11	0.269	0.22	0.052	−4.26	< 0.001	4.84	0.935	−5.18	< 0.001
Level of participation in religious activity	−0.16	0.037	−4.41	< 0.001	0.00	0.006	−0.02	0.987	−0.15	0.100	−1.48	0.139
Level of participation in senior center activity	−0.23	0.038	−6.02	< 0.001	0.02	0.006	3.45	0.001	0.03	0.105	0.26	0.798
Level of participation in leisure/cultural/sports activity	−0.26	0.049	−5.35	< 0.001	0.02	0.007	2.25	0.025	0.12	0.133	0.88	0.381
Level of participation in alumni societies or family councils	−0.24	0.067	−3.66	< 0.001	0.05	0.010	4.48	< 0.001	0.67	0.182	3.66	< 0.001

SE, standard error; ref., reference.

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under 75 years of age. The accessibility of senior center activities enables older adults to engage with others, supporting their physical and mental health [30]. Our findings indicated that increased participation by adults over 75 years of age and older women did not correspond to higher life satisfaction, despite their frequent attendance at senior centers [3,30]. Therefore, the role of senior centers should be expanded beyond simply serving as a gathering place for older adults, instead offering programs tailored to the specific needs of these demographics [30,31]. With adequate government support, older adults, especially those with physical limitations, could better benefit from the programs offered at senior centers.

Third, increased participation in religious activities was associated with a lower rate of depression [27,32]. Engaging in religious activities, such as attending church, can offer health-promoting benefits through psychosocial pathways. These include providing opportunities for socialization beyond the family circle and fostering a sense of motivation, inner direction, and purpose [32,33]. Moreover, involvement in religious organizations may protect mental health through various mechanisms, such as influencing lifestyle factors, bolstering social support networks, and offering strategies for coping with stress [33].

Finally, this study indicated that the sole social activity positively influencing mental and self-rated physical health, as well as life satisfaction, was involvement in alumni societies or family councils. No significant age or sex differences were observed in this regard. The results indicate that engaging with individuals who share common memories from specific life stages— such as growing up in the same hometown or attending school together—can beneficially impact health and overall well-being. These interactions, characterized by their informal and voluntary nature and distinct from participation in religious activities, appear to improve physical and mental health and life satisfaction in association with the level of participation.

This study demonstrates that it is not simply engagement in social activities that should be considered to improve the mental and physical health and life satisfaction of older adults, but rather active and regular participation. Furthermore, sex and age group differences should be considered when determining which types of activities are most beneficial to health. For older adults who are unable to directly engage in social activities due to poor health or limited mobility, government strategies that support the community, such as programs offering visiting services for older adults, are essential. These strategies help maintain a network of connections within the community and encourage activity participation.

This study is meaningful for several reasons. First, it explored the relationship between social activities and a number of health outcomes in community-dwelling older adults, utilizing nationally representative panel data. Second, it examined the impacts of the intensity and type of social activity on self-rated health, depression, and life satisfaction. Third, it analyzed the effects of social activity type and intensity by sex. However, the study is not without its limitations. One issue is that the independent variables, namely social participation, and the various dimensions of health were measured using self-reported information, which could introduce a reporting bias. Additionally, while empirical evidence indicates that the quality of social interactions may be more important for predicting health outcomes than the quantity, this study only assessed social activity based on frequency. Lastly, due to the cross-sectional research design, reverse causality is possible.

Conclusion

Three-quarters of seniors aged 60 and older in this sample participated in at least one social activity. Participation in social activities was significantly associated with self-rated health and life satisfaction. However, the intensity of participation in each social activity had a proportional effect on reducing depression, and there was a linear relationship between subjective health and the intensity of participation in some social activities (i.e., senior centers, alumni societies, or family councils).

Thus, this study confirms that not all forms of participation in social activities are associated with improved mental, physical, and quality of life in older adults, but that the intensity of participation in social activities is significantly associated with reduced depression in older adults.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Chung-Ang University (IRB No. 1044396-202203-HR-073-01) and performed in accordance with the principles of the Declaration of Helsinki.
The requirement for informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

The datasets generated and/or analyzed during the current study are available in the KEIS repository (http://survey.keis.or.kr/klosa/klosa04.jsp).

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Original Article

Effectiveness of a cognitive behavioral therapy program in stroke patients in the Republic of Korea: a mixed-methods study

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ABSTRACT

Objectives: This study aimed to explore the effects of a cognitive behavioral therapy (CBT) program on stroke patients, as well as their experiences participating in the program.
Methods: This study employed a mixed-methods design, integrating qualitative case studies with quantitative analysis. We included 20 stroke patients, randomly divided into 2 groups of 10 each: an experimental group and a control group. The experimental group underwent a CBT program comprising 20 sessions, in addition to receiving general occupational therapy. Conversely, the control group participated in meditation relaxation sessions alongside their general occupational therapy. Both interventions were administered daily for 60 minutes, 5 days a week, over a 4-week period.
Results: After the intervention, the experimental group exhibited significant improvements in depression, anxiety, self-efficacy, and rehabilitation motivation ($p < 0.01$, $p < 0.05$). In contrast, the control group only demonstrated a significant reduction in anxiety ($p < 0.05$). A comparison of the changes between the 2 groups showed significant differences in depression and anxiety ($p < 0.01$), but no significant differences in self-efficacy and rehabilitation motivation ($p > 0.05$). In-depth interviews with 10 participants from the experimental group were conducted and analyzed, revealing 4 core themes: "psychological stability," "physical symptom relief," "altered daily routines," and "challenges and hopes for change."
Conclusion: The findings of this study suggest that CBT programs may serve as a valuable intervention, offering psychological support and rehabilitation for stroke patients.

Keywords: Anxiety; Cognitive behavioral therapy; Depression; Rehabilitation motivation; Self efficacy; Stroke

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Introduction

Stroke is a major cerebrovascular disease caused by the hemorrhage or infarction of a blood vessel in the brain, leading to a decline in motor, cognitive, sensory, and emotional abilities. This functional decline makes it challenging for individuals to perform daily activities [1]. Long-term functional impairment in stroke patients leads to life-altering experiences that necessitate constant care, impose financial burdens from rehabilitation and medical expenses, and result in role changes that limit their independence and autonomy [2]. The complex disabilities arising from stroke also limit an individual's ability to engage in various activities and tasks [3]. In addition to these challenges, stroke survivors face psychosocial issues, including a decreased quality of life due to impaired physical function and altered appearance [4]. They suffer from negative social relationships due to their changed circumstances, economic losses from sequelae, and depression stemming from feelings of psychological helplessness and shame about their altered selves [5]. Anxiety is another prevalent stress factor among stroke patients, exacerbated by concerns over physical imperfections, the burden of hospitalization, and the difficulties associated with returning to work [6]. This anxiety persists for years after the stroke onset, adversely affecting social functioning, disease prognosis, and activities of daily living [7–9].

Rehabilitation motivation significantly impacts the recovery rate from post-stroke sequelae [10,11], and it is crucial to motivate hospitalized stroke patients to engage in rehabilitation to enhance outcomes [12]. This motivation encompasses the psychological desire to adapt quickly to a changed lifestyle and includes the desire, trust, and courage to undergo rehabilitation [13,14]. Active engagement in treatment is essential for successful rehabilitation, necessitating strong rehabilitation motivation [15]. Self-efficacy refers to an individual's confidence in their ability to successfully perform specific actions [16] and encompasses the belief in one's capacity to organize and execute the steps required to achieve desired outcomes [17,18]. Higher self-efficacy levels can boost rehabilitation motivation, enhancing the performance of purposeful activities and participation in rehabilitation [19]. Therefore, it is critical to focus on both self-efficacy and rehabilitation motivation to ensure active involvement in rehabilitation, and implementing effective clinical interventions to improve these factors is crucial [20–22]. Currently, rehabilitation treatments for stroke patients typically include occupational, physical, cognitive, swallowing, and speech therapies. Although these therapies improve physical function, they fall short in addressing psychosocial issues and do not constitute a comprehensive approach to rehabilitation that ultimately enhances patients' quality of life [23]. Cognitive behavioral therapy (CBT) is a widely used intervention proven effective for managing psychosocial issues, particularly depression and anxiety. The fundamental premise of CBT is that symptoms like depression can be alleviated through cognitive restructuring, which involves identifying, challenging, and correcting faulty core beliefs and negative automatic thoughts about oneself that exacerbate negative feelings [24,25]. In addition to cognitive restructuring, behavioral modification plays a key role in CBT. Techniques such as behavioral activation, social skills training, assertiveness training, and role-playing are commonly employed. Behavioral activation specifically addresses the tendency of depressed individuals to avoid goal-oriented or enjoyable activities and instead engage in behaviors that perpetuate a depressed mood. This method involves a systematic analysis of behavioral patterns within specific contexts and promotes activities that provide pleasure and fulfillment [26].

Occupational therapists play a key role in mental health rehabilitation. In both the United Kingdom and the United States, they receive training in CBT and apply it in practice. Although occupational therapists in various countries are using CBT for a range of conditions, including insomnia and traumatic brain injury [27,28], its application in stroke patients is notably rare. Furthermore, no studies have been conducted that combine qualitative analysis of participants' experiences with quantitative analysis. Therefore, this study aimed to explore the effects of a CBT program developed by the author on stroke patients by conducting a quantitative analysis to compare the assessment scores of stroke patients before and after their participation in the program, as well as

HIGHLIGHTS

- This study conducted a quantitative analysis of the effects of a cognitive behavioral therapy (CBT) program administered to stroke patients and a qualitative analysis of the participation experience.
- The CBT program showed positive effects on stroke patients' mental health, self-efficacy, and motivation for rehabilitation.
- The findings suggest that CBT may serve as a useful intervention method in the field of rehabilitation treatment.

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a qualitative analysis to examine their experiences during the program.

Materials and Methods

Participants

The study was conducted from June to September 2023 and involved 20 stroke patients who were selected from those receiving inpatient treatment at C General Hospital, I Rehabilitation Hospital, and O General Hospital in Cheongju City. These patients met the following inclusion criteria: (1) a stroke diagnosis confirmed by a physician; (2) a Korean Mini-Mental Examination-2 (K-MMSE-2) score of 24 or higher; (3) the ability to write, read, and communicate without impairment; and (4) no presence of aphasia. The exclusion criteria included: (1) recent participation in a drug trial; (2) severe vision impairments; and (3) current use of psychiatric medications.

Protocol

This study was designed as a single-blind, randomized controlled trial (RCT). A total of 20 participants who met the inclusion criteria were enrolled. An occupational therapist, who was not involved in the study, assigned 10 subjects to each of the experimental and control groups using block randomization and a table of random numbers. The assignment results were communicated to the researcher by phone, and the group assignment process was concealed. The experimental group underwent 30 minutes of CBT followed by 30 minutes of general occupational therapy, totaling 60 minutes per session, 5 times a week, for 4 weeks. Similarly, the control group participated in 30 minutes of meditation relaxation followed by 30 minutes of general occupational therapy, also totaling 60 minutes per session, 5 times a week, for 4 weeks. An in-depth interview was conducted with the experimental group at the end of the intervention. To maintain single-blindness, all participants were unaware of their group assignments. The sessions were conducted in separate rooms, and the purpose of the experiment was not disclosed. The study was carried out by 3 occupational therapists, each with at least 5 years of experience, and included pre-assessment, intervention, post-assessment, and in-depth interviews with the experimental group.

The author trained 2 therapists before the study began, instructing them on the use of Socratic questioning throughout the program, the application of the negative automatic thought checklist after the sixth session, and the implementation of behavioral techniques in each session. Throughout the program, they maintained regular communication through Zoom video chats, phone calls, and face-to-face meetings to discuss progress and provide feedback. In the control group experiments, participants were blinded to their group assignment and were asked to work individually in separate rooms. Therapists who provided interventions to both the experimental and control groups received the same training and participated in identical meetings to ensure consistent treatment fidelity across both groups. The procedure is visually depicted below (Figure 1).

Measurements

Cognition

The K-MMSE-2 was utilized as a screening tool for cognitive impairment. This scale comprises 11 items across 7 domains: memory registration, time perception, spatial perception, memory recall, attention and computation, language, and drawing. The total score is derived by adding the scores from each item, ranging from a minimum of 0 to a maximum of 30 points. Scores of 17 or below indicate moderate cognitive impairment, scores between 18 and 23 suggest mild cognitive impairment, and scores of 24 or higher denote

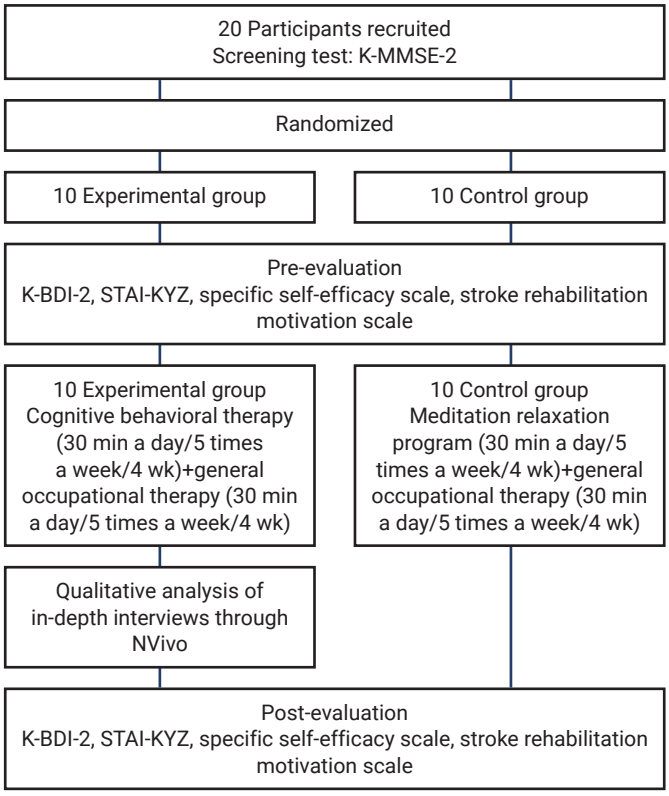

Figure 1. Flow chart of the study process.
K-MMSE-2, Korean Mini-Mental Examination-2; K-BDI-2, Korean Beck Depression Inventory-2; STAI-KYZ, State Trait Anxiety Inventory-Korean YZ.

normal cognitive function. According to the study by Kang et al. [29], the test-retest reliability was 0.69, and the interrater reliability was 0.99.

Depression

The Korean Beck Depression Inventory-2 (K-BDI-2) was utilized to evaluate depression levels. This 21-item questionnaire encompasses behavioral, emotional, cognitive, and physiological symptoms of depression. Each item is rated on a scale from 0 to 3 points, with the scores then aggregated to yield a total score. The total score can range from 0 to 63 points, where a higher score reflects a greater level of depression. Specifically, scores from 0 to 9 suggest no depression, scores from 10 to 15 indicate mild depression, scores from 16 to 23 suggest moderate depression, and scores of 24 or above indicate severe depression. The reliability of the scale was reported as 0.80 [30].

Anxiety

The State Trait Anxiety Inventory-Korean YZ (STAI-KYZ) was utilized to evaluate changes in anxiety levels. Anxiety psychology is divided into state anxiety and trait anxiety. The inventory comprises 20 items, each rated on a 4-point scale, yielding a total score range of 20 to 80 points. A higher score indicates a greater level of anxiety. State anxiety measures the emotional state of a participant at a specific moment, characterized by subjective feelings of agitation, tension, worry, and concern. These feelings are typically due to the activation or arousal of the autonomic nervous system. Conversely, trait anxiety evaluates the general emotional disposition of the participant, aiding in distinguishing between neuroticism and depression in patients. The reliability of the scale was reported to be 0.88 [31].

Self-efficacy

A self-efficacy scale was utilized to evaluate changes in self-efficacy. This scale comprises 10 items, each rated on a Likert scale that spans from 1 point, indicating "not confident at all," to 10 points, signifying "very confident." These ratings assess how confident stroke patients feel about performing common activities of daily living. The scale includes 1 item each for eating, personal hygiene, and dressing; 2 items each for toileting and walking; and 3 items for repositioning. The total score can range from 10 to 100 points, with higher scores reflecting greater self-efficacy. According to the study by Kim and Kim [32], the reliability of the scale was 0.97.

Rehabilitation motivation

The stroke rehabilitation motivation scale was utilized to evaluate rehabilitation motivation. This multidimensional scale comprises 27 items, each scored on a 4-point scale. It categorizes motivation into 5 types according to the level of self-determination: task-oriented motivation (8 items), change-oriented motivation (7 items), obligatory motivation (4 items), external motivation (4 items), and amotivation (4 items). Higher scores on this scale indicate greater motivation. In the study conducted by Kim et al. [33], the scale demonstrated a reliability of 0.86.

In-depth interview questionnaire

In-depth interviews were conducted for the qualitative analysis of this study. The researcher established rapport with participants during treatment sessions, forming close relationships and explaining the study's purpose and the significance of their participation. Consent was obtained from participants prior to the interviews, which were recorded and lasted approximately 50 minutes to 1 hour each. The in-depth questionnaire was developed based on a survey and literature review addressing common complaints among stroke patients. The interview questions were organized around key themes the author aimed to explore. The main questionnaire included semi-structured, open-ended items such as: "How has your experience in the program influenced your relationships with other patients?"; "How has your mood (anxiety, self-efficacy, reactivity) changed since joining the program?"; "How have your thoughts shifted in response to negative situations since your participation?"; "Can you describe your experience with breathing exercises in the program?"; and "How do you think your experience in the program will impact your life after discharge?"

CBT Program Develop Process

A semi-open questionnaire was developed to draft a CBT program. This questionnaire was designed to gather expert opinions by presenting components, related topics, and descriptive questions that encouraged open-ended responses. Ten experts, each with over 3 years of clinical and educational experience in mental health, were selected to provide their insights. The first Delphi survey was conducted to categorize responses by domain, extract relevant items, and classify them based on the feedback obtained through the semi-open questionnaire. Following this, the second Delphi survey was carried out to develop a questionnaire informed by the results of the first survey. A 4-point Likert scale was used to assess the appropriateness of each item for inclusion in the CBT program. The data from the second Delphi survey were then organized to calculate the mean, standard deviation, content validity ratio (CVR), item-level content validity index (I-CVI), and the degrees of stability, consensus, and convergence for each item. In

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the third Delphi survey, feedback was solicited only for items where there was a lack of consensus among the experts, as indicated by the results of the second survey. The collected data were analyzed to calculate the mean, standard deviation, CVR, I-CVI, and the degrees of stability, consensus, and convergence for all items. The final program was established based on the outcomes of the third Delphi survey.

Intervention

The CBT program implemented for the experimental group in this study included cognitive restructuring activities aimed at correcting distorted negative automatic thoughts and beliefs throughout the participants' involvement. It also featured self-administered worksheet activities based on behavioral techniques to foster emotional and behavioral changes, training in behavioral techniques, and interactive feedback and dialogue with the therapist. The program was structured into 3 phases: Sessions 1 to 3 constituted the introduction phase, focusing on general education about stroke and CBT principles; sessions 4 to 17 formed the development phase, emphasizing cognitive restructuring and behavioral interventions; and sessions 18 to 20 marked the termination phase, during which the skills acquired were reviewed and solidified through the completion of a termination log (Table 1). The control group participated in a meditation relaxation program, specifically the Korean Mindfulness Based Stress Reduction (K-MBSR) program, which was adapted and translated by Bae and Chang [34]. This program, designed by the author to suit an appropriate level of difficulty, comprises 4 components: breathing meditation, body scan, seated meditation, and walking meditation (Table 2).

Statistical Analysis

All statistical analyses for the quantitative data in this study were performed using IBM SPSS ver. 27.0 (IBM Corp.). The normality of the study subjects was assessed using the Shapiro-Wilk test. Due to the non-normal distribution of data, non-parametric methods were employed. Chi-square and descriptive statistics were utilized to analyze the general characteristics of the participants. The Mann-Whitney U test

Table 1. Cognitive behavioral therapy program

Session	Contents	
1	Understanding stroke	Introduction and education program
2	Understanding cognitive behavioral therapy	
3	Identifying cognitive errors	
4	Gathering information about myself	Cognitive restructuring - Self-assessment - Changing negative thoughts to positive ones
5	Identifying rational and irrational thinking	
6	Creating a checklist for negative automatic thoughts → Write after each session starting from session 6	
7	Checking evidence	
8	Recording changes in thinking	
9	Creating weekly activity plans	Behavioral Intervention 1 - Develop weekly activity plans for a structured lifestyle - Reduce tension through relaxation and breathing exercises
10	Learning progressive muscle relaxation (encouraged to do daily in the hospital thereafter)	
11	Learning breathing techniques (encouraged to do daily in the hospital thereafter)	
12	Learning stretching exercises (encouraged to do daily in the hospital thereafter)	
13	Trying meditation (encouraged to do daily in the hospital thereafter)	
14	Expressing positive experiences	Behavioral intervention 2 - Build confidence through social skills training
15	Evaluating and transforming my thoughts	
16	Practicing assertive communication	
17	Practicing problem-solving skills	
18	Engaging with authors in books	Commitment to positive living and conclusion
19	Creating coping cards	
20	Writing a conclusion sheet	

Table 2. Meditation relaxation program

Type	Composition and contents
Breathing meditation	- Meditation that guides participants to notice how breathing changes according to their emotions - Meditation that involves repeating the abdominal breathing that allows one to relax, feeling how one's breathing changes depending on one's state of mind, and looking at the thoughts that come to mind and then focusing attention on breathing again.
Body scan	- Close one's eyes, lie on one's back, relax, and focus on the sensations of the parts of the body that are touching the floor, starting with the left toes and slowly moving the focus toward the head, keeping an open mind about what sensations one feels in each body part and only feeling the sensations that are occurring in the present moment.
Sitting meditation	- Meditation in which one sits in a comfortable position on a chair or cushion, straightens one's back, closes one's eyes slightly, and observe whatever comes into consciousness without judging it.
Walking meditation (only applicable to those who can walk)	- A meditation that focuses on the physical sensations and balance felt while walking, when lifting the legs, when trying to balance the body, when moving the body, and the movements and sensations of the feet and legs related to walking.

was conducted to ensure functional homogeneity prior to the intervention. Within each group, the Wilcoxon signed rank test was used to assess pre-post differences, while the Mann-Whitney U test compared differences between the 2 groups. The level of statistical significance was set at $p < 0.05$. For the qualitative data, in-depth interviews were analyzed using NVivo (Lumivero), a qualitative analysis tool. The analysis was conducted in 4 steps: import data, set up a coding table, coding, and data analysis. During the import data step, files containing the transcripts of the in-depth interviews were imported. In the set up a coding table step, categories were established. The coding step involved creating nodes, coding textual materials sentence by sentence, and assigning them to the appropriate categories. Finally, in the data analysis step, a list of frequently used words and the frequency of each word were obtained.

Ethics Statement

The study protocol received approval from the Institutional Review Board (IRB) of the Science Research Ethics Committee at Cheongju University (IRB No: 1041107-202304-HR-078-01). The IRB also confirmed that informed consent was obtained.

Results

Quantitative Analysis Results

Demographics and baseline characteristics

The general characteristics of the participants are shown in Table 3. In terms of gender distribution, the experimental group included 6 men (60.0%) and 4 women (40.0%), whereas the control group comprised 4 men (40.0%) and 6 women (60.0%). The average age was 62.90 ± 10.14 years in the experimental group and 60.10 ± 8.18 years in the control group. Regarding the type of onset, the experimental group had 7 participants with infarction (70%) and 3 with hemorrhage (30%), while the control group had 6 with infarction (60.0%) and 4 with hemorrhage (40.0%). The mean duration of onset was 4.30 ± 1.05 months in the experimental group and 4.40 ± 1.07 months in the control group. There were no significant differences between the 2 groups in the initial assessment scores, which included gender, age, type of disease, paralyzed side, duration of disease, and K-MMSE-2 score ($p > 0.05$).

Table 3. General characteristics of research participants

Variable	EG ($n = 10$)	CG ($n = 10$)	p
Age (y)	62.90 ± 10.14	60.10 ± 8.18	0.545
Sex			0.371
Male	6 (60.0)	4 (40.0)	
Female	4 (40.0)	6 (60.0)	
Type of stroke			0.639
Infarction	7 (70.0)	6 (60.0)	
Hemorrhage	3 (30.0)	4 (40.0)	
Paralyzed side			
Right	4 (40.0)	4 (40.0)	0.100
Left	6 (60.0)	6 (60.0)	
Onset period (mo)	4.30 ± 1.05	4.40 ± 1.07	0.875
Baseline characteristics			
K-BDI-2	38.30 ± 11.98	32.00 ± 11.43	0.226
STAI-KYZ(S)	65.90 ± 6.02	68.40 ± 7.47	0.405
STAI-KYZ(T)	61.80 ± 8.84	62.10 ± 8.62	0.910
Self-efficacy	50.80 ± 25.15	50.70 ± 21.17	0.880
Rehabilitation motivation	77.50 ± 13.83	83.20 ± 14.99	0.427

Data are presented as mean ± standard deviation or *n* (%).
EG, experimental group; CG, control group; K-BDI-2, Korean Beck Depression Inventory-2; STAI-KYZ(S), State Trait Anxiety Inventory-Korean YZ-State Anxiety; STAI-KYZ(T), State Trait Anxiety Inventory-Korean YZ-Trait Anxiety.

Intervention outcomes

Table 4 shows the pre- and post-intervention results for depression, anxiety, specific self-efficacy, and rehabilitation motivation. In terms of depression and anxiety, the experimental group exhibited statistically significant

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Table 4. Comparison of depression, anxiety, self-efficacy, and rehabilitation motivation between pre-test and post-test and differences between the control and experimental groups

Variable	Pre-test	Post-test	Z	$p^{a)}$	Between groups	Z	$p^{b)}$
K-BDI-2						−3.115	0.002**
EG	38.30±11.98	27.20±7.39	−2.701	0.007**	−11.10±7.21		
CG	32.00±11.43	30.70±9.95	−1.867	0.062	−1.30±2.05		
STAI-KYZ(S)						−2.775	0.006**
EG	65.90±6.02	57.80±7.96	−2.805	0.005**	−8.10±4.77		
CG	68.40±7.47	66.30±8.39	−2.446	0.014*	−2.10±2.13		
STAI-KYZ(T)						−2.730	0.006**
EG	61.80±8.84	50.70±8.46	−2.668	0.008**	−10.40±7.48		
CG	62.10±8.62	59.10±8.81	−2.530	0.011*	−3.00±2.44		
Self-efficacy						−1.031	0.303
EG	50.80±25.15	55.00±24.26	−2.613	0.009**	4.20±4.44		
CG	50.70±21.17	53.30±20.74	−1.785	0.074	2.60±4.45		
Rehabilitation motivation						−1.109	0.267
EG	77.50±13.83	81.00±14.96	−2.527	0.012*	3.50±3.02		
CG	83.20±14.99	84.90±14.87	−1.907	0.056	1.70±2.35		

Data are presented as mean±standard deviation unless otherwise stated.
EG, experimental group; CG, control group; K-BDI-2, Korean Beck Depression Inventory-2; STAI-KYZ(S), State Trait Anxiety Inventory-Korean YZ-State Anxiety; STAI-KYZ(T), State Trait Anxiety Inventory-Korean YZ-Trait Anxiety.
[a)]A significant difference from baseline after intervention in each group using Wilcoxon signed rank test. [b)]A significant difference between the 2 groups using Mann-Whitney U-test.
*$p<0.05$, **$p<0.01$.

improvements in depression, state anxiety, and trait anxiety after the intervention compared to before ($p<0.01$). The control group demonstrated significant reductions in state anxiety and trait anxiety ($p<0.05$), but no statistically significant changes were observed in depression scores ($p>0.05$). Significant between-group differences were noted in the changes in both depression and anxiety ($p<0.01$).

Regarding specific self-efficacy, the experimental group exhibited a statistically significant change post-intervention compared to pre-intervention ($p<0.01$). In contrast, the control group also demonstrated an improvement in scores post-intervention compared to pre-intervention, though this change was not statistically significant ($p>0.05$). Although the experimental group achieved greater score gains than the control group, the difference in changes between the 2 groups was not statistically significant ($p>0.05$).

For rehabilitation motivation, post-intervention scores in the experimental group showed a statistically significant improvement ($p<0.05$), whereas the control group did not exhibit a significant change ($p>0.05$). Although the experimental group demonstrated greater gains in scores compared to the control group, the difference in changes between the 2 groups was not statistically significant ($p>0.05$).

Qualitative Analysis Results; Experience Participating in the CBT Program

A qualitative analysis was conducted of the experiences of 10 participants in the experimental group who took part in the CBT program. This analysis identified 45 meaning units, 13 subcategories, and 4 core themes. The core themes were identified as psychological stability, physical symptom relief, altered daily routines, and challenges and hopes for change. The key findings from the study are summarized in the participant responses attached (Table 5). Additionally, NVivo was utilized to examine the 50 most frequently used words in the participants' interviews. The analysis revealed that words such as "positive," "thinking," "relaxation," "breathing," "rehabilitation," and "better" were commonly used (Figure 2).

Psychological stability

Alleviating depression

Most participants experienced depression following their stroke, which was a significant obstacle their emotional regulation.

"I would burst into tears talking about nothing. I would burst into tears even talking about something good. I couldn't control my emotions, and I was very depressed. But I got better when I realized that I had to be realistic about my condition and keep doing things that I liked." (Participant 2)

"My depression was so severe that I kept crying whenever I spoke. But when I practiced writing down my negative thoughts and feelings every day, I was really surprised to realize, 'Oh, I have so many bad thoughts during the day.' I practiced thinking positively a lot, and it really helped me." (Participant 7)

Table 5. Experience participating in cognitive behavioral therapy programs

Meaning units	Subcategories	Core themes
Learning to regulate depressive emotions	Alleviating depression	Psychological stability
Reducing anxiety by discarding unnecessary thoughts		
Decreasing depression through positive thinking		
Reducing anxiety by identifying cognitive errors	Reducing anxiety	
Alleviating despairing thoughts and easing depression		
Decreasing anxiety by correcting negative predictions		
Enhancing self-esteem through realizing strengths	Improving self-esteem	
Acting confidently without concern for others' opinions		
Boosting self-Esteem by finding things to be grateful for		
Accepting current situations comfortably	Accepting the current circumstances	
Transitioning from negative to accepting thoughts		
Acknowledging and accepting myself through meditation		
Relaxing the body through meditation	Reducing tension and relaxing the body	Physical symptom relief
Reducing body tension through stretching		
Easing body tension through progressive muscle relaxation		
Reducing headaches through stretching and muscle relaxation	Relieving pain	
Relieving lower back pain through meditation		
Relieving shoulder pain and enhancing body awareness through meditation		
Improving sleep quality through body relaxation	Improving sleep quality	
Experiencing comfort and ease in bed		
Enhancing sleep quality through meditation		
Reducing stress from others' words	Improving the ability to cope with stress	Different daily routines
Applying stress coping techniques in daily life		
Using breathing techniques as stress coping methods		
Coping with stress through changing thoughts		
Focusing on what I can do and feeling gratitude	Focus on things one can do	
Concentrating on what I can do and engaging in productive thinking		
Focusing on tasks I can accomplish and finding joy		
Improving relationship with a difficult father	Improving real-world relationships	
Speaking to family members with positive language		
Improving relationship with my wife through change negative thoughts		
Learning emotional expression and improving relationship with my wife		
Applying assertiveness in daily life for clear communication		
Accepting negative situations with a rational attitude	Aiming for a positive and rational attitude	Challenges and hopes for change
Turning negative biases towards others into positive ones		
Recognizing cognitive errors and transitioning to positive thinking		
Developing positive thinking through cognitive error checks		
Participating in rehabilitation with expectations of improvement	Active participation in rehabilitation	
Feeling accomplishment and increased enthusiasm for rehabilitation		
Discarding negative thoughts and enhancing passion for rehabilitation		
Committing to a planned life and dedicating myself to treatment		
Discovering my continuous growth	Expectations for future changes	
Determined to become a strong mother for my children		
Setting a goal to return to work		
Committing to maintaining positive thinking after discharge		

Reducing anxiety

The participants expressed anxiety about their uncertain futures, potential for physical recovery, and negative prognoses. After engaging in the program, they noted a decrease in anxiety, which they attributed to recognizing cognitive errors and concentrating on their achievable actions.

"Without a caregiver by my side, I was always anxious and constantly looking for one, and I couldn't focus on my

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Figure 2. Frequent words that appeared in the interviews.

treatment. I felt like I would fall if I was alone for even a moment. But now I know that the scary thoughts are not actually true, which has reduced my anxiety." (Participant 4)

"I think I was anxious and worried about every little thing because bad things kept happening to me. Whenever I would get on and off my bike, or get up from a chair, my heart would race wondering if I was going to fall again. Once I realized that I was freaking out about things that hadn't happened, and I tried to fix that, I felt a lot better." (Participant 9)

Improving self-esteem

Many participants experienced low self-esteem and self-consciousness due to their altered physical appearance and reduced ability to perform daily activities. After participating in the program, they acquired skills to manage stress, recognize their blessings, concentrate on their strengths, and enhance their self-esteem.

"I've learned to love myself by giving myself compliments and looking for the things I'm good at. I was good at more things than I thought. I was too busy hating myself." (Participant 4)

"When I started looking for things I'm grateful for, I realized I'm pretty good at a lot of things. In some ways, compared to the general population, I seem to have a severe disorder because I look a little unnatural, but compared to other patients, I am in good shape. I think it boosted my self-esteem a lot." (Participant 10)

Accepting the current circumstances

Many participants found it challenging to accept the sudden changes in their appearance and were stressed by the decline in physical function and hospitalization. They reported that the program helped them release negative thoughts and accept their current circumstances.

"I used to have a lot of bad thoughts when I saw a code blue announcement, thinking, 'I would end up like that.' Now I do not feel that way because I think of myself as someone who will get better with a few months of rehabilitation." (Participant 2)

"I was so embarrassed to wear an L-tube that even when my best friends came to visit, I turned them away, insisting that I would not come down. I didn't want to look ugly to others. I felt so humiliated and ashamed. Now I try not to think about things that make me miserable, thinking, 'Oh well, I'm sick now!' This is how I cope with it." (Participant 4)

Physical symptom relief

Reducing tension and relaxing the body

Many participants reported body tension and stiffness, which they attributed to repeated rehabilitation treatments and decreased muscle strength. By consistently practicing behavioral activation methods, including stretching, progressive muscle relaxation, and body scan meditation, participants noted a significant reduction in tension and an increase in relaxation.

"I always felt tense and stiff except when the therapists were working on my limbs, but after meditating, I felt more relaxed. I feel much better." (Participant 4)

"After a muscle relaxation workout, my body feels relaxed and tired. It feels a lot less tense after you keep tensing and releasing." (Participant 10)

Relieving pain

The participants described experiencing back pain due to fear of falling, headaches due to stress and sensitivity, and shoulder pain due to poor upper extremity strength. After participating in the program, they achieved pain relief through methods such as stretching, progressive muscle relaxation, and body scan meditation.

"I was sensitive and stressed; my blood pressure would go up, and I would get headaches because my neck was always tense. After stretching and relaxing my muscles, I feel like I am unwinding. I do it every day in the hospital room." (Participant 5)

"I feel much more comfortable listening to my own recordings with my own voice. When I'm doing this (body scan meditation), my shoulder feels a little less painful, but strangely, the soles of my feet and palms of my hands on the paralyzed side, which felt numb, feel a little more sensitive." (Participant 9)

Improving sleep quality

Some participants reported fatigue linked to poor sleep quality, which included difficulties such as not achieving deep sleep due to stress, frequent awakenings, or prolonged time taken to fall asleep. By engaging in meditation and stretching exercises, they were able to clear their minds of unnecessary thoughts, relax their bodies, and increase their comfort in bed.

"Learning to stretch and meditate has helped me the most. I always do one of those exercises before I go to bed, which has really reduced my stiffness." (Participant 1)

"My daughter has recorded it and I listen to it all the time. When I listen to this (body scan meditation), I fall asleep quickly and my senses come alive as I focus on each and every part of my body." (Participant 7)

Different daily routines

Improving the ability to cope with stress

Participants experienced heightened self-consciousness, reduced motivation for rehabilitation, and frequent impulsive negative thoughts due to disruptions in their routine and the stress impacting their physical functioning. After participating in the program, they learned various self-management techniques to cope with stress, including adopting positive thought patterns and practicing breathing and meditation techniques, which they can incorporate into their daily lives.

"I used to be a little bit snarky and aggressive, but now I feel like I am not as swayed by what people say, and I try to think positively. I realized that I was too conscious of what people around me were saying and letting my emotions take over." (Participant 1)

"There are still a lot of situations that are similar to before, but I've learned how to deal with them and I'm mostly okay now. I'm doing a good job, but when I write it down and go back over it, there's nothing that I should be particularly stressed about." (Participant 3)

Focus on things one can do

The participants expressed dissatisfaction with the pace of their recovery and harbored pessimistic beliefs about their ability to resume their former lifestyles. However, after engaging in the program, they reported a shift towards a more positive outlook, an appreciation for the small joys in life, and a focus on the possibilities within their current circumstances.

"By focusing on what I can do and being grateful, I can see my improvement, even if it's just a slight difference. (Demonstrates) Last week I could only twitch my finger, and now I can make a full fist and stretch it out. Before, I used to be annoyed at how little things got better and how I could even make ramen by myself. Now I am grateful for these little things." (Participant 3)

"It made me realize that some of the things I thought were the worst things might not be as bad as I thought. It's not just like, 'Oh, what am I going to do now?' I try to think of productive things and ways to do things, and I try to find things that I can do myself, even the smallest things." (Participant 3)

Improving real-world relationships

The participants, who had become less independent and required the assistance of a guardian or caregiver in their daily lives, began to criticize themselves, harbored negative thoughts, and struggled to express their thoughts and feelings accurately. The program taught them to think positively, assert themselves, and express their emotions appropriately, resulting in improved relationships with others.

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"I felt so sorry for my daughter and husband, but I decided not to feel sorry for them from now on. My daughter says she doesn't want to hear me say I'm sorry. So now I'm grateful and I say thank you." (Participant 2)

"The assertiveness training was probably the most helpful for someone like me. I'm a little bit self-centered, so... I realized that it doesn't sound rude to use phrases that start with "I" when I have a complaint or want something, instead of blaming others. I try to say it that way nowadays." (Participant 9)

Challenges and hopes for change

Aiming for a positive and rational attitude

Most participants experienced negative automatic thoughts stemming from their uncertain future, sudden decline in physical function, and frustration. However, after participating in the program, they recognized the cognitive errors they were repeatedly making in their daily routines. They endeavored to eliminate these errors and replace them with positive thinking. The program also encouraged them to seek evidence that contradicted their negative thoughts and to adopt a more rational perspective.

"Before, I used to be annoyed by grandpa making noise in the hospital room and other caregivers asking me what happened to me at such a young age, but now I'm not so angry because I've learned to think positively and rationalize things a little bit." (Participant 1)

"I found it helpful to identify the errors in my thinking and how to turn them into good thoughts. When I tried to think about it that way, there was no emotion I could not overcome. It is a mindset that I hope to pass on to my students when I am able to go back to school." (Participant 7)

Active participation in rehabilitation

After participating in the program, participants who initially found the rehabilitation period stressful due to psychological depression and anxiety reported a greater acceptance of their current situation and a more positive mindset. They achieved psychological stability, set personal goals through weekly activity plans, and engaged more actively in their rehabilitation.

"By thinking, 'I'm going to be better this month than I was last month, and I'm going to be better next month,' I am more focused and work harder. I used to try to leave 5 minutes early because I didn't want to be bothered, but now I joke that they should let me do it more." (Participant 3)

"I am supposed to write my rehabilitation goals in my planner every day. It makes me work harder. I am proud of myself on days when my achievement and enjoyment scores are both high. I did not think about having fun, but when I was scoring myself, it made me want to have fun and work harder." (Participant 4)

Expectations for future changes

The participants, who initially were self-critical, suffered from low self-esteem, and lacked hope for the future, experienced a shift in mindset after engaging in the program. They began to appreciate the small joys in life. Furthermore, they reported that setting personal goals post-discharge has given them something to look forward to, fostering a sense of growth and change.

"I cried a lot when I read something written by someone who had a stroke. Like me, this person was scared to go back home, but in the end, did it for the kids. My kids are old enough to know better, but they're still kids to me. I'm determined to be a strong mom." (Participant 4)

"I have a renewed enthusiasm for returning to work. I used to have a reputation in the hospital as someone who cried at the slightest thing, but now my depression has gotten a lot better and I've found things I'm good at that I can do with a little help. I set a goal to rehabilitate myself and go back to school." (Participant 7)

Discussion

This study aimed to explore the effects of a CBT program for stroke patients, focusing on its impact on depression, anxiety, self-efficacy, and rehabilitation motivation, as well as the patients' experiences of participating in the program.

When comparing changes in depression levels before and after the intervention, a significant decrease was observed only in the experimental group, with a notable difference in the extent of change between the 2 groups. Initially, many members of the experimental group experienced depression post-stroke and struggled with emotional regulation. However, after engaging in the program, they reported a more positive outlook and developed effective stress management strategies. Thomas et al. [35] conducted a study where 48 stroke patients were divided into 2 groups: one receiving a behavioral activation intervention and the other receiving usual care. The results indicated that the experimental group experienced a reduction in depression. Similarly, Peoples et al. [36] found that when CBT was administered to cancer patients, those in the experimental group who received CBT exhibited a more

significant reduction in depression compared to the control group, which did not participate in CBT. These findings align with previous research confirming the efficacy of CBT in alleviating depression.

The anxiety scores in this study exhibited a significant decrease in both the experimental and control groups. However, the reduction was more pronounced in the experimental group, with a statistically significant difference in the degree of change between the 2 groups. The control group participated in a meditation relaxation program derived from the K-MBSR program.

These findings align with those reported by Seo et al. [37], who found that participants in a mindfulness meditation group experienced significant reductions in anxiety compared to their control counterparts. Similarly, You et al. [38] observed that middle-aged women engaging in mindfulness meditation showed significant decreases in state anxiety scores relative to a control group that did not participate in the meditation. Additionally, the CBT program implemented in this study incorporated various relaxation techniques, including progressive muscle relaxation, stretching, breathing, and meditation, as well as cognitive restructuring activities. These components likely contributed to the enhanced psychological stability and more substantial anxiety reduction observed in the experimental group compared to the control group.

The self-efficacy test only showed a significant difference in the experimental group. In a RCT conducted by Johansson et al. [39], patients with cardiovascular disease who participated in an Internet-based CBT program exhibited a significant increase in self-efficacy compared to a control group that received conventional care. Similarly, Hyun [40] reported notable improvements in self-efficacy among chronic schizophrenia patients in the experimental group who received group CBT, as opposed to those in the control group. These findings suggest that CBT is an effective intervention for enhancing self-efficacy, which is defined as the "belief in one's ability to organize and execute the behaviors necessary to successfully manage a given situation or task." This is in line with the observed significant improvements in specific self-efficacy scores in the experimental group of this study, relative to the control group.

The experimental group exhibited a statistically significant increase in rehabilitation motivation scores, whereas the control group also showed an increase, but it was not statistically significant. Numerous rehabilitation experts contend that boosting a patient's motivation for rehabilitation is crucial for successful outcomes [41]. They also emphasize that high rehabilitation motivation is essential for minimizing functional impairment and maximizing residual capabilities [42]. Following a stroke, patients often experience various disabilities that can lead them to become psychologically withdrawn, lose confidence, and disengage from the rehabilitation process. This disengagement can result in a passive approach to rehabilitation and ultimately delay recovery. Song et al. [43] discovered that depression, stemming from physical deterioration and maladaptation, diminishes adherence to rehabilitation. Similarly, Neau et al. [44] reported that depression not only increases fatigue and feelings of inadequacy but also lowers rehabilitation motivation, thereby reducing functional capacity and complicating the return to work. These findings align with the results of this study, where participants reported increased feelings of accomplishment, reduced depression, and enhanced engagement in rehabilitation after participating in the program. Notably, there were significant improvements in rehabilitation motivation among members of the experimental group compared to those in the control group.

To explore the experiences of stroke patients participating in a CBT program, interviews were conducted with 10 participants from the experimental group of this study. The qualitative analysis of these interviews yielded 45 semantic units, 13 subcategories, and 4 core themes. These themes were identified as "psychological stability, physical symptom relief, altered daily routines, and challenges and hope for change."

The participants experienced enhanced psychological stability, reduced depression and anxiety, and improved self-esteem. These benefits arose from identifying their cognitive errors, practicing the release of unnecessary thoughts, avoiding extremes, and recognizing their capabilities and strengths. In this study, patients were instructed to maintain a thought-reframing log to document their automatic thoughts and emotions during stressful situations. This process helped them pinpoint cognitive errors and discover rational alternatives. Dobson et al. [45] noted that CBT can initiate behavioral changes, which foster rational cognitive adjustments, subsequently leading to effective coping behaviors. Similarly, Franklin et al. [46] observed functional changes in neural circuits involved in emotion regulation, reward processing, and cognitive control related to depression. These changes were noted after participants engaged in a cognitive task, lending support to the findings of this study.

The participants reported physical issues including stiffness, shoulder pain, headaches, and insomnia. However,

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their involvement in the program led to a more relaxed body, reduced pain, and better sleep quality. Nguyen et al. [47] conducted a study on stroke patients and found that those in an experimental group participating in a CBT program experienced less fatigue and improved sleep quality compared to a control group that received standard rehabilitation. Similarly, Murphy et al. [48] applied CBT to patients with osteoarthritis, achieving reductions in pain, stiffness, and fatigue. In a RCT involving patients with diabetic peripheral neuropathic pain [49], a CBT intervention was linked to decreased neuropathic pain intensity and enhanced mental health scores, in contrast to a control group that received diabetes education. These findings suggest that CBT not only positively impacts emotional issues such as depression and anxiety but also improves physical symptoms and sleep quality through its behavioral techniques.

After participating in the program, participants reported an increase in their ability to communicate positively and effectively with their families, as well as a boost in their motivation for rehabilitation. The program also instilled in them future goals and altered expectations about potential changes in their lives. This improvement may be attributed to various program components such as assertive communication, planning weekly activities, practicing problem-solving skills, and creating coping card strategies. These elements were instrumental in helping participants replace negative thoughts with positive ones, devise reasonable solutions and coping strategies, achieve a sense of accomplishment, manage stress, and learn effective self-expression. Furthermore, many participants noted an improved ability to concentrate on their current capabilities. This shift is likely due to the cognitive restructuring activities included in the program, which addressed their pervasive negative thoughts about never being able to return to their previous lives. These activities taught them to think positively, appreciate the small joys in life, and maintain a focus on the present.

Participants were asked to repeatedly identify their cognitive errors, substitute them with positive thoughts, and gather evidence to challenge their negative beliefs. In-depth interviews indicated that participants experienced personal growth throughout the program, which enhanced their eagerness to return to work, strengthened their resolve to be better mothers, helped them recognize their competencies, and fostered hope and a plan for post-discharge change. This improvement may have stemmed from program activities that involved rating their negative emotions in challenging situations, as well as assessing their sense of accomplishment and enjoyment from their planned activities. As the sessions advanced, participants could visually observe their progress, evidenced by a decrease in their negative emotions scores and an increase in their scores for accomplishment and enjoyment.

There are several limitations to this study. First, the small sample size makes it difficult to generalize the findings to all hospitalized stroke patients. Second, participants with paralysis in their dominant hand may not have been able to describe their feelings in sufficient detail, as they could only complete the worksheet with assistance from family, caregivers, or therapists. Third, there has been no follow-up to verify the sustainability of the study's results. To address these limitations, future research should increase the sample size, develop programs that utilize tablets or computer to allow participants to engage with just a simple touch, conduct follow-ups to ensure the program's lasting effects, and create a detailed guidebook for therapists to facilitate professional intervention. Recent research trends in other countries have included telephone-based CBT, Internet-based CBT, and self-help programs. However, more research is needed in Korea using a broader approach. This would expand the scope of the study to not only include hospitalized stroke patients but also those receiving home-based care and patients with other conditions.

Conclusion

This study aimed to implement a CBT program developed by the author for stroke patients and to evaluate its effectiveness through both quantitative and qualitative analyses. The quantitative analysis demonstrated that CBT positively impacted depression, anxiety, self-efficacy, and rehabilitation motivation among stroke patients. Meanwhile, the qualitative analysis offered deeper insights into the participants' subjective experiences and perceptions of the program, which were not captured by the quantitative data. The findings from the qualitative analysis revealed psychological stability and alleviation of physical symptoms, leading to changes in daily routines. The challenges faced by the participants instilled a sense of hope. Given the lack of systematic studies on CBT programs for stroke patients both nationally and internationally, this study suggests that CBT could be a valuable intervention within the field of occupational therapy.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Science Research Ethics Committee of Cheongju University (IRB No: 1041107-

202304-HR-078-01) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained for publication of this study and accompanying images.

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

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None.

Availability of Data
The datasets are not publicly available but are available from the corresponding author upon reasonable request.

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All papers, including those invited by the editor, are subject to peer review. PHRP has adopted a double-blind peer review policy, where the author identities remain anonymous to the reviewers, and vice versa, and the identities of the reviewers and authors are visible to (decision-making) the editor throughout the peer review process. The Editorial Board selects reviewers based on expertise, publication history, and past reviews. During the peer review process, reviewers can interact directly or exchange information (e.g., via submission systems or email) with only an editor, which is known as "independent review." An initial decision will normally be made within 4–6 weeks after the reviewers agree to review a manuscript. No information about the review process or editorial decision process is published on the article page.

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- The Editorial Office of PHRP receives and reviews all submitted manuscripts, and all submitted manuscripts are considered confidential. The submitted manuscripts are initially screened for formatting. Once the manuscript is provisionally accepted, it is sent to the 2 most relevant referees for review.
- The referees are selected by the editor from the Editorial Board's database or the board members' recommendation. The referees are then requested to evaluate the manuscript based on originality, validity, presentation, and importance and interest, and, when considered necessary, statistics.
- Acceptance of a manuscript depends on the evaluation, critiques, and recommended decision made by the referees. A referee may recommend "accept," "minor revision," "major revision," and "reject." If there are conflicting decisions between referees, or between the author and referee(s), the Editor-in-Chief has the full right to decide whether the manuscript will be published in the journal. Three repeated decisions of "major revisions" are equivalent to rejection, and rejected papers will not be considered further.
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- When the final decision on the acceptance of the manuscript is made, the Editorial Office notifies the corresponding author. The peer-review process takes approximately 8–12 weeks.

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- All pages should be paginated consecutively.
- All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
- Abbreviations: Where a term/definition is repeatedly referred to (i.e., 3 times in the text), it is written in full when it first appears, followed by the subsequent abbreviation in parentheses (even if it was previously defined in the abstract); thereafter, the abbreviation is used.
- Gene nomenclature: Current standard international nomenclature for genes should be adhered to. Genes should be typed in italic font and include the accession number. For human genes, use the genetic notation and symbols approved by the HUGO Gene Nomenclature Committee (http://www.genenames.org/) or refer to PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez).
- Units: Système International (SI) units must be used, with the exception of blood pressure values, which are to be reported in mmHg. Please use the metric system for expressions of length, area, mass, and volume. There should be a space between the numerals and the unit symbol.

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Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors are encouraged to consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

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- **Original articles** are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. These articles should be written in the following format: title page; abstract and keywords; main body (introduction, materials and methods, results, discussion, conclusion [if any]); references; and tables and figure legends. Manuscript limitations are 5,000 words, excluding the abstract, references, and tables and figure legends.
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of up to 150 words, a maximum of 4 tables and figures, and no more than 30 references.

- **Editorials** provide invited perspective on an area of PHRP, dealing with very active fields of research, current interests, fresh insights, and debates. An abstract is not required and a brief unstructured text should be prepared. Although editorials are normally invited or written by an editor, unsolicited editorials may be submitted. Manuscript limitations are 1,000 words and 20 references.
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Title Page

Title page should include (1) the title of the article (less than 50 words); (2) name of the authors (first name, middle initial, last name in capitals) and institutional affiliation including the name of department(s) and institution(s) of each author; (3) name, full address (including the postal code) of the institutional affiliation, telephone and e-mail address of the corresponding author; (4) a running title of 50 characters or less including blank spaces; and (5) notes (disclaimers). Notes include ethics approval and consent to participate, conflict of interest, funding, availability of data, authors' contributions, additional contributions, and ORCID of all authors. All contributors who do not meet the criteria for authorship as defined above should be listed in an additional contribution section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

Abstract and Keywords

An abstract and 3–6 relevant keywords (in alphabetical order) are required. Abstracts should be no more than 250 words in length. Abstracts should be structured, with the following section headings: Objectives, Methods, Results, Conclusion. For selecting keywords, refer to the MeSH browser (http://www.ncbi.nlm.nih.gov/mesh).

Highlights

All papers must include 3–5 short sentences presenting short summary or findings in the next of title page. The highlight section should be no more than 100 words, including spaces.

Main Body

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name of the manufacturer. All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms "sex" (when reporting biological factors) and "gender" (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was confirmed (or waived) by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the

text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.

- **Discussion** should contain an interpretation and explanation of the results and important aspects of the study, followed by the conclusions drawn from them. Information already mentioned in the Introduction or Results sections should not be repeated and the main conclusions of the study may be presented in the discussion.
- **Conclusion** (if any) must be linked with the purpose of the study stated in the abstract, and clearly supported by the data produced in the study. New hypotheses may be stated when warranted, but must be clearly labeled.

References

Authors are responsible for the accuracy and completeness of their references and for correct text citations.

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by "et al."
- When citing organizations that are national bodies such as government agencies, if a nationality is not part of the name, place the country in parentheses after the name, using the two-letter ISO country code.
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Please refer to the following examples.

- **Journal articles**
  1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. Osong Public Health Res Perspect 2021; 12:37-43.
  2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and clinical characteristic of COVID-19 28 cases in South Korea. Public Health Wkly Rep 2020;13:464-74. Korean.
  3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. J Integr Bioinform 2021 Mar 15 [Epub]. https://doi.org/10.1515/jib-2021-0001.
- **Books**
  1. Riffenburgh RH, Gillen DL. Statistics in medicine. 4th ed. Academic Press; 2020.
  2. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. Fennema's food chemistry. 5th ed. CRC Press; 2017. p. 627-80.
  3. Ministry of Employment and Labor (KR). Statistics on occupational injuries and illnesses, 2008. Ministry of Employment and Labor; 2009. Korean.
- **Websites**
  1. World Health Organization (WHO) (CH). COVID-19 vaccines [Internet]. WHO; 2021 [cited 2021 Mar 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
- **Conference papers**
  1. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, IE. Springer; 2002. p. 182-91.
- **Dissertation**
  1. Park HY. The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]. Yonsei University; 2000.

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Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table ([a], [b], [c], [d]...), and notes on level of probability (*, **, *** for *p*).

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Appendix and Supplemental Data

If any materials are not enough to be included in the main text such as questionnaires, they can be listed in the Appendix. Any supplementary materials that help the understanding of readers or contain too great an amount of data to be included in the main text may be placed as supplementary data. Not only a recording of the abstract, text, audio or video files, but also data files should be added here.

FINAL PREPARATION FOR PUBLICATION

Final Version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher-resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

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Title Page

- ▫ The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
- ▫ The title page is arranged in the following order: article title, authors' full name(s), affiliation(s), and corresponding author's information, running title (less than 50 characters), notes.
- ▫ The notes section including (1) ethics approval and consent to participate, (2) conflicts of interest, (3) funding, (4) availability of data, (5) author contributions, (6) additional contributions, and ORCID is in title page, not in the manuscript.

Abstract

- ▫ The abstract does not exceed 250 words (Objectives, Methods, Results, Conclusion) for original articles and 200 words for reviews. Up to 3–6 keywords are listed at the bottom of the abstract.

Main Text

- ▫ The manuscript is organized according to following sequence: Title page, Abstract and keywords, Main text, References, Tables, and Figure legends.

Tables and Figures

- ▫ All tables and figures are numbered in the order of their appearance in a main text.
- ▫ Tables are included at the end of the manuscript as editable text and not as images.
- ▫ Figures are as separate files, in jpg, ppt, tiff, or pdf format.

References

- ▫ References are listed in proper format.
- ▫ All references listed in the reference section are cited in the text and vice versa.

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