

The association of mortality with vaccination and underlying disease among COVID-19 patients in long term care hospitals at Daegu and Gyeongsangbuk-do in Korea

Hanul Park

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Chungmin Park

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Seong-Ju Choi

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Yeon Haw Jung

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Myung-Jae Hwang

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Junseock Son

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Inyeong Seo

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

Taeyeon Park

Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu

You Kyung Kim

Gyungsangbuk-do Welfare and health Bureau infectious Disease control Division, Gyungsangbuk-do

Ji-Seon Seong

Division of Infectious Disease Control, Daegu Metropolitan City Hall, Daegu

Taejong Son (✉ sontaejong@korea.kr)

Research Article

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Abstract

Background

This study aimed to estimate the effects of vaccine on reducing the mortality rate and the relationship between underlying diseases and death among long term care hospital residents during the Omicron epidemic.

Methods

This study included 2,507 inpatients at 18 long term care hospitals that experienced COVID-19 outbreaks more than twice in Daegu Metropolitan City and Gyeongsangbuk-do in Korea, from January 2022 to August 2022. Descriptive statistics were used to analyze participants' demographic characteristics and mortality, which were expressed as percentages (%). Logistic regression analysis was performed to compare mortality, and the crude risk ratio (cRR) and adjusted risk risk (aRR) were estimated. The analysis model was adjusted for sex, age, region, history of Paxlovid prscription, vaccine status, reinfection, and presence, type, and number of underlying diseases.

Results

In terms of vaccination status, the aRR in the group with < 90 days after the 3 doses was 0.20 (CI:0.09–0.45) and \geq 90 days was 0.14 (CI:0.06–0.32), that in the group with < 90 days after 4 doses was 0.18 (CI:0.06–0.43), compared with the non-vaccinated group. The fatality rate in the group prescribed Paxlovid was higher than that in the non-prescribed group. However, the difference was not statistically significant. The aRR of hypothyroidism was 5.75 (CI:1.10–30.13) and that of COPD and asthma were 2.84 (CI:1.15–6.99), compared with the group that did not have each underlying disease.

Conclusion

We confirmed the preventive effects of vaccination on death and the high risk of death from hypothyroidism, COPD, and asthma in COVID-19-confirmed patients in long term care hospitals.

Introduction

The Omicron variant of SARS-CoV-2 (COVID-19) was first identified in Botswana on November 11, 2021, and was reported to the World Health Organization (WHO) on November 24, 2021, in South Africa. On November 26, 2021, the WHO classified this newly reported mutation into the B.1.1.529 system through the Technical Advisory Group on SARS-CoV-2 Virus Evolution, designated it as a variant of concern (VOC), and named it as Omicron [1, 2]. Compared to the Delta variant, the Omicron variant had a high propagation rate, but the severity rate was estimated to be low [3]. As of February 7, 2023, according to

the Global Influenza Surveillance and Response System (GISAIID), 7,458,737 Omicron genome sequences were shared by 209 countries, and the Omicron variant was reported to have triggered the fourth and fifth waves of COVID-19 worldwide [4, 5]. Vaccine effectiveness and vaccine effectiveness against transmission (VET) for Omicron mutations have been confirmed; but [6, 7], COVID-19-confirmed cases and deaths continue to occur worldwide [3]. As of January 18, 2023, the number of cumulative global confirmed cases and deaths were 663,001,898 and 6,707,959, respectively, with a mortality rate of 84 per 100,000 and a fatality rate of 1.0% [8].

The Republic of Korea first reported the Omicron variant on December 1, 2021, and subsystem mutations in Omicron variants such as BA.1, BA.1.1, BA.2, BA.2.3, BA.4/5, and BN.1, continued to spread until January 31, 2023. As of February 25, 2023, the BN.1 variant accounted for 59.1% of cases. Between January 16 and July 23, 2022, BA.1 and BA.2 were the dominant species in the country, with severity and fatality rates of 0.14% and 0.10%, respectively. Subsequently, BA.5 was dominant from July 24 to September 3, 2022, but the severity rate (0.10%) and fatality rate (0.05%) were lower than those of the previous mutations. By 2022, there were 28,428,190 confirmed cases in Korea, of which 26,593 suffered death, corresponding to a fatality rate of 0.094%. The age distribution of deaths after confirmed COVID-19 in Korea was 59.11% in those aged ≥ 80 years; 22.93%, 70–79 years; and, 11.55%, 60–69 years, accounting for 93.59% of the deaths in those aged ≥ 60 years [9]. The World Health Organization classifies residents of long-term care facilities, which include a large number of older people, as high-risk groups, and has issued guidelines for preventing and controlling infections among individuals in long-term care facilities [10]. The Korean health authorities classified facilities where older people are concentrated, such as long term care hospitals, as facilities vulnerable to infection, and are conducting management, such as PCR testing, about once a week and continuous monitoring of critical cases and fatalities. Studies investigating the risk of death due to underlying disease in patients with COVID-19 reported that comorbidities are related to the severity and mortality of COVID-19[11, 12]. Most patients in long term care hospitals are old and have underlying diseases; therefore, they are highly likely to die from complications when they are affected by COVID-19. Therefore, we needed to confirm the effect of the vaccines and the underlying disease on death in COVID-19-confirmed patients in long term care hospitals. This study aimed to estimate the effects of vaccine on reducing the mortality rate and the relationship between underlying diseases and death among long term care hospitals residents during the Omicron epidemic.

Methods

Participants

This study included 2,507 inpatients who confirmed to have COVID-19 at 18 long term care hospitals that experienced COVID-19 outbreaks more than twice in Daegu and Gyeongsangbuk-do, which have similar geographical, social, and cultural characteristics in Korea, from January 2022 to August 2022. COVID-19-confirmed patients were defined as those reported to the KDCA as positive for SARS-CoV-2 polymerase chain reaction test (PCR) or Rapid Antigen Test (RAT) results in accordance with the Korea Disease

Control and Prevention Agency (KDCA)'s notification of diagnostic criteria for reporting infectious diseases. A deceased person was defined as one who died within 28 days of COVID-19 confirmation. All confirmed patients were quarantined and treated in long term care hospitals. Of the 3,755 patients in the 18 long term care hospitals, 343 patients who had missing information of confirmed date, date of death, or vaccination history were excluded from the analysis.

Data sources and variants definition

Data on the patients' underlying disease and prescription history of Paxlovid were collected by long term care hospitals, and sex, age, confirmation date, and death date were obtained from the COVID-19 Patient Management Information System of the Korea Centers for Disease Control and Prevention. The vaccination information for confirmed patients was obtained from the COVID-19 vaccination system of the Korea Center for Disease Control and Prevention.

A history of Paxlovid (nirmatrelvir + ritonavir) was defined by its prescription after COVID-19 was confirmed. Vaccination status was classified into not vaccinated, 1 dose, 2 doses, 3 doses, and 4 doses, and it was additionally classified into the "<90 days" group and the "≥90 days" group based on the period of three months when antibody titers generated after vaccination decrease. The reinfection variables were classified based on a history of infection. The underlying disease variables were classified based on the presence of underlying diseases and their type according to the Korean Standard Classification of Diseases.

Statistical analysis

Descriptive statistics were used to analyze participants' demographic characteristics and mortality, which were expressed as percentages (%). Logistic regression analysis was performed to compare mortality, and the crude risk ratio (cRR) and adjusted risk ratio (aRR) were estimated. The analysis model was adjusted for sex, age, region, history of Paxlovid prescription, vaccine status, reinfection, and presence, type, and number of underlying diseases. Statistical significance was set at $p < 0.05$, and confidence intervals (CI) were calculated. All data were analyzed using the R software (version 4.1.2).

Results

Of the 2,507 study subjects, 68 (2.71%) were confirmed to have died from COVID-19. The proportion of women (65%) was higher than that of men (35%); the proportion of those aged ≥ 75 years was 73.9%; 60–74 years, 19.1%; and, ≤ 59 years, 7%. The number of confirmed cases was higher in Gyeongsangbuk-do (58.6%) than that in Daegu (41.4%). Among the confirmed patients, 1,567 (62.5%) were not prescribed Paxlovid, whereas 910 (37.5%) were prescribed. In terms of vaccination status, 703 (28.0%) were given 3 doses (≥ 90 days); 491 (19.6%), 3 doses (< 90 days); and 302 (12.0%), and 4 doses (< 90 days), and 417 (16.6%) were not inoculated. In the past, 87.2% of the patients did not experience COVID-19. There were 2,310 participants (92.1%) with underlying diseases, and the average number of underlying diseases among all the study participants was 2.14. The fatality rate according to the general characteristics was the highest in each category in 2.7% in men, 3.0% in those aged ≥ 75 years, 3.2% in

Gyeongsangbuk-do province, and 2.8% in those prescribed Paxlovid. The unvaccinated group showed the highest mortality rate (7.2%), and the group comprising patients inoculated after > 90 days had the lowest mortality rate (0.5%). (Table 1).

Table 1

General characteristics of patients with COVID-19 in 18 long term care hospital, 1 January 2022 ~ 31 August 2022(Period of Omicron variant dominance), Daegu Metropolitan City and Gyeongsangbuk-do of Korea.

Characteristics	Total	(%)	Death	(%)
Total	2,507	(100)	68	(100)
Sex				
Male	877	(35.0)	24	(35.3)
Female	1,630	(65.0)	44	(64.7)
Age (y)				
≤ 59	176	(7.0)	4	(5.9)
60–74	478	(19.1)	8	(11.8)
≥ 75	1,853	(73.9)	56	(82.4)
Region				
Daegu Metropolitan City	1,037	(41.4)	21	(30.9)
Gyeongsangbuk-do	1,470	(58.6)	47	(69.1)
Paxlovid				
No	1,567	(62.5)	42	(61.8)
Yes	940	(37.5)	26	(38.2)
Vaccination status				
Unvaccinated	417	(16.6)	30	(44.1)
1 Dose				
< 90days	24	(1.0)	0	(0.0)
≥ 90days	35	(1.4)	2	(2.9)
2 Doses				
< 90days	162	(6.5)	7	(10.3)
≥ 90days	189	(7.5)	6	(8.8)
3 Doses				
< 90days	491	(19.6)	8	(11.8)
≥ 90days	703	(28.0)	8	(11.8)
4 Doses				

Characteristics	Total	(%)	Death	(%)
< 90days	302	(12.0)	6	(8.8)
≥ 90days	184	(7.3)	1	(1.5)
Reinfection				
No	2,187	(87.2)	0	(0.0)
Yes	320	(12.8)	68	(100.0)
Underlying disease				
No	197	(7.9)	3	(4.4)
Yes	2,310	(92.1)	65	(95.6)
Comorbidities (Mean,SD)	2.14(1.37)		2.19(1.22)	

We estimated the aRR to identify mortality risk factors according to general characteristics. By region, the aRR was 2.05 (CI:1.17–3.57) in Gyeongsangbuk-do compared to Daegu. In terms of vaccination status, the aRR in the group with < 90 days after the 3 doses was 0.20 (CI:0.09–0.45) and > 90 days was 0.14 (CI:0.06–0.32), that in the group with less than 90 days after 4 doses was 0.18 (CI:0.07–0.47), and that in the group with more than 90 days was 0.05 (CI:0.01–0.38). In the past, there were zero deaths in the group that experienced infection (Fig. 1).

The most common underlying diseases were dementia (2,190), high blood pressure (1,310), and stroke (850). The fatality rates of the underlying disease were 8.70% for hypothyroidism; 7.22%, chronic obstructive pulmonary disease (COPD) and asthma; 3.23%, Parkinson disease; 2.98%, dementia; 2.90%, stroke; and, 2.87%, high blood pressure. We estimated aRR to identify mortality risk factors according to the characteristics of the underlying diseases. The aRR of hypothyroidism was 5.75 (CI:1.10–30.13) and that of COPD and asthma were 2.69 (CI:1.10–6.58) (Fig. 2).

Discussion

This study confirmed the effect of vaccines on reducing the mortality rate and the relationship between underlying diseases and death in 18 long term care hospitals that experienced more than two COVID-19 outbreaks during the Omicron variant epidemic in Daegu and Gyeongsangbuk-do, which have similar geographical, social, and cultural characteristics. Among those with underlying diseases, COVID-19-confirmed patients with hypothyroidism and COPD and asthma had high mortality rates.

We estimated the aRR to confirm the relationship between the general characteristics and death of patients with COVID-19 and the effectiveness of vaccination in long term care hospitals. In terms of sex the fatality rate of men (2.74%) was higher than that of women (2.70%), and by age group, the fatality rate was the highest in the group aged ≥ 75 years. However, the differences between sexes and ages were

not statistically significant. Previous study reported that among COVID-19 confirmed cases, men had a higher risk of death than women, and the risk of death from COVID-19 in older people was approximately 1.31 times higher than that in other age groups [13].

In terms of the regional categories, the risk of death was higher in Gyeongsangbuk-do than that in Daegu. Studies conducted in China have shown a sharp increase in the number of infected people in certain regions as the reason for the difference in COVID-19 mortality between regions of the country, which causes a scarcity of medical resources [14]. We also identified continental differences in the mortality rates in previous studies. Studies confirming the relationship between comorbidities and mortality in patients with COVID-19 by geographic location, age, and sex observed the highest prevalence of COVID-19 in the United States, but the severity was the highest in Asia, and mortality was the highest in Europe and Latin America [12]. In addition, a study investigating the impact of the COVID-19 pandemic on excess regional deaths in European countries emphasized the community's large transportation hubs as the cause of excess deaths and proposed the rapid blocking of transportation hubs to prevent further transmission [15]. Gyeongsangbuk-do did not have advanced general hospitals with more than 20 medical subjects, whereas Daegu had five. In addition, cumulatively, there were 62,384 more COVID-19-confirmed patients in Gyeongsangbuk-do than those in Daegu. Our results showed that the medical burden due to the increasing number of confirmed cases has increased in Gyeongsangbuk-do Province [16].

In our study, the fatality rate in the group prescribed Paxlovid was higher than that in the non-prescribed group; however, the difference was not statistically significant. In our study, the direct effect of Paxlovid on death could not be confirmed because the prescription record did not indicate whether the patient was administered Paxlovid. Another study that evaluated the effectiveness and safety of Paxlovid in 163 older patients with an average age of 82 years in 2022 reported that hospitalization periods after Paxlovid treatment were shortened from 15 to 13 days, and virus emission periods were shortened from 20 to 16.5 days. In addition, the group that did not receive Paxlovid tended to require more supportive treatment, such as use of a high-flow nasal cannula, intensive care unit admission, and mechanical ventilation than the group that received it [17]. In a study that evaluated the effectiveness of Paxlovid in 2,241 patients at five long term care hospitals in Korea, the group prescribed Paxlovid had a 51% lower risk of severe disease and death than the group not prescribed [18]. Due to concerns about the side effects of Pax and difficulties in how to take it, medical staff in long-term care facilities tend not to prescribe Pax in advance to prevent critical conditions in COVID-19 confirmed patients. It can be assumed that medical staff use it to prevent death in COVID-19 patients who are already in a critical condition.

The effect of COVID-19 vaccination on death was confirmed to be 80% in the group infected in less than 90 days after 3 doses and 82% in the group infected in less than 90 days after 4 doses, compared with the non-vaccinated group. These results can be the basis for encouraging vaccination among residents of long term care hospitals who are vulnerable to COVID-19 infection and death. A previous meta-analysis evaluating the effect of vaccination on Omicron infections confirmed an effect of 51.1–85.1% on infection and severe disease for Omicron infection in those with tertiary vaccinations (< 90days), and an

effect of 50.3–86.0% in those with quaternary vaccinations (< 90days). In addition, the group comprising patients 3–6 months after the third inoculation showed a 32.8% reduction in mild infections and 88.0% reduction in severe infections. The effect against mild infection decreased compared with that in the group less than three months after inoculation, but the effect against severe infection continued or increased [19]. These results show a similar level of vaccine effect as the results of our study and can be used as evidence to support vaccination efficacy to prevent severe disease in high-risk groups, such as long term care hospitals.

Our study evaluated the relationship between past infection experiences and death; however, there were no deaths among patients once infected in the past, and the mortality rate of confirmed patients reinfected was 21.25%. This result can be referred to evaluate the effects of reinfection on severity and death prevention. A study evaluating the relationship between COVID-19 reinfection and severity risk reported that reinfected patients had a 90% lower risk of severity than once-infected patients [20], whereas another study reported that two out of 209 reinfected patients died, but the difference was not statistically significant [21]. Most of the patients admitted to long-term care hospitals are vulnerable to health, and COVID-19 reinfection is likely to increase their risk of death. The relationship between reinfection and death needs to be further studied for them.

As 92.1% of the participants in our study had underlying diseases, the presence and the number of underlying diseases did not show statistical significance. Previous meta-analyses confirming the prevalence of underlying diseases in patients who died after COVID-19 confirmed that 46% of patients had hypertension; 26%, diabetes; 21%, cardiovascular disease; 11%, lung disease; 8%, COPD; and, 9%, asthma [22, 23].

We estimated the aRR to confirm the relationship between several underlying diseases and death in COVID-19-confirmed patients. The fatality rate in the hypothyroidism group was 8.7% and that in the COPD and asthma group was 7.2%. In our study, the aRR of death in COVID-19-confirmed patients with hypothyroidism was 5.75 (1.10–30.13). Previous studies have reported that the tissue distribution of angiotensin-converting enzyme 2 (ACE-2), which SARS-CoV-2 uses as a cell inlet receptor, is affected by the serum concentration of thyroid hormones, and COVID-19-confirmed patients with hypothyroidism may have a high risk of severe disease and death due to the burden of comorbid diseases [24, 25]. However, a large Danish study reported that patients with COVID-19 treated for hypothyroidism did not have an increased risk of hospitalization and death and that the observed excess risk was mainly caused by comorbidities. However, this Danish study did not perform a causal analysis of the interaction between thyroid dysfunction and treatment, combination of drugs, or co-prescriptions [26]. A large-scale study is needed to evaluate the risk of severe disease and death in patients with hypothyroidism among COVID-19-confirmed patients; our study had limitations in estimating their specific relationship.

Our study confirmed that there was a 2.69 times higher risk of death from COVID-19 in the group with COPD and asthma among confirmed patients compared to the group without it. An Italian study evaluating the association COPD with comorbidities reported that patients with COPD have many

comorbidities, which lead to higher mortality in COVID-19 infections but are not directly related to mortality [27]. However, studies evaluating the impact of COVID-19 on respiratory diseases reported that COVID-19 increases the likelihood of hospitalization in patients with COPD and that patients infected with the virus need more attention and personalized rehabilitation protocols [28]. In patients with COPD and asthma, the effects of the acetylcholine system cause airway contraction, mucus hyperdivision, and aerobic respiratory difficulties due to contractions of the small smooth muscle [29]. Patients with COPD infected with the virus may experience increased systemic inflammation with slow recovery, and high mortality rates have been confirmed in studies using National COVID Cohort Collaboration (N3C) data. [30, 31] This result can be explained by an increase in ACE-2 in bronchial epithelial cells. [32, 33] A meta-analysis systematically reviewed the relationship between mortality and COPD and asthma in patients with COVID-19 and reported a mortality risk approximately 2.29 times higher in patients with COPD than in those without COPD, similar to our result of 2.69 times higher risk, but the mortality difference in patients with asthma was not statistically significant [13]. Other meta-analyses also confirmed that, among patients with COVID-19, asthma did not significantly affect mortality, but patients with COPD had a 3.8-fold increase in mortality risk [34].

Our study has some limitations. First, the patients' underlying disease information was collected from long term care hospitals, but the code information of each disease was not included. Therefore, there was a limit to detailed classification by matching it with the Korean standard disease sign classification information. However, because it was completely classified based on large classification criteria, it was possible to estimate the risk of death due to underlying diseases using a large classification. Second, because the influence of comorbidities on patients could not be evaluated, the types and numbers of underlying diseases were adjusted for. Finally, this study could not adjust for factors such as the number of medical staff at each hospital and the method of medical treatment, which could have affected patient death. However, data were collected from long term care hospitals with similar response levels in Daegu and Gyeongsangbuk-do, and efforts were made to reduce the difference in medical levels that may occur by adjusting the "regional" variable.

The participants of our study were older individuals admitted to long term care hospitals, most of whom had comorbidities. We confirmed the preventive effects of vaccination on death and the association high risk of death with hypothyroidism, COPD, and asthma in COVID-19-confirmed patients in long term care hospitals. In addition, none of the patients who had previously experienced COVID-19 infection once in the past died. These results can be used as a basis for important response strategies to prevent or slow the progression of severe diseases by setting priorities for patient management according to the underlying diseases and vaccination histories of individuals.

Abbreviations

COVID-19 : SARS-CoV-2

WHO : World Health Organization

VOC : Variant of Concern

GISAID : Global Influenza Surveillance and Response System

VET : Vaccine Effectiveness against Transmission

PCR : Polymerase Chain Reaction test (PCR)

RAT : Rapid Antigen Test (RAT)

KDCA : Korea Disease Control and Prevention Agency (KDCA)

cRR : crude Risk Ratio

aRR : adjusted Risk Ratio

CI : Confidence Intervals

Declarations

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AUTHOR CONTRIBUTIONS

Conceptualization: H Park, C Park, MJ Hwang. Data curation: MJ Hwang, H Park, C Park, YK Kim, JS Seong. Formal analysis: H Park, C Park. Funding acquisition: None. Methodology: H Park, T Song. Project administration: H Park, I Seo. Visualization: H Park. Writing – original draft: H Park, C Park, YH Jung, SJ Choi, JS Son, T Park. Writing – review and editing: H Park, C Park, YH Jung, SJ Choi, MJ Hwang, JS Son, T Park, I Seo, YK Kim, JS Seong, T Son.

FUNDING

None.

Availability of data and materials

The datasets are not publicly available. If you have any question about this study, contact the corresponding author(sontaejong@korea.kr)

Ethics approval and consent to participate

Information about all study participants was obtained after obtaining informed consent based on the Infectious Diseases Control and Prevention Act. Our study was performed in accordance with the Declaration of Helsinki and we complied with its relevant guidelines and regulations. The present study was reviewed and approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (2022-10-05-PE-A).

Consent for publication

Not applicable.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare for this study.

Author' information

¹Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency (KDCA), Daegu, Republic of Korea;

²Gyungnsangbuk-do Welfare and health Bureau Infectious Disease Control Division;

⁴Division of Infectious Disease Control, Daegu Metropolitan City Hall, Daegu, Korea;

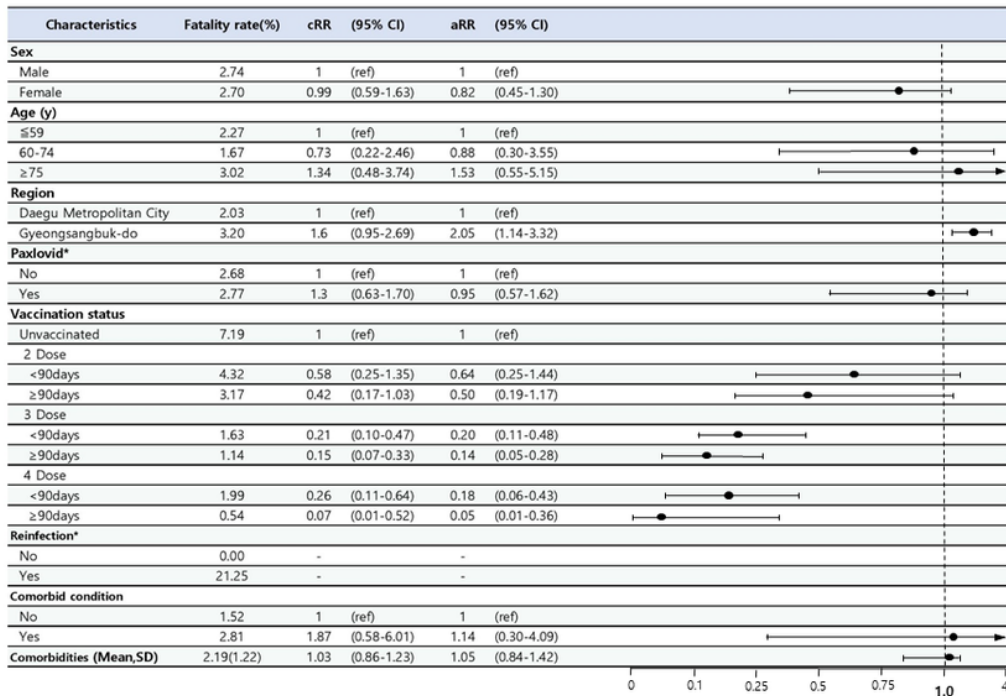
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Figures



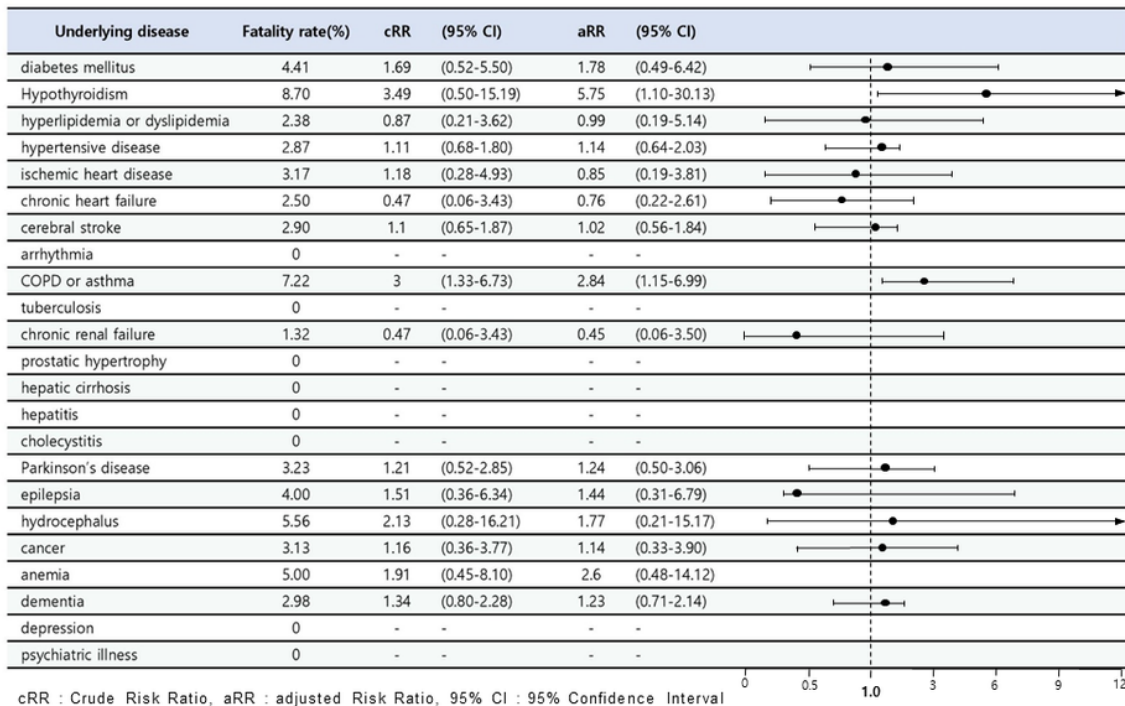
cRR : Crude Risk Ratio, aRR : adjusted Risk Ratio, 95% CI : 95% Confidence Interval

* Adjusted by Sex, Age, Region, Paxlovid, Vaccination status, Reinfection, Underlying disease

Figure 1. The Risk factor of death by general characteristics and vaccine status of patients in 18 long term care hospital, 1 January 2022 ~ 31 August 2022(Period of Omicron variant dominance), Daegu Metropolitan City and Gyeongsangbuk-do of Korea.

Figure 1

See image above for figure legend



cRR : Crude Risk Ratio, aRR : adjusted Risk Ratio, 95% CI : 95% Confidence Interval

* Adjusted by Sex, Age, Region, Paxlovid, Vaccination status, Reinfection, Underlying disease

Figure 2. The Risk factor of death by underlying diseases of patients in 18 long term care hospital, 1 January 2022 ~ 31 August 2022(Period of Omicron variant dominance), Daegu Metropolitan city and Gyeongsangbuk-do of Korea.

Figure 2

See image above for figure legend

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