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Impact of underlying diseases and complications on COVID-19 mortality in South Korea: analysis of national health insurance service data

Kyunghee Lee[1] and Jieun Hwang[2,3*]

Abstract

Background Comorbidities or complications significantly influence coronavirus disease-2019 (COVID-19) severity and mortality risk. Therefore, this study aimed to compare treatment outcomes of COVID-19 inpatients by underlying diseases or complications.

Method Data on COVID-19 patients from the National Health Insurance Service customized research database were analyzed while focusing on eight underlying diseases and complications: diabetes, hypertension, heart disease, kidney disease, liver disease, dementia, depression, and respiratory disease.

Results Of the 377,812 COVID-19 patients in 2021, 51.47% were male and 48.53% were female, and post-diagnosis mortality was 2.04%; 68.7% ($n=259,560$) of patients had at least one underlying condition, with the following frequency: respiratory disease (78.88%), heart disease (33.84%), hypertension (30.29%), liver disease (21.38%), depression (9.32%), kidney disease (4.89%), and dementia (3.87%). Among patients without any underlying diseases, 19.8% ($n=74,925$) were treated for post-diagnosis complications, with the following frequency: respiratory disease (89.21%), liver disease (19.12%), heart disease (14.90%), diabetes (10.37%), hypertension (8.22%), depression (3.86%), kidney disease (2.04%), and dementia (0.64%). Except for liver disease, all underlying diseases were associated with mortality. COVID-19 patients with diabetes exhibited a 1.42-fold higher mortality risk (95% confidence interval [CI]1.35–1.50). All complications were associated with death, with kidney-related complications conferring a 4.84-fold higher mortality risk (95% CI 3.62–6.48).

Conclusion Underlying diseases and complications in COVID-19 patients were associated with death. Even with the same disease, the timing of onset, before or after COVID-19 diagnosis, induced a difference in the mortality risk. Both underlying diseases and complications should be considered for more proactive medical interventions.

Keywords Complications, COVID-19, Mortality, Underlying diseases

*Correspondence:
Jieun Hwang
hwang0310@dankook.ac.kr
[1]Department of Healthcare Management, Eulji University of Korea, 553 Sanseongdaero, Sujeong-gu, Seongnam city, Kyeonggi-do 13135, Republic of Korea
[2]Department of Health Administration, College of Health Science, Dankook University, 119 Dandaero, Dongnam-gu, Cheonan city, Chungcheongnam-do 31116, Republic of Korea
[3]Institute of Covergence Healthcare, Dankook University, 119 Dandaero, Dongnam-gu, Cheonan city, Chungcheongnam-do 31116, Republic of Korea

Text box 1. Contributions to the literature

Previous studies have often overlooked distinguishing between underlying diseases and complications in assessing their differential impact on COVID-19 mortality.

This research highlights that the same health condition, whether present as an underlying disease or as a complication after COVID-19 diagnosis, significantly alters mortality risk.

The study emphasizes the critical need for proactive management strategies that account for both underlying conditions and potential post-infection complications to reduce mortality in COVID-19 patients.

Our findings provide foundational evidence for developing targeted public health interventions tailored to high-risk groups, contributing to more effective healthcare policies.

Background

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome that is caused by the pathogenic severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), which was first discovered in Wuhan, People's Republic of China, in December 2019. The national-level response to the outbreak in South Korea included the categorization of COVID-19 as a severe infectious disease in February 2020. More than 3 years after the initial outbreak, the COVID-19 pandemic continues, with persistent infections and deaths due to the emergence of variants and other factors [1, 2]. Among the reasons for the persistence or increase in severe COVID-19 cases and deaths is that many of those infected are older individuals or have underlying diseases and complications [1]. An underlying disease refers to a pre-existing condition that may impact the progression or severity of illness, whereas complications are conditions that arise after the onset of infection and are directly linked to the disease process. The frequently occurring underlying diseases and complications of COVID-19 include heart disease, kidney disease, pneumonia and respiratory diseases, liver disease, depression, sleep disorders, loss of smell, lipid metabolic disorders, obesity, and diabetes [3–9]; furthermore, these are chronic diseases that are closely related to the onset of COVID-19 [10], whereas complications, which are acute conditions, tend to appear during the treatment process and have a high correlation with disease severity [11]. In pediatric patients, underlying conditions, such as asthma, obesity, and neurodevelopmental disorders, affect the severity of COVID-19 [12].

A distinctive feature of SARS-CoV-2 infection is its ability to induce systemic infection and multiorgan failure. Moreover, the presence of comorbidities frequently influences disease severity and mortality risk [13, 14]. Notably, renal failure, characterized by the loss of renal function, is closely linked to dysfunctions in other organs and increases the risk of severe disease progression and mortality in patients with COVID-19 [15]. Acute kidney injury as a COVID-19-related complication often manifests secondary to other pathologies, such as liver, heart, lung, and autoimmune diseases, and influences the disease severity and mortality rate [16]. Additionally, patients with chronic renal failure typically exhibit a diminished immune response, increasing their susceptibility to COVID-19 infection and the possibility of acute renal failure [17]. Although both acute and chronic kidney failures similarly influence the disease severity, their onset mechanisms vary. Furthermore, depression and dementia following SARS-CoV-2 infection can adversely impact the quality of life and create barriers to the resumption of daily activities, rehabilitation, and attainment of social well-being. With the advent of the long-term COVID-19 era, managing the abovementioned issues has gained crucial importance [18, 19].

The influence of diverse comorbidities on the clinical condition of patients with COVID-19 underscores the paramount importance of their prevention and management. During the transition into the "With-COVID-19 Era," strategic prevention combined with effective treatment is essential to curtail the severity and fatalities associated with COVID-19. Therefore, obtaining a comprehensive, precise understanding of diseases intrinsically linked to the severity of, and mortality from, COVID-19 is imperative. One approach to this goal is to delineate treatment plans rooted in a nuanced understanding of treatment outcomes while factoring in the timing of diagnosis of the comorbidities associated with disease severity. However, previous studies rarely differentiated between underlying diseases and complications in relation to their impact on treatment outcomes.

Therefore, this study aimed to evaluate the role of common diseases previously identified as underlying conditions or complications and to compare their impact, whether as an underlying disease or a complication, on the treatment outcomes for COVID-19 inpatients. The findings could provide foundational data for developing policies tailored to managing the underlying diseases and complications in COVID-19 patients.

Material and method

Research data

This study utilized data from the customized research database, the National Health Information Database (NHID), provided by the National Health Insurance Service (NHIS). The NHIS, which provides comprehensive health insurance coverage to over 50 million people in South Korea, was established to ensure nationwide access to healthcare [20]. Created in 2012, the NHID integrates medical treatment records, health screening data, and insurance eligibility information from pre-existing database systems to form a comprehensive health data repository. The customized research database includes health information tailored to meet specific policy and

research needs. Researchers seeking to use this data must submit a detailed research proposal to the NHIS, which is evaluated by a review committee for approval. Upon approval, the requested data is extracted, validated, and made accessible at the Big Data Analysis Center, where researchers can analyze the information after paying a fee. For this study, we requested information from the NHIS on records of inpatient and outpatient usage for individuals diagnosed with COVID-19 in 2021, covering the period from 2020 to 2021. We received data for a total of 377,812 confirmed COVID-19 patients in 2021.

Research variables

Dependent variables

The dependent variable of this study was the mortality status based on the death date and cause of death code (ICD-10) indicated in the death database. Specifically, patients diagnosed with COVID-19 in 2021, who had both a recorded date of death and an associated ICD-10 cause-of-death code, were categorized as deceased. All other participants were designated as survivors.

Independent variables

In this study, "underlying diseases" and "complications" were categorized based on whether they were present before or emerged after a COVID-19 diagnosis, defined within the 1-year periods preceding and following the COVID-19 diagnosis, respectively (Fig. 1). The analysis focused on eight specific diseases, assessed both as underlying conditions and potential complications. A patient was classified as having a specific disease if either the primary diagnosis or any of the five supplementary diagnoses included one of the following codes: diabetes (E10–E14), hypertension (I10), heart disease (I01–I51), kidney disease (N00–N19), liver disease (K70–K77), dementia (F00–F03), depression (F03–F39), and respiratory diseases (J00–J47, J84–J99).

Covariates

Based on general characteristics and COVID-19 related variables, the participants were categorized by sex (male or female), age (teens, 20s, 30s, 40s, 50s, 60s, 70s, or ≥ 80), source of infection (domestic or foreign), cause of infection (arrivals from abroad, arrival-related infection, nosocomial infection, local outbreak, contact with a confirmed case, or unclassified), and the reporting region (Seoul Capital Area, Chungcheong, Honam, Gyeongbuk, Gyeongnam, Gangwon, Jeju, or border quarantine).

Data analysis

We conducted a frequency analysis to assess the characteristics of COVID-19 patients, examined the incidence of underlying diseases and complications, and conducted chi-square tests to ascertain the statistical significance of differences between groups with underlying diseases and complications. After adjusting for factors such as sex, age, and cause of infection, logistic regression analysis was employed to evaluate the influence of the presence or absence of each underlying disease and complication on mortality. For the assessment of mortality risk associated with underlying diseases, the reference group consisted of patients without any underlying diseases during the year preceding their COVID-19 diagnosis, regardless of whether they had complications. Similarly, for the assessment of mortality risk associated with complications, the reference group consisted of patients without any complications during the year following their COVID-19 diagnosis and who also had no underlying diseases. The findings were presented using the adjusted odds ratio (aOR) and 95% confidence interval (CI). All analyses were performed using SAS version 9.4, with statistical significance set at $p < .05$.

Results

General characteristics

In 2021, of the 377,812 confirmed COVID-19 cases, 51.47% occurred in males and 48.53% in females. The average age was 46 years (± 21.67). The age distribution showed that individuals in their 60s constituted the largest proportion (16.19%), followed by those in their 50s (15.29%), 40s (14.18%), and teens (14.06%). Regarding the source of infection, 98.64% of cases were domestic, whereas 1.36% were from abroad. The most prevalent cause of infection was through contact with a confirmed case (42.95%). In terms of reporting regions, the Seoul Capital Area recorded the majority of cases at 68.6%, followed by Gyeongnam (10.43%), Chungcheong (8.09%), and Gyeongbuk (5.85%). The post-diagnosis mortality rate was 2.04% (Table 1).

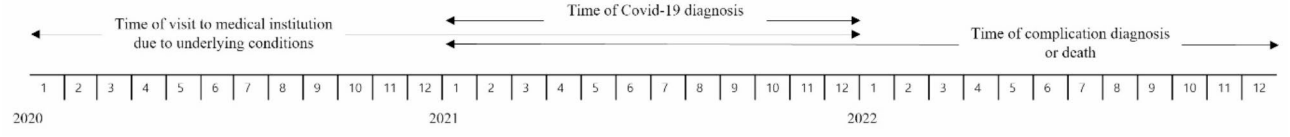

Fig. 1 Flow diagram of the study design

Table 1 General characteristics of Covid-19 patients in South Korea, 2021 ($n = 377,812$)

Category		*n*	%
Sex	Male	194,468	51.47
	Female	183,344	48.53
Age, years (decade)	Mean ± SD	46 ± 21.67	
	10s	53,112	14.06
	20s	47,838	12.66
	30s	50,158	13.28
	40s	53,586	14.18
	50s	57,773	15.29
	60s	61,171	16.19
	70s	33,529	8.87
	≥ 80	20,645	5.46
Source of infection	Domestic	372,656	98.64
	Foreign	5,156	1.36
Cause of infection	Arrivals from abroad	5,156	1.36
	Arrival-related infection	174	0.05
	Nosocomial infection	18,344	4.86
	Local outbreak	77,386	20.48
	Contact with a confirmed case	162,284	42.95
	Unclassified	114,468	30.3
Reporting region	Seoul Capital Area	259,168	68.6
	Chungcheong	30,567	8.09
	Honam	14,765	3.91
	Gyeongbuk	22,093	5.85
	Gyeongnam	39,410	10.43
	Gangwon	6,392	1.69
	Jeju	3,607	0.95
	Border quarantine	1,810	0.48
Outcome status	**Survival**	**370,109**	**97.96**
	Death	**7,703**	**2.04**

Comparison of disease distribution between the underlying disease and complication groups

In total, 68.7% ($n = 259,560$) of the participants had at least one underlying disease. Respiratory diseases were the most common underlying disease (78.88%), followed by heart disease (33.84%), hypertension (30.29%), liver disease (21.38%), depression (9.32%), kidney disease (4.89%), and dementia (3.87%). Among those without underlying diseases, 74,925 participants sought treatment for complications after their COVID-19 diagnosis, corresponding to 19.8% of all confirmed cases and 63.4% of those without underlying diseases. As shown in Table 2, respiratory diseases were the most frequent complication (89.21%), followed by liver disease (19.12%), heart disease (14.90%), diabetes (10.37%), hypertension (8.22%), depression (3.86%), kidney disease (2.04%), and dementia (0.64%).

Association between underlying diseases and mortality

Except for liver disease, all underlying diseases were associated with mortality (Fig. 2). Specifically, diabetes conferred a 1.42-fold higher mortality risk (95% CI 1.35–1.50, $p < .0001$), followed by hypertension (aOR = 1.24, 95% CI 1.17–1.30, $p < .0001$), heart disease (aOR = 1.36, 95% CI 1.28–1.43, $p < .0001$), kidney disease (aOR = 2.33, 95% CI 2.17–2.50, $p < .0001$), dementia (aOR = 1.55, 95% CI 1.45–1.66, $p < .0001$), and depression (aOR = 1.28, 95% CI 1.20–1.37, $p < .0001$). Participants with respiratory diseases had a decreased mortality risk (aOR = 0.94, 95% CI 0.89–0.99, $p = .012$).

Association between complications and mortality

All complications were associated with mortality (Fig. 3). Particularly, participants with kidney disease as a complication had a 4.84-fold higher mortality risk (95% CI 3.62–6.48, $p < .0001$), followed by those with heart disease (aOR = 3.05, 95% CI 2.58–3.61, $p < .0001$), diabetes (aOR = 2.31, 95% CI 1.92–2.77, $p < .0001$), depression (aOR = 1.64, 95% CI 1.22–2.21, $p = .001$), dementia (aOR = 1.39, 95% CI 1.02–1.90, $p = .04$), hypertension (aOR = 1.36, 95% CI 1.12–1.66, $p = .002$), and liver disease (aOR = 1.32, 95% CI 1.09–1.61, $p = .004$). In contrast to the finding in underlying diseases, respiratory diseases as a complication increased the mortality risk 2.31-fold (95% CI 1.89–2.82, $p < .0001$).

Discussion

As of August 2023, approximately 9% of the global population ($n = 688,711,061$) had been diagnosed with COVID-19, with a mortality rate of approximately 1%.

Table 2 Distribution of disease categories among underlying disease and complication groups in Covid-19 patients

Category		Underlying Disease Group ($n = 259,560$)		Complication Group ($n = 74,925$)		*p*-value
		n	%	*n*	%	
Diabetes	E10–E14	51,851	19.98	7,767	10.37	< 0.0001
Hypertension	I10	78,631	30.29	6,162	8.22	< 0.0001
Heart	I01–I51	87,826	33.84	11,163	14.90	< 0.0001
Kidney	N00–N19	12,682	4.89	1,529	2.04	< 0.0001
Liver	K70–K77	55,485	21.38	14,323	19.12	< 0.0001
Dementia	F00–F03	10,046	3.87	483	0.64	< 0.0001
Depression	F30–F39	24,183	9.32	2,894	3.86	< 0.0001
Respiratory	J00–J47, J85–J99	204,744	78.88	66,839	89.21	< 0.0001

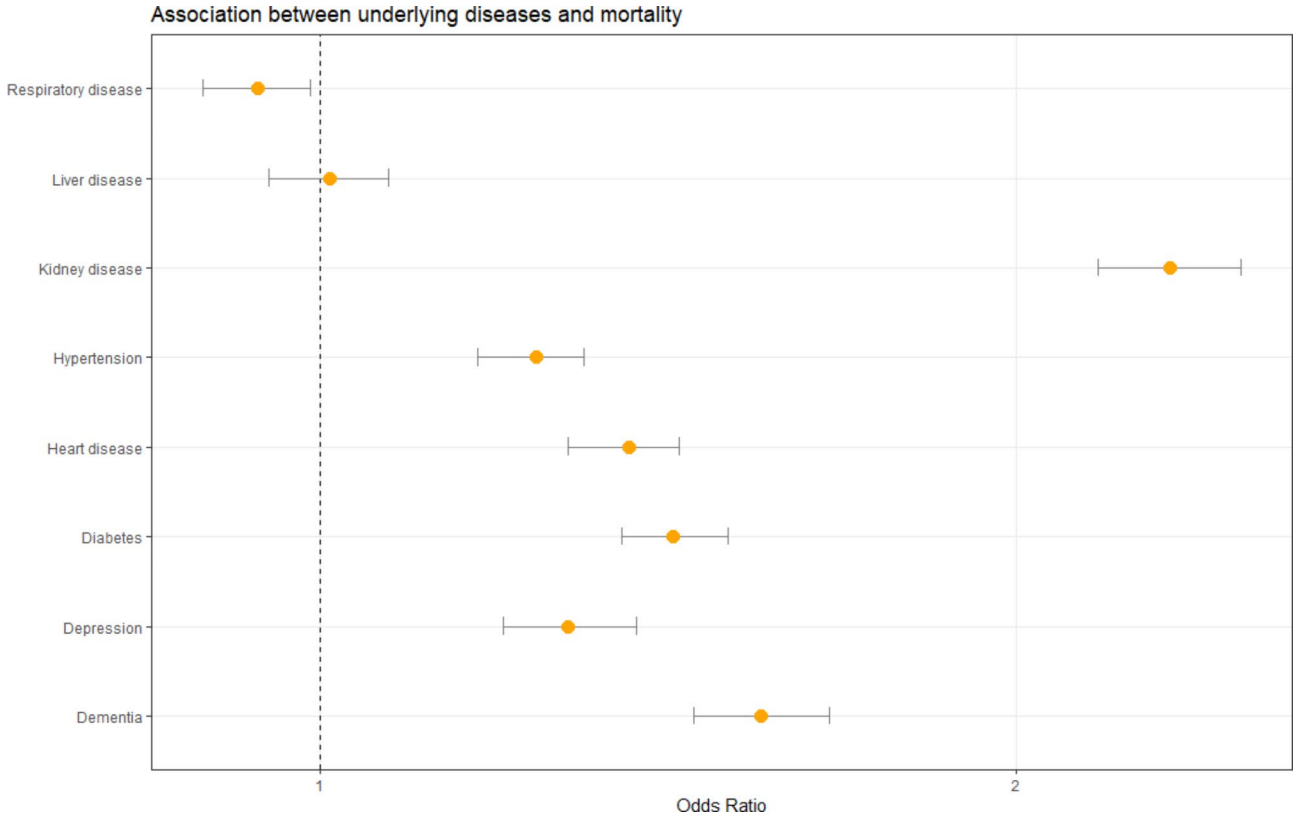

Fig. 2 Association between underlying diseases and mortality in Covid-19 patients from 2021 to 2022, South Korea

The pandemic instigated profound changes not only in sectors such as education, retail, tourism, and the broader economy but also in the way healthcare services were utilized. This study focused on 377,812 COVID-19 cases from 2021 and analyzed the association between diseases identified either before or after a COVID-19 diagnosis and subsequent mortality. The results of this study indicate that both underlying diseases and complications were significantly correlated with post-diagnosis mortality. Notably, the mortality risk was higher when the same condition was identified as a complication rather than an underlying disease.

The analysis of general characteristics revealed that, out of the total 377,812 participants, 7,703 (2.04%) died. Participants in their 60s constituted the age group with the highest infection rate, which suggests that among older adults, who are vulnerable to infection, those in their 60s are still active socially and have a higher prevalence of chronic underlying diseases [2, 7].

Among COVID-19 patients, the most frequent underlying conditions were respiratory diseases, followed by heart disease and hypertension. In terms of complications, respiratory diseases topped the list, followed by liver and heart disease. These findings indicate that liver diseases manifest prominently as COVID-19-related complications. Despite the absence of a significant association between liver disease as an underlying condition and mortality, the presence of liver disease as a complication post-diagnosis was strongly correlated with mortality, highlighting the need for targeted care after a COVID-19 diagnosis. Furthermore, patients with pre-existing liver conditions are often prescribed antiviral or liver-protective medications due to an elevated risk of drug-induced hepatic damage [21–23], which explains its minimal association with mortality. In contrast, acute liver damage as a COVID-19 complication often coincides with other severe conditions, such as pneumonia-induced hypoxia, antiviral drug-induced liver maladies, vascular impairments, and right ventricular failure, which augment disease severity and the resultant mortality risk [24], emphasizing the importance of meticulous liver complication management in COVID-19 patients.

The high frequency of respiratory disease comorbidities observed in COVID-19 patients may reflect their prevalence in the general population, rather than indicating an inherent susceptibility to the virus. This underscores the critical need for careful management of such conditions during COVID-19 treatment. Effective use of antibiotics and other therapeutic interventions can help manage underlying conditions and mitigate the risk of exacerbations [25]. However, respiratory complications of COVID-19 showed a heightened association with

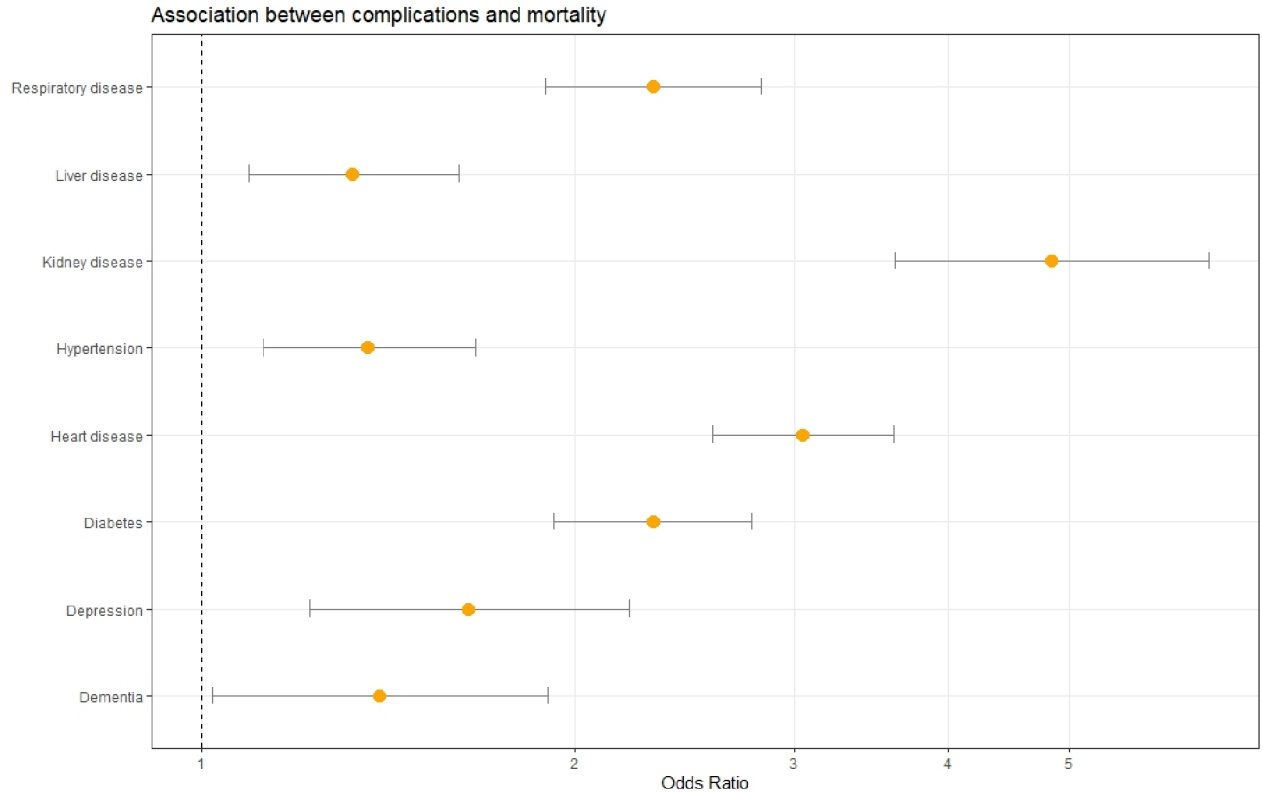

Fig. 3 Association between complications and mortality in Covid-19 patients from 2021 to 2022, South Korea

mortality, especially among older adults, consistent with previous studies' findings [26–28]. Thus, it is crucial to meticulously investigate the factors triggering respiratory complications and to implement both preventative and therapeutic interventions.

Cardiovascular diseases presented a higher mortality risk when they emerged as complications rather than just underlying conditions. Notably, acute cardiovascular conditions elevate cardiac troponin levels, which can result in cardiac muscle damage, myocarditis, acute myocardial infarction, and acute heart failure – each contributing to increased mortality [29]. Furthermore, chronic cardiovascular diseases heighten the risk of these acute cardiovascular events and can compromise the efficacy of treatments. This underscores the importance of prevention and the vigilant management of cardiovascular conditions arising in the context of COVID-19 by minimizing the risk of acute complications through efficient chronic disease management [30].

Although kidney diseases did not show a significantly higher frequency among SARS-CoV-2 infections compared to other underlying conditions, they were associated with the highest mortality risk. Notably, complications arising from acute kidney diseases presented a 4.84-fold increase in the mortality risk, emphasizing the need for intensive management. As indicated in prior research [31], approximately 4% of COVID-19 patients suffer from acute kidney damage; despite this low incidence, the mortality rate surges when the condition coexists with liver, lung, and heart diseases or immune dysfunction [16, 32, 33]. Moreover, chronic kidney failure increases the risk of acute kidney failure, and a weakened immune system further increases the disease severity and mortality risk [34]. Consequently, although managing underlying conditions is essential, particular attention needs to be given to complication management by proactively addressing the causative factors of secondary acute kidney damage.

Depression has emerged as a critical concern for management, particularly as a complication of COVID-19. Beyond its association with mortality, depression considerably diminishes the quality of life. In the unfolding "With-COVID-19 Era," depression has been spotlighted for managing enduring complications and sequelae [4, 35]. The psychological aftereffects of a COVID-19 infection can impede the return to daily life, rehabilitation, and societal well-being [18, 19]. This highlights the urgency of focused intervention [36] to foster psychological recovery in long COVID-19 [37, 38].

Diabetes exhibited a more pronounced association with mortality when present as a complication rather than as an underlying condition. Specifically, when

diabetes pre-exists as an underlying condition, it can lead to metabolic disturbances as a complication of COVID-19. Coupled with the COVID-19-induced systemic infection, which compromises the immune system, these metabolic disturbances can induce the progression of the disease state to severe illness; notably, as reported in previous studies, this trajectory amplifies the mortality risk [38, 39]. Given its status as a prevalent chronic condition in adults, thorough management and education regarding diabetes are imperative in mitigating the risks associated with COVID-19 infections.

To summarize the study's results, we found that both underlying diseases and complications in COVID-19 patients had clear associations with mortality. Notably, the mortality risk differed based on the timing of the disease's onset, whether pre- or post-COVID-19 diagnosis. Furthermore, diseases manifesting as complications were more strongly associated with death. Although the presence of an underlying condition increases the risk of infection, proactive identification and management of these risk factors during treatment have led to a diminished association with mortality, as compared to complications that arise after diagnosis. This suggests that for severe COVID-19 cases, it is vital to account for underlying conditions and complications when determining treatment strategies, emphasizing the need for more proactive interventions. To optimize outcomes, it is imperative not only to manage existing conditions but also to meticulously recognize and address risk factors for post-infection complications. Importantly, this approach enables focused management, preventive measures, and targeted treatments [29, 39–42]. The findings of this study could provide foundational data for managing the variability in disease severity and mortality based on the timing of onset for comorbidities associated with COVID-19, highlighting the significance of our research.

Nevertheless, this study has some limitations. First, patients were defined by the primary and supplementary diagnosis codes reported when using healthcare facilities in the year before and the year after a COVID-19 diagnosis, implying a potential underestimation of the number of patients. In fact, overall hospital visits decreased during the COVID-19 pandemic, and some confirmed patients might not have sought medical care for their underlying diseases. Even with the expected underestimation of the number of patients, the proportion of deaths due to underlying diseases and complications was noticeable, indicating the associated risks. Second, underlying diseases and complications were defined without considering their severity, limiting our ability to capture differences in treatment outcomes based on disease severity. Future studies should incorporate severity assessments to provide a more precise analysis of mortality risk. Furthermore, it is necessary to evaluate the association between the number of underlying diseases/complications and mortality risk to explore potential dose-response relationships. This approach could more clearly illustrate the impact of the cumulative burden of comorbidities on mortality risk. Third, it is important to consider potential biases in our study. For example, surveillance bias may have influenced our findings, as individuals with severe COVID-19 were more likely to receive diagnoses for comorbidities, especially complications. Additionally, the timing of the COVID-19 outbreak in 2020 may have affected testing behaviors, with patients having pre-existing respiratory diseases in 2020 and 2021 being more likely to seek COVID-19 testing. This could partly explain the observed protective effect of pre-existing respiratory conditions, as individuals with respiratory comorbidities may have experienced less severe COVID-19 symptoms. Fourth, secondary data provided by the NHIS was utilized for analysis in this study; thus, other potential influencing factors for the mortality risk of patients with COVID-19 were not considered. Fourth, as the study could not identify the risk factors for complications, it does not offer solutions for reducing mortality. In the future, more advanced research might be carried out using the preliminary findings of this study to enable a close examination of the risk factors for complications related to each disease. Fifth, the observed associations between specific diseases and COVID-19 outcomes may be influenced by their prevalence in the general population rather than direct susceptibility to the virus. Additionally, some conditions categorized as 'post-COVID-19 complications' might represent undiagnosed pre-existing conditions, potentially leading to misclassification. Future research should incorporate control groups representing the general population and employ longitudinal designs to distinguish between true post-COVID complications and pre-existing conditions, thereby reducing potential biases and enhancing the accuracy of findings. Lastly, treatment results were only observed in association with COVID-19-related mortality. Future research that considers the length of hospital stay, intensive treatment details, and cost differences would provide a more comprehensive view of treatment outcomes in relation to underlying diseases and complications.

Conclusion

Underlying diseases and complications were associated with the mortality risk following a COVID-19 diagnosis, and the risk level varied based on the specific disease. Notably, even for the same disease, the mortality risk varied significantly depending on the timing of onset, highlighting the importance of differentiating between underlying conditions and complications when interpreting their impact on COVID-19 outcomes. As such, to enhance treatment efficacy, this study emphasizes the

importance of factoring in both underlying diseases and complications when establishing treatment and management strategies in confirmed cases of viral diseases such as COVID-19.

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Author contributions
KL has made substantial contributions to the conceptualization of the research and the formal analysis. KL acquired funding for the study, while JH managed the project. Both KL and JH contributed to the review and interpretation of the results. KL drafted the original manuscript, and JH reviewed and edited it. All authors have read and approved the final manuscript.

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Data availability
The datasets analyzed during the current study are available from the National Health Insuranc Sharing Service on reasonable request.[https://nhiss.nhis.or.kr/].

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board of the Eulji University of South Korea (IRB no. EUIRB2022-073). Informed consent was not required.

Competing interests
The authors declare no competing interests.

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