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Predictors for cause-specific and timing of deaths in patients with COVID-19: a cohort study in Taiwan

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Abstract

Background This cohort study determines the predictors for cause-specific and timing of deaths in patients with COVID-19 in Taiwan.

Methods Patients with laboratory-confirmed COVID-19 admitted to Taipei City Hospital from January 1 to July 31, 2022, were recruited in this cohort. All patients were followed up until death, discharge from the hospital, or August 31, 2022. Early deaths within the first 2 weeks were recorded, and the cause of death was confirmed by the death certificate database of Taiwan. Predictors of cause-specific and timing of deaths of patients with COVID-19 were determined using multinomial Cox proportional hazards regression analysis.

Results Of the 195 (8.0%) patients who died during hospitalization, 147 (84.0%) had COVID-19-specific deaths. Moreover, 54.9% of the deceased patients had early death. After controlling for other covariates, patients aged ≥ 65 years had a higher risk of COVID-19-specific, non-COVID-19-specific, early, and late deaths [adjusted hazards ratio (AHR): 3.85, 6.45, 3.33, and 6.57; 95% confidence interval (CI): 1.91–7.78, 1.17–35.68, 1.51–7.36, and 2.18–19.76, respectively]. Fully vaccinated patients had a lower risk of COVID-19-specific (AHR: 0.68; 95% CI: 0.47–0.98) and early deaths (AHR: 0.54; 95% CI: 0.35–0.84), whereas comorbid patients with chronic obstructive pulmonary disease had a higher risk of non-COVID-19-specific deaths (AHR: 5.43; 95% CI: 1.73–17.03).

Conclusions This study suggests that prioritizing COVID-19 vaccination and carefully monitoring comorbid patients during hospitalization can reduce the risk of COVID-19-specific and early deaths and non-COVID-19-specific mortalities, respectively.

Keywords Cohort study, COVID-19, Mortality, Taiwan

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Background

Since its discovery in January 2020, the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide [1]. By the end of 2022, over 649 million individuals were infected with SARS-CoV-2, resulting in 6.6 million deaths globally [2].

Previous reports showed that male sex [3], presence of diabetes [4], end-stage renal disease [4], cancer [5], and hypertension [4] were associated with a higher risk of mortality in patients with COVID-19. However, previous reports have defined mortality as any death that occurs during treatment, regardless of the cause [3–5]. However, some patients with COVID-19 die from other pre-existing conditions, such as end-stage renal diseases, rather than COVID-19 itself. Moreover, few studies have explored the differences between COVID- and non-COVID-specific mortalities in COVID-19 treatment outcomes. To the best of our knowledge, only one study determined the factors associated with COVID-19- and non-COVID-19-specific deaths in patients infected with SARS-CoV-2 [6]. The study, including 1283 patients from March through December 2020 in the US, found that being non-Hispanic Black and having a history of chronic health condition were significantly associated with COVID-19-specific deaths [6]. However, this previous study examining the factors associated with COVID-19- and non-COVID-19-specific deaths had the potential misclassification of confirmed COVID-19-specific deaths because of limited COVID-19 testing availability in the early pandemic in 2020 [6].

Approximately 81% of patients with COVID-19 experience mild symptoms and have a lower risk of mortality [7, 8]; however, hospitalized patients with COVID-19 can develop severe complications (e.g., acute respiratory distress syndrome) and have higher mortality rates [9]. A previous study in China found that the median time from hospitalization to acute respiratory distress syndrome was 2 days [10]. Another prospective study in France showed that the median time from intensive care unit (ICU) admission to death was 14 days in patients with COVID-19 [11]. Moreover, the timing of death in infectious patients varied according to comorbidities and severity of illness [11]. However, few studies have determined the predictors of mortality with respect to the timing of death in patients with COVID-19. Therefore, this cohort study aimed to determine the predictors for cause-specific and timing of deaths in hospitalized patients infected with SARS-CoV-2 in Taiwan.

Methods

Background information

In Taiwan, COVID-19 is a reported infectious disease during the pandemic. Healthcare institutes in Taiwan are required to report a new COVID-19 case to the Taiwan CDC within 24 h through an Internet-based notification system. Patients infected with SARS-CoV-2 in Taiwan must be admitted to the designated COVID-19 hospitals for further treatment [12].

The Taipei City Hospital (TCH) is the largest designated healthcare institute that accommodates patients diagnosed with COVID-19 in northern Taiwan. Patients infected with SARS-CoV-2 admitted to the TCH are cared for by a designated healthcare professional team.

Study participants

This cohort study consecutively recruited 2,518 patients diagnosed with COVID-19 who were admitted to the TCH between January 1, 2022, and July 31, 2022. The diagnosis of COVID-19 was confirmed by a positive real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test. All patients with COVID-19 were followed up until death or discharge from the hospital, whichever applied to the patient. This study linked the TCH COVID-19 dataset to the death certificate database of Taiwan [13] to determine the cause of death for the study participants. In Taiwan, when a patient dies, it is regulated by the law that the patient's death certificate must be issued and registered by the physician in charge according to the International Classification of Diseases (ICD) 9 or 10. Trained medical registrars review and code all death certificates at the central office of the National Death Certification Registry. Therefore, the cause-of-death coding in Taiwan has been considered very accurate [13].

The Institutional Review Board of TCH (no. TCH-IRB-10904014-E) approved the study protocol. The requirement for informed consent was also waived by the Institutional Review Board of TCH (no. TCHIRB-10904014-E). All related procedures were performed in accordance with the relevant national and institutional guidelines and along with those stipulated in the Declaration of Helsinki.

Outcome variables

The outcome variable of interest was treatment outcome, which was categorized as successful treatment or mortality. Mortality was classified as COVID-19-specific and non-COVID-19-specific deaths, as determined by the death certificate database of Taiwan [13]. Additionally, mortality among study participants was classified as early or late death based on the timing of death. A prior prospective study showed that the median time from ICU hospitalization to death was 14 days in patients with COVID-19 [11]. In our cohort study, early death was defined as occurring within the first two weeks of hospitalization, while late death was defined as occurring more than two weeks after hospitalization.

Covariates

The covariates entered in the core analyses included sociodemographic characteristics, comorbidities, COVID-19 vaccination status, COVID-19 severity, mode of oxygen therapy, and treatment regimens. The sociodemographic characteristics included age and sex. Comorbidities at the time of COVID-19 admission, including cancer, heart failure, diabetes, end-stage renal disease, and chronic obstructive pulmonary disease, were collected. The COVID-19 vaccination status in study subjects was classified into unvaccinated, vaccinated with a single dose, and fully vaccinated (at least two doses of vaccination). COVID-19 severity was classified as mild, moderate, or severe [14]. Mild COVID-19 symptoms were defined as the presence of fever, cough, and other non-specific symptoms without evidence of pneumonia. Moderate COVID-19 symptoms were defined as the presence of pneumonia, requiring supplemental oxygen but not reaching severe status. Severe COVID-19 symptoms were defined as the presence of pneumonia, requiring supplemental oxygen, along with at least one of the following conditions: acute respiratory distress syndrome, septic shock, or the need for intensive care unit admission. The mode of oxygen therapy included high-flow nasal oxygen, BiPAP (bilevel positive airway pressure) ventilation, and mechanical ventilation. Treatment regimens for COVID-19 disease included tocilizumab, Paxlovid, Molnupiravir, and dexamethasone therapy.

Statistical analyses

First, the demographic data of the study participants were analyzed. Continuous data are presented as mean (standard deviation [SD]), and one-way analysis of variance (ANOVA) was used for intergroup comparisons. Categorical data were analyzed using Pearson's χ^2 test, as appropriate.

This study assessed the crude associations of factors associated with mortality by computing hazard ratios (HR) and the corresponding 95% confidence intervals (CI). We then used a multivariate analysis to identify the factors associated with mortality among patients with COVID-19 after adjusting for demographics, comorbidities, COVID-19 severity, mode of oxygen therapy, and treatment regimens. Furthermore, we used a multinomial Cox proportional hazards regression to identify the factors associated with cause-specific mortality (e.g., COVID-19- and non-COVID-19-specific mortalities) and timing of death (e.g., early and late death), respectively. Adjusted HRs (AHRs) with 95% CIs are reported to indicate the strength and direction of the association. All data management and analyses were performed using SAS 9.4 statistical software package (SAS Institute, Cary, NC, USA).

Results

Participant selection

This cohort study included 2,518 SARS-CoV-2 infected patients admitted to the Taipei City Hospital between January 1, 2022 and July 31, 2022. After excluding those aged < 18 years ($n = 322$), the remaining 2,196 patients were included in the analysis (Fig. 1). The overall mean (SD) age was 62.3 (22.9) years; 53.8% of the patients were men, and 8.0% died during hospitalization. Of the 175 patients who died with COVID-19, 147 (84.0%) had COVID-19-specific deaths, while 28 (16.0%) had non-COVID-19-specific deaths. Among the 28 non-COVID-19-specific deaths, 9 (32.1%) were attributed to cardiovascular diseases, 4 (14.3%) to malignancies, and 2 (7.1%) to septic shock. Moreover, 54.9% and 45.1% of the deceased patients with COVID-19 died within the first 2 weeks and later than 2 weeks after hospitalization, respectively.

Characteristics of patients according to age group

Table 1 shows patient characteristics based on age group. Patients aged ≥ 65 years had a higher proportion of comorbidities and were more likely to be fully vaccinated than those aged 18–64 years. Additionally, the proportion of patients receiving oxygen treatment, including high-flow nasal oxygen, BiPAP ventilation, and mechanical ventilation, was higher in the ≥ 65-age group than that in the 18–64-age group.

Factors associated with mortality in patients with COVID-19

Table 2 shows the univariate and multivariate analyses of factors associated with mortality in patients with COVID-19 during hospitalization. After controlling for demographics, comorbidities, COVID-19 severity, mode of oxygen treatment, and treatment regimens, risk factors for mortality included age ≥ 65 years (AHR = 4.03; 95% CI: 2.21–7.34), cancer (AHR = 2.20; 95% CI: 1.37–3.54), moderate (AHR = 1.82; 95% CI: 1.03–3.20) and severe COVID-19 infection (AHR = 2.64; 95% CI: 1.30–5.32) (mild COVID-19 infection: reference), and receiving dexamethasone treatment (AHR = 2.03; 95% CI: 1.40–2.94).

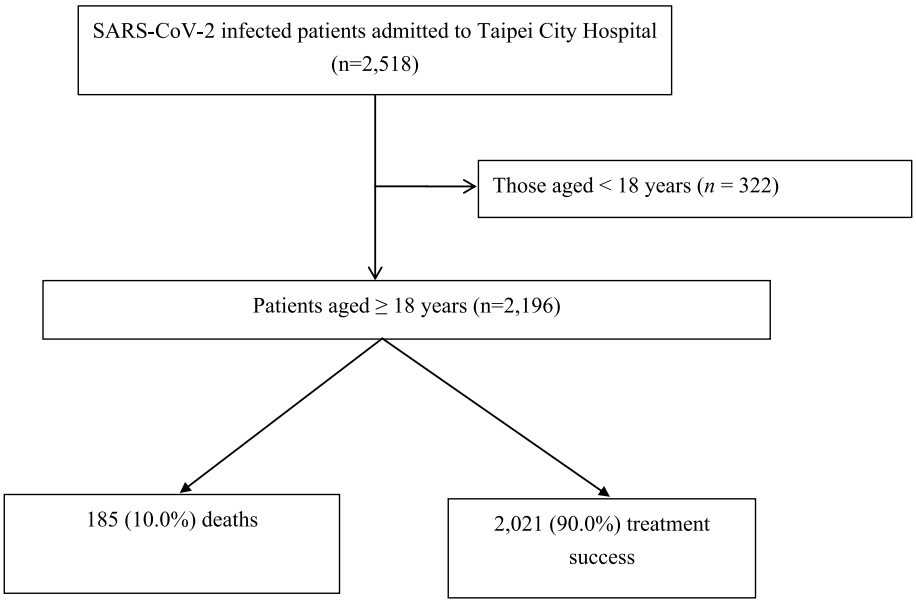

Fig. 1 Flow diagram for the selection of the study population

Factors associated with COVID-19- and non-COVID-19-specific mortalities

We used multinomial Cox regression analysis to determine the risk factors associated with COVID-19- and non-COVID-19-specific mortalities in infectious patients. After adjusting for other covariates, age ≥ 65 years was associated with a higher risk of COVID-19-specific (AHR = 3.85; 95% CI: 1.91–7.78) and non-COVID-19-specific (AHR = 6.45; 95% CI: 1.17–35.68) deaths (Table 3). Moreover, fully vaccinated patients (AHR = 0.68; 95% CI: 0.47–0.98) had a lower risk of COVID-19-specific death than unvaccinated patients. Furthermore, comorbid patients with chronic obstructive pulmonary disease had a higher risk of non-COVID-19-specific deaths (AHR = 5.43; 95% CI: 1.73–17.03).

Predictors of early and late death in COVID-19 patients

A multinomial Cox proportional hazards model was conducted to determine the risk factors associated with early and late mortality in patients with COVID-19. After adjusting for potential confounders, age ≥ 65 years was associated with a higher risk of early (AHR = 3.33; 95% CI: 1.51–7.36) and late deaths (AHR = 6.57; 95% CI: 2.18–19.76). Moreover, fully vaccinated patients had a lower risk of early death (AHR = 0.54; 95% CI: 0.35–0.84), while comorbid patients with cerebrovascular disease had a higher risk of late mortality (AHR = 2.43; 95% CI: 1.38–4.25) (Table 4).

Discussion

This cohort study found that the mortality rate was 8.0% among hospitalized COVID-19 patients. Of all deceased patients, 147 (84.0%) had COVID-19-specific deaths, and 96 (54.9%) died within the first 2 weeks of hospitalization. After controlling for demographics, comorbidities, COVID-19 severity, and treatment regimens, age ≥ 65 years was associated with a higher risk of COVID-19-specific, non-COVID-19-specific, early, and late deaths. Moreover, fully vaccinated patients had a lower risk of COVID-19-specific and early deaths, whereas comorbid patients with chronic obstructive pulmonary disease had a higher risk of non-COVID-19-specific deaths.

This study found that the mortality rate among hospitalized patients with COVID-19 in 2022 was 8.0%, which is lower than the 11.1% and 12.0% rates observed in the US [9] and UK [15], respectively, in 2020. The lower mortality rate in our cohort in 2022 may be attributed to the implementation of vaccination programs [16] and improvements in COVID-19 management from 2020 through 2022 [17, 18]. Although 81% of patients with COVID-19 did not require hospitalization due to mild symptoms and low death rate [7], the mortality risk in hospitalized patients with COVID-19 was high [9, 15]. Our study findings suggest that hospitalized patients

Table 1 Characteristics of the patients according to age group

Characteristics	Number (%) of patients[a]			*P*-value
	Total, $n=2,196$	Aged 18–64 years, $n=971$	Aged ≥ 65 years, $n=1,225$	
Demographics				
Sex				
Female	1015 (46.2)	457 (47.1)	558 (45.6)	0.48
Male	1181 (53.8)	514 (52.9)	667 (54.4)	
Vaccination Status				
Unvaccinated	751 (34.2)	359 (37.0)	392 (32.0)	0.011
Vaccinated with a single dose	169 (7.7)	61 (6.3)	108 (8.8)	
Fully vaccinated	1276 (58.1)	551 (56.7)	725 (59.2)	
Comorbidities				
Cancer	66 (3.0)	10 (1.0)	56 (4.6)	< .001
Heart failure	287 (13.1)	37 (3.8)	250 (20.4)	< .001
Diabetes	403 (18.4)	70 (7.2)	333 (27.2)	< .001
End-stage of renal disease	200 (9.1)	37 (3.8)	163 (13.3)	< .001
Chronic obstructive pulmonary disease	120 (5.5)	9 (0.9)	111 (9.1)	< .001
Categorization of COVID-19 severity				
Mild	1080 (49.2)	687 (70.7)	393 (32.0)	< .001
Moderate	970 (44.2)	254 (26.2)	716 (58.5)	
Severe	146 (6.7)	30 (3.1)	116 (9.5)	
Mode of oxygen treatment				
High-flow nasal oxygen				
No	2151 (98.0)	965 (99.4)	1186 (96.8)	< .001
Yes	45 (2.1)	6 (0.6)	39 (3.2)	
BiPAP Ventilation				
No	2179 (99.2)	969 (99.8)	1210 (98.8)	0.007
Yes	17 (0.8)	2 (0.2)	15 (1.2)	
Mechanical ventilation				
No	2147 (97.8)	959 (98.8)	1188 (97.0)	0.005
Yes	49 (2.2)	12 (1.2)	37 (3.0)	
Treatment regimens				
Tocilizumab				
No	2129 (97.0)	961 (99.0)	1168 (95.4)	< .001
Yes	67 (3.0)	10 (1.0)	57 (4.6)	
Paxlovid				
No	1976 (90.0)	928 (95.6)	1048 (85.6)	< .001
Yes	220 (10.0)	43 (4.4)	177 (14.4)	
Molnupiravir				
No	1946 (88.6)	929 (95.7)	1017 (83.0)	< .001
Yes	250 (11.4)	42 (4.3)	208 (17.0)	
Dexamethasone				
No	1624 (74.0)	873 (89.9)	751 (61.3)	< .001
Yes	572 (26.1)	98 (10.1)	474 (38.7)	
Cause-specific mortality				
COVID-19-specific death	147 (6.7)	11 (1.1)	136 (11.1)	< .001
Non-COVID-19-specific death	28 (1.3)	2 (0.2)	26 (2.1)	
Timing of death				
Early death	96 (4.4)	10 (1.0)	86 (7.0)	< .001
Late death	79 (3.6)	3 (0.3)	76 (6.2)	

COVID-19 coronavirus disease 2019, *SD* standard deviation, *BiPAP* bilevel positive airway pressure

[a] Unless stated otherwise

Table 2 Factors associated with mortality among patients with COVID-19 based on univariate and multivariate analyses

Variables	Number of patients	Death during hospitalization	Univariate	Multivariate analysis
		n (%)	HR (95%CI)	AHR (95%CI)
Demographics				
Age, years				
18–64	971	13 (1.3)		1
≥ 65	1225	162 (13.2)	6.55 (3.71–11.56)***	4.03 (2.21–7.34)***
Sex				
Female	1015	78 (7.7)		1
Male	1181	97 (8.2)	0.91 (0.68–1.23)	0.81 (0.59–1.10)
Vaccination Status				
Unvaccinated	751	83 (11.1)		1
Vaccinated with a single dose	169	15 (8.9)	0.90 (0.52–1.56)	0.89 (0.51–1.57)
Fully vaccinated	1276	77 (6.0)	0.67 (0.49–0.92)*	0.76 (0.55–1.06)
Comorbidities				
Cancer				
No	2130	153 (7.2)		
Yes	66	22 (33.3)	2.08 (1.31–3.33)**	2.20 (1.37–3.54)**
Heart failure				
No	1909	132 (6.9)		
Yes	287	43 (15.0)	1.49 (1.05–2.12)*	1.20 (0.82–1.74)
Diabetes				
No	1793	128 (7.1)		
Yes	403	47 (11.7)	1.20 (0.85–1.68)	0.89 (0.62–1.27)
End-stage of renal disease				
No	1996	147 (7.4)		
Yes	200	28 (14.0)	1.44 (0.96–2.16)	1.08 (0.69–1.68)
Chronic obstructive pulmonary disease				
No	2076	153 (7.4)		
Yes	120	22 (18.3)	1.57 (1.00–2.47)*	1.03 (0.63–1.69)
Categorization of COVID-19 severity				
Mild	1080	17 (1.6)	1	1
Moderate	970	107 (11.0)	4.07 (2.42–6.85)***	1.82 (1.03–3.20)*
Severe	146	51 (34.9)	8.63 (4.90–5.21)***	2.64 (1.30–5.32)**
Mode of oxygen treatment				
High-flow nasal oxygen				
No	2151	158 (7.4)	1	
Yes	45	17 (37.8)	2.97 (1.79–4.94)***	1.23 (0.65–2.30)
BiPAP Ventilation				
No	2179	166 (7.6)		
Yes	17	9 (52.9)	2.08 (1.04–4.13)*	0.93 (0.44–1.97)
Mechanical ventilation				
No	2147	151 (7.0)		
Yes	49	24 (49.0)	2.38 (1.51–3.74)***	1.28 (0.73–2.23)
Treatment regimens				
Tocilizumab				
No	2129	151 (7.1)	1	
Yes	67	24 (35.8)	2.87 (1.85–4.44)***	1.58 (0.98–2.57)
Paxlovid				
No	1976	164 (8.3)		
Yes	220	11 (5.0)	0.69 (0.38–1.27)	0.69 (0.37–1.30)

Table 2 (continued)

Variables	Number of patients	Death during hospitalization	Univariate	Multivariate analysis
		n (%)	HR (95%CI)	AHR (95%CI)
Molnupiravir				
No	1946	154 (7.9)		
Yes	250	21 (8.4)	0.90 (0.57–1.43)	0.82 (0.50–1.33)
Dexamethasone				
No	1624	53 (3.3)		
Yes	572	122 (21.3)	3.80 (2.72–5.32)***	2.03 (1.40–2.94)***

COVID-19 coronavirus disease 2019, *AHR* adjusted hazard ratio, *CI* confidence interval, *BiPAP* bilevel positive airway pressure

* < .05; ** < .01; *** < .001

with COVID-19 require close monitoring and careful treatment during hospitalization.

This study showed that age ≥ 65 years was associated with a higher risk of COVID-19-specific, non-COVID-19-specific, early, and late deaths. The age-associated decline of adaptive immunity against SARS-CoV-2 may account for the high mortality in older patients with COVID-19. A previous study found that aging was associated with defects in B- and T-cell immunity [19], which could inhibit the control of viral replication and may lead to high mortality in patients with COVID-19 [19]. Another study found that older macaques inoculated with SARS-CoV had stronger innate immune responses to infection than those of younger adults, which caused an increase in the differential expression of genes associated with inflammation and severe illness [20]. Since older age was related to a higher risk of death in infectious patients, the findings of our report suggest that older adults should be prioritized in the implementation of preventive measures.

In the present study, we observed that full vaccination reduced the risk of COVID-19-specific mortality by 32% and early mortality by 46%. During the pandemic, the Taiwanese government encouraged individuals to receive at least two doses of the COVID-19 vaccine to achieve sufficient immunity against SARS-CoV-2 infection [21]. As of December 1, 2022, 88% of the Taiwanese population had received at least two doses of COVID-19 vaccines [21]. Vaccines are the most important strategy for preventing SARS-CoV-2 infection [22, 23]. Moreover, COVID-19 vaccines can elicit immune responses and induce the production of neutralizing antibodies [24], which could reduce the severity of infection. In our cohort, 34.1% of patients with COVID-19 were unvaccinated, which accounted for 69 (46.9%) COVID-19-specific and 47 (49.0%) early deaths. As unvaccinated patients have a higher risk of mortality [25], the findings of our study suggest that vaccination is imperative in reducing COVID-19-specific mortalities.

This cohort study found that, of all deceased patients infected with SARS-CoV-2, 84.0% had COVID-19-specific deaths, and 54.9% died within the first 2 weeks of hospitalization. Nonetheless, several limitations should be considered when interpreting the findings of this cohort study. First, important factors such as the severity and duration of existing comorbidities, obesity, and the interval between individuals' vaccination and COVID-19 infection, which may be associated with patient mortality, were not collected in this study. Second, this study only included patients with COVID-19 during the implementation of vaccine programs in 2022. Future studies are required to determine the predictors of cause-specific mortality and the timing of deaths in patients with COVID-19 before the implementation of vaccine programs. Third, the COVID-19 reinfection rate in Taiwan was approximately 0.1% in 2022 [26]. However, data on the reinfection status of our study participants are not available. Finally, since all study participants were Taiwanese, the external validity of our findings may be a concern. Therefore, the generalizability of our findings to other non-Asian ethnic groups needs further verification.

Conclusion

This cohort study found that, of all deceased patients infected with SARS-CoV-2, 84.0% had COVID-19-specific, and 54.9% died within the first 2 weeks of hospitalization. After controlling for demographics, comorbidities, COVID-19 severity, and treatment regimens, age ≥ 65 years was associated with a higher risk of COVID-19-specific, non-COVID-19-specific, early, and late deaths. Moreover, fully vaccinated patients had a lower risk of COVID-19-specific and early deaths, whereas comorbid patients with chronic obstructive pulmonary disease had a higher

Table 3 Multinomial regression analysis of risk factors of COVID-19-specific and non-COVID-19-specific deaths[s]

Factors	COVID-19-specific deaths		Non-COVID-19-specific deaths	
	AHR (95% CI)	***P* value**	**AHR (95% CI)**	***P* value**
Demographics				
Age, years				
18–64	1		1	
≥ 65	3.85 (1.91–7.78)	< .001	6.45 (1.17–35.68)	0.033
Sex				
Female	1		1	
Male	0.74 (0.53–1.03)	0.077	1.06 (0.41–2.77)	0.901
Vaccination Status				
Unvaccinated	1		1	
Vaccinated with a single dose	0.82 (0.43–1.54)	0.535	2.10 (0.46–9.65)	0.340
Fully vaccinated	0.68 (0.47–0.98)	0.04	1.79 (0.63–5.11)	0.275
Comorbidities				
Cancer	2.11 (1.24–3.57)	0.006	2.29 (0.75–6.98)	0.145
Heart failure	1.24 (0.82–1.89)	0.313	0.43 (0.15–1.22)	0.112
Diabetes	0.94 (0.62–1.40)	0.744	0.42 (0.11–1.55)	0.192
End-stage of renal disease	0.93 (0.56–1.55)	0.773	3.50 (0.77–15.82)	0.104
Chronic obstructive pulmonary disease	0.88 (0.48–1.61)	0.678	5.43 (1.73–17.03)	0.004
Categorization of COVID-19 severity				
Mild	1		1	
Moderate	4.01 (1.68–9.55)	0.002	0.15 (0.04–0.58)	0.006
Severe	2.11 (1.07–4.17)	0.031	0.53 (0.12–2.34)	0.405
Oxygen treatment				
High-flow nasal oxygen				
No	1		1	
Yes	1.01 (0.50–2.03)	0.978	4.94 (0.65–37.58)	0.123
BiPAP Ventilation				
No	1		1	
Yes	1.11 (0.51–2.40)	0.797	0.40 (0.10–1.60)	0.196
Mechanical ventilation				
No	1		1	
Yes	1.36 (0.74–2.53)	0.326	0.58 (0.16–2.11)	0.410
Treatment regimens				
Tocilizumab				
No	1		1	
Yes	1.54 (0.91–2.60)	0.106	2.36 (0.53–10.39)	0.258
Paxlovid				
No	1		1	
Yes	0.59 (0.30–1.19)	0.141	1.63 (0.45–5.97)	0.458
Molnupiravir				
No	1		1	
Yes	0.79 (0.46–1.38)	0.414	1.34 (0.29–6.35)	0.709
Dexamethasone				
No	1		1	
Yes	2.09 (1.32–3.31)	0.002	1.52 (0.53–4.32)	0.433

COVID-19 Coronavirus disease 2019, *AHR* adjusted hazard ratio, *CI* confidence interval, *BiPAP* bilevel positive airway pressure

[a] Successfully treated COVID-19 patients were used as the reference

Table 4 Multinomial regression analysis of risk factors of early and late mortality in patients with COVID-19[a]

Factors	Early deaths		Late deaths	
	AHR (95% CI)	*P* value	AHR (95% CI)	*P* value
Demographics				
Age, years				
18–64	1		1	
≥ 65	3.33 (1.51–7.36)	0.003	6.57 (2.18–19.76)	0.001
Sex				
Female	1		1	
Male	0.74 (0.49–1.13)	0.168	0.80 (0.49–1.30)	0.362
Vaccination status				
Unvaccinated	1		1	
Vaccinated with a single dose	0.68 (0.31–1.48)	0.325	1.31 (0.53–3.21)	0.561
Fully vaccinated	0.54 (0.35–0.84)	0.006	1.37 (0.81–2.32)	0.247
Comorbidities				
Cancer	1.77 (0.84–3.75)	0.136	2.43 (1.38–4.25)	0.002
Heart failure	1.07 (0.61–1.89)	0.806	1.28 (0.76–2.16)	0.346
Diabetes	1.00 (0.61–1.63)	0.997	0.65 (0.36–1.19)	0.162
End-stage of renal disease	0.93 (0.50–1.73)	0.816	1.39 (0.66–2.95)	0.388
Chronic obstructive pulmonary disease	1.04 (0.52–2.08)	0.922	1.02 (0.46–2.27)	0.960
Categorization of COVID-19 severity				
Mild	1		1	
Moderate	4.44 (1.58–12.43)	0.005	1.28 (0.39–4.21)	0.683
Severe	1.93 (0.90–4.11)	0.091	1.47 (0.56–3.84)	0.431
Oxygen treatment				
High-flow nasal oxygen				
No	1		1	
Yes	1.18 (0.48–2.92)	0.720	1.33 (0.50–3.54)	0.572
BiPAP Ventilation				
No	1		1	
Yes	0.22 (0.03–1.74)	0.151	1.91 (0.77–4.72)	0.164
Mechanical ventilation				
No	1		1	
Yes	1.52 (0.70–3.33)	0.292	1.04 (0.44–2.50)	0.924
Treatment regimens				
Tocilizumab				
No	1		1	
Yes	1.36 (0.71–2.63)	0.354	1.66 (0.81–3.40)	0.167
Paxlovid				
No	1		1	
Yes	0.40 (0.14–1.17)	0.094	1.16 (0.53–2.50)	0.713
Molnupiravir				
No	1		1	
Yes	0.89 (0.43–1.84)	0.754	0.85 (0.42–1.72)	0.649
Dexamethasone				
No	1		1	
Yes	2.15 (1.19–3.88)	0.011	2.03 (1.15–3.57)	0.015

COVID-19 coronavirus disease 2019, *AHR* adjusted hazard ratio, *CI* confidence interval, *BiPAP* bilevel positive airway pressure

[a] Successfully treated COVID-19 patients were used as the reference

risk of non-COVID-19-specific deaths. The findings of our study suggest that the provision of COVID-19 vaccination is imperative to reduce SARS-CoV-2-specific and early deaths, and comorbid patients with COVID-19 require close monitoring and careful treatment during hospitalization to reduce the non-COVID-19-specific mortalities.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ICU	Intensive care unit
TCH	Taipei City Hospital
RT-PCR	Real-time reverse transcription-polymerase chain reaction
SD	Standard deviation
ORs	Odds ratios
Cis	Confidence intervals

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Authors' contributions
Y.F.Y, S.Y.C, Y.J.L, C.C.C, and M.J.C. conceived and designed the study; Y.F.Y, S.Y.C, Y.J.L, M.Y.Y, C.C.C, and M.J.C. analyzed and interpreted the data. All authors contributed to drafting the manuscript and revising it critically for important intellectual content, and read and approved the final version.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Taipei City Hospital (no. TCHIRB-10904014-E). Formal consent is waived for this type of study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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References

1. Hiscott J, Alexandridi M, Muscolini M, Tassone E, Palermo E, Soultsioti M, Zevini A. The global impact of the coronavirus pandemic. Cytokine Growth Factor Rev. 2020;53:1–9.
2. World Health Organization: Coronavirus disease (COVID-19) Pandemic. https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update---21-december-2022. Accessed 16 July 2023.
3. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities. Cardiovasc Res. 2020;116(14):2197–206.
4. Peña JE, Rascón-Pacheco RA, Ascencio-Montiel IJ, González-Figueroa E, Fernández-Gárate JE, Medina-Gómez OS, Borja-Bustamante P, Santillán-Oropeza JA, Borja-Aburto VH. Hypertension, diabetes and obesity, major risk factors for death in patients with COVID-19 in Mexico. Arch Med Res. 2021;52(4):443–9.
5. Meng Y, Lu W, Guo E, Liu J, Yang B, Wu P, Lin S, Peng T, Fu Y, Li F, et al. Cancer history is an independent risk factor for mortality in hospitalized COVID-19 patients: a propensity score-matched analysis. J Hematol Oncol. 2020;13(1):75.
6. Yung J, Li J, Kehm RD, Cone JE, Parton H, Huynh M, Farfel MR. COVID-19-Specific Mortality among World Trade Center Health Registry Enrollees Who Resided in New York City. Int J Environ Res Public Health. 2022;19(21):14348.
7. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42.
8. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141–54.
9. Finelli L, Gupta V, Petigara T, Yu K, Bauer KA, Puzniak LA. Mortality among US patients hospitalized with SARS-CoV-2 infection in 2020. JAMA Netw Open. 2021;4(4):e216556.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497–506.
11. de Roquetaillade C, Bredin S, Lascarrou JB, Soumagne T, Cojocaru M, Chousterman BG, Leclerc M, Gouhier A, Piton G, Pène F, et al. Timing and causes of death in severe COVID-19 patients. Crit Care (London, England). 2021;25(1):224.
12. Taiwan Centers for Disease Control and Prevention. [Surveillance of COVID-19]. https://www.cdc.gov.tw/En. Accessed 29 Apr 2020.
13. Lu TH, Lee MC, Chou MC. Accuracy of cause-of-death coding in Taiwan: types of miscoding and effects on mortality statistics. Int J Epidemiol. 2000;29(2):336–43.
14. Taiwan Centers for Disease Control and Prevention: Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). https://www.cdc.gov.tw/Category/Page/xCSwc5oznwcqunujPcqmQ. Accessed 21 Mar 2023.
15. Gray WK, Navaratnam AV, Day J, Wendon J, Briggs TWR. Changes in COVID-19 in-hospital mortality in hospitalised adults in England over the first seven months of the pandemic: an observational study using administrative data. Lancet Reg Health Eur. 2021;5:100104.
16. Rahmani K, Shavaleh R, Forouhi M, Disfani HF, Kamandi M, Oskooi RK, Foogerdi M, Soltani M, Rahchamani M, Mohaddespour M, et al. The effectiveness of COVID-19 vaccines in reducing the incidence, hospitalization, and mortality from COVID-19: a systematic review and meta-analysis. Front Public Health. 2022;10:873596.
17. Mølhave M, Agergaard J, Wejse C. Clinical management of COVID-19 patients - an update. Semin Nucl Med. 2022;52(1):4–10.
18. Kabir MA, Ahmed R, Chowdhury R, Iqbal SMA, Paulmurugan R, Demirci U, Asghar W. Management of COVID-19: current status and future prospects. Microbes Infect. 2021;23(4–5):104832.
19. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis. 2005;41(Suppl 7):S504-512.
20. Smits SL, de Lang A, van den Brand JM, Leijten LM, van IWF, Eijkemans MJ, van Amerongen G, Kuiken T, Andeweg AC, Osterhaus AD, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS pathogens. 2010;6(2):e1000756.
21 Sheng WH, Hsieh SM, Chang SC. Achievements of COVID-19 vaccination programs: Taiwanese perspective. J Formos Med Assoc. 2024;123(Suppl 1):S70-s76.

22. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis. 2022;22(9):1293–302.
23. Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. Int J Infect Dis. 2022;114:252–60.
24. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol. 2021;21(8):475–84.
25. Berrino F, Donzelli A, Bellavite P, Malatesta G. COVID-19 vaccination and all-cause and non-COVID-19 mortality. A revaluation of a study carried out in an Italian Province. Epidemiologia e prevenzione. 2023;47(6):374–8.
26. Chen YH, Cheuh YN, Chen CM, Kuo HW. Epidemiological characteristics of the three waves of COVID-19 epidemic in Taiwan during April 2022 to March 2023. J Formos Med Assoc. 2023;122(11):1174–82.

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