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Original Article

Risk factors and mortality of SARS-CoV-2 reinfection during the Omicron era in Taiwan: A nationwide population-based cohort study

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KEYWORDS
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Abstract *Background:* Prior to 2022, Taiwan had effectively contained the domestic COVID-19 epidemic. However, during 2022, the country encountered multiple large outbreaks of COVID-19, with patients experiencing their first or second infection (reinfection) were both predominantly caused by the Omicron variant. Data are lacking on the risk factors and mortality of COVID-19 reinfection in Omicron era.

Methods: In this retrospective population-based cohort study, we recruited COVID-19 patients with their first episode confirmed between April 1, 2022 and June 11, 2022. A reinfection patient was defined as an individual who infected again by SARS-CoV-2 with an interval of more than 90 days. Demographic characteristics, severity of underlying diseases, and vaccination status were adjusted to identify risk factors for reinfection and to further evaluate the hazard of all-cause mortality within 30 days between reinfection and non-reinfection patients.

Results: There were 28,588 reinfection patients matched with 142,940 non-reinfection patients included in this study. We found that being female, younger in age, having more severe underlying diseases, and not being fully vaccinated against COVID-19 were risk factors for reinfection. After adjusting for confounding factors, reinfection patients were at a significantly higher risk of all-cause mortality within 30 days (aHR = 4.29, 95% CI: 3.00—6.12, $p < 0.001$) comparing with non-reinfection patients.

Conclusion: During the SARS-CoV-2 Omicron era, reinfection patients were observed to have an increased risk of all-cause mortality. To reduce the disease burden and minimize the risk of reinfection, it is crucial for vulnerable patients to receive full vaccination and adhere to recommended precautions.

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Introduction

Since the emergence of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the global pandemic has resulted in nearly 750 million reported cases and 6.8 million deaths by the end of 2022.[1]

During 2020—2021, Taiwan effectively contained the domestic epidemic of COVID-19, with only sporadic cases and small-scale outbreaks reported.[2,3] However, in 2022, after the introduction of the SARS-CoV-2 Omicron variant, the epidemic began to spread rapidly and extensively. During May and September, the county encountered two large waves of outbreak, dominant by Omicron BA.2 and Omicron BA.5, respectively. These two waves lasted for about eight months and caused nearly 8.4 million of people (35.7% of the population) being reported with COVID-19 infection.[2,4] In most countries across the world, however, they have experienced multiple waves of COVID-19 since 2020, and people experiencing COVID-19 reinfection were not uncommon. In comparison to other regions, Taiwan's experience was relatively unique in that the majority of COVID-19 cases were concentrated within a single year, and patients with both first and second infections predominantly occurred during the Omicron era.

Furthermore, the severity of COVID-19 reinfection has been a subject of debate in previous studies, with no clear consensus.[5] Some studies suggested that individuals who got COVID-19 infection again may experience milder symptoms and lower mortality,[6—9] while others reported an increased risk of mortality and hospitalization.[10] This inconsistent results underscore the importance of investigating the characteristics of COVID-19 reinfection, and further estimate the disease burden as well as facilitate adequate mitigating policies.

In this study, we aim to identify the risk factors and mortality associated with COVID-19 reinfections in a population level during Omicron era in Taiwan.

Methods

Study design

We conducted a retrospective population-based cohort study. A COVID-19 patients was defined as a person with laboratory confirmation of SARS-CoV-2 infection by RT-PCR or diagnosed with positive result of rapid antigen test.[11] For symptomatic COVID-19 patients, index date was defined as the date of symptoms onset, and for asymptomatic or symptomatic cases with missing onset date, it was the notification receiving date of public health authority. We recruited COVID-19 cases with their first infection episode confirmed between April 1 and June 11, 2022, and excluded patients who were non-citizen, imported cases, died before their index date, children under the age of seven (due to the vaccine campaign for this group started from July 21, 2022, in Taiwan[12]), immunocompromised patients, lacked National Health Insurance data, or reinfection within 90 days. Reinfection and non-reinfection patients were matched on a 1:5 ratio by index date, with random selection. The outcome was all-cause mortality within 30 days, followed until November 30, 2022.

COVID-19 reinfection

The CECC defined COVID-19 reinfection based on two scenarios. The first scenario involves patients with a positive RT-PCR/rapid antigen test with worsened symptoms within 90 days of the initial infection, confirmed by a medical professional. The second scenario includes patients with a positive RT-PCR/rapid antigen test occurred more than 90 days after the initial infection.[13] The rational to choose a 90-day interval was based on several virological studies,[14—16] and it also aligns with guidelines from the US CDC and several EU/EEA countries.[17,18] However, since there were no clear criteria of worsen symptoms and may cause variation, we only recruited patients got reinfection more than 90 days in this study. In addition, considering that previous studies have suggested that immunocompromised patients may experience prolonged viral shedding and present challenges in differentiating between relapse and reinfection when the second COVID-19 test is positive,[19—21] we opted to exclude immunocompromised patients from our study.[22]

Data sources and collection

COVID-19 is one of the notifiable communicable diseases in Taiwan.[23,24] All patients confirmed with COVID-19 infection must be reported to Taiwan Centers for Disease Control via National Infectious Disease Reporting System (NIDRS).[25,26] We retrieved the socio-demographic and epidemiological data of COVID-19 cases from NIDRS database, including: identity number (ID), age, gender, residence area, date of symptom onset, notification receiving date of public health authority, and date of death. COVID-19 vaccination status was obtained from the National Immunization Information System database by linking to patients' ID. Given the induction time of immune response after vaccination,[27] we considered the last vaccine dose receiving 14-day before index date as effective vaccination. People who received fewer than two doses of vaccine were considered as not-fully vaccinated.[28] Accessing the electronic medical records acquired from The National Health Insurance Research Database, we calculated the Charlson Comorbidity Index (CCI) for every patient as a proxy indicator for the

severity of their underlying diseases.[22,29] We considered one's underlying disease(s) if he/she had at least three outpatient diagnoses or one inpatient diagnosis during January 1, 2021 to April 1, 2022, and calculate one's CCI by different weights based on different diseases.[30]

Statistical analyses

In the descriptive analyses, continuous variables were presented as means and standard deviations (SD) to quantify the dispersion between individual data points and the mean; and categorical variables were reported as counts and percentages. To assess the probability of mortality among reinfection and non-reinfection patients, we constructed Kaplan—Meier curves. As investigating the risk factors associated with reinfection, death represents a competing risk for experiencing reinfection, which means that if a patient passes away, they are no longer at risk of experiencing reinfection. To address this scenario, we employed cause-specific hazard function (CSH) to conduct competing risk analyses. When comparing mortality between reinfection and non-reinfection groups, conditional Cox regression model was applied. Above regression models were matched by index date and both univariable and multivariable analyses were performed. Subgroup analyses were conducted by stratifying age group, vaccination status and time interval of reinfection to determine whether the mortality of reinfection was consistent across different populations. All statistical analyses were conducted using R (version 4.2.2). All comparisons were two-tailed and a p-value of <0.05 was considered statistically significant.

Ethical approval

This study was approved by the Institutional Review Board of Taiwan Centers for Disease Control (IRB No.112103), with a waiver of informed consent.

Results

A total of 2,871,446 COVID-19 patients were confirmed between April 1 and June 11, 2022. After excluding patients based on the exclusion criteria, there were 2,507,133 (87.3%) patients included in our study. Among them, 28,588 patients met our definition of reinfection and 142,940 non-reinfection patients were matched (Fig. 1).

Reinfection occurred in patients with a median interval of 133 days (interquartile range: 115—148 days) between

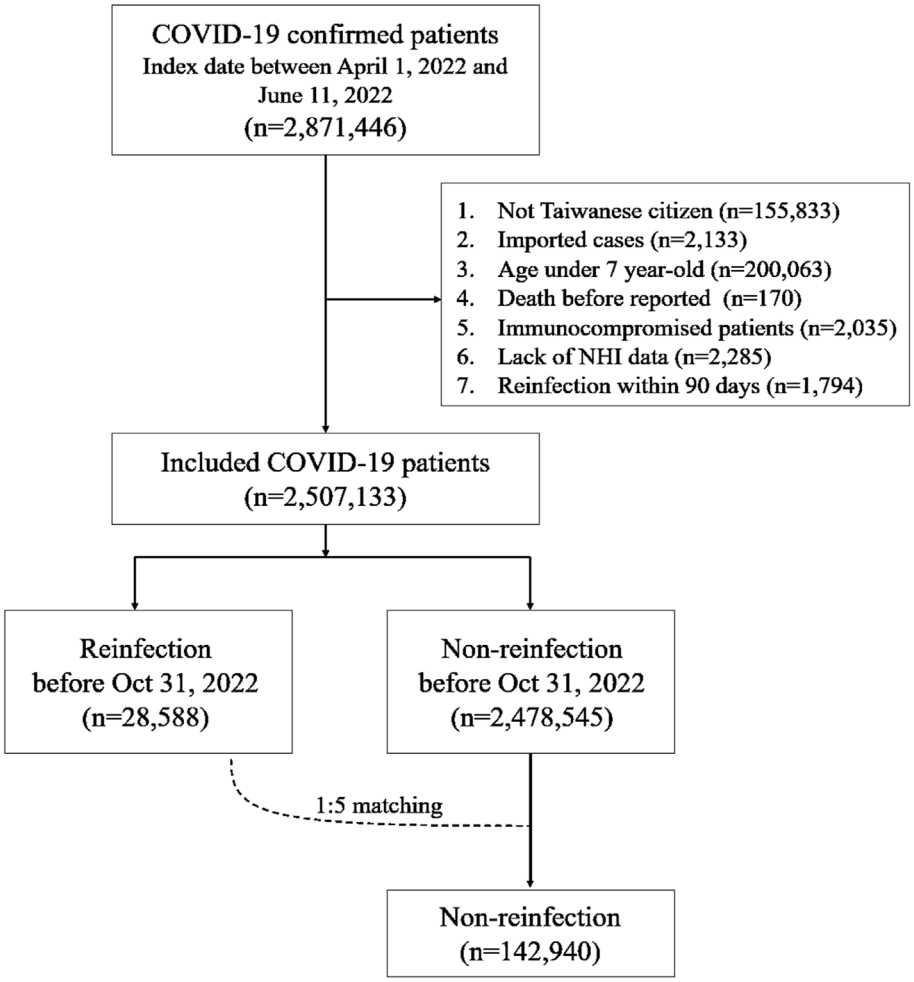

Figure 1. Data flow chart.

Table 1 Baseline characteristics of reinfection and non-reinfection patients.

Variables	Reinfection patients		Non-reinfection patients	
	n	%	n	%
Number of patients	28,588		142,940	
Gender				
Male	12,209	42.7%	67,815	47.4%
Female	16,379	57.3%	75,125	52.6%
Age (years) mean ± SD	35.4 ± 19.4		40.4 ± 19.1	
7–17	5085	17.8%	17,624	12.3%
18–49	17,611	61.6%	80,672	56.4%
50–64	2853	10.0%	27,229	19.0%
65–74	1730	6.1%	11,342	7.9%
75+	1309	4.6%	6073	4.2%
Living in municipalities[a]				
Yes	21,502	75.2%	110,142	77.1%
No	7086	24.8%	32,798	22.9%
CCI score				
0	27,030	94.6%	136,801	95.7%
1	851	3.0%	3674	2.6%
2	398	1.4%	1610	1.1%
3	111	0.4%	356	0.2%
4+	198	0.7%	499	0.3%
Vaccination status[b]				
None/one dose	5810	20.3%	23,129	16.2%
Two doses	3706	13.0%	27,083	18.9%
Booster	19,072	66.7%	92,728	64.9%
All-cause mortality within 30 days	199	0.7%	412	0.3%

[a] Municipalities include: Taipei City, New Taipei City, Taoyuan City, Taichung City, Tainan City and Kaohsiung City.
[b] Vaccination status in the reinfection group refers to their status in their second episode of infection.
Abbreviation: SD, standard deviation; CCI, Charlson Comorbidity Index.

the two episodes. Reinfection patients had a lower mean age of 35.4 years (with SD of 19.4), compared to non-reinfection patients with a mean age of 40.4 years (with SD 19.1) (Table 1). The proportion of patients with at least one score of CCI was slightly higher in reinfection group (Table 1). Over 60% of patients in both groups received booster doses of COVID-19 vaccine before infection (Table 1). All-cause mortality rate within 30 days among reinfection group were higher than that of non-reinfection patients (Table 1).

Regarding the risk factors of reinfection, univariable and multivariable cause-specific hazard models yield similar results and indicated that COVID-19 patients who were female, younger in age, not living in municipalities, and with higher CCI were associated with significant higher risk of reinfection (Table 2). However, those who got two doses (adjusted hazard ratio [aHR] = 0.68, 95% confidence interval [CI]: 0.65–0.71, $p < 0.001$) or booster (aHR = 0.81, 95% CI: 0.78–0.85, $p < 0.001$) vaccination were less likely to acquire reinfection (Table 2).

The crude all-cause mortality rate within 30 days of reinfection patients was 0.7% and 0.3% in non-reinfection patients (Table 1). The Kaplan–Meier curve showed that reinfection group had a significantly higher probability of all-cause mortality (Supplementary Figure 1). In Cox regression analyses, univariable and multivariable models yield similar results. It showed that reinfection patients had a significantly increased risk (aHR = 4.29, 95% CI: 3.00–6.12, $p < 0.001$) of all-cause mortality within 30 days in comparison with non-reinfection patients. Furthermore, COVID-19 patients who were male, older in age, higher CCI and not fully-vaccinated also raised the risk of all-cause mortality (Table 3). Across different subgroups, regardless of age groups, vaccine status or different interval between two episodes of reinfection (shorter or longer), the results were consistent that reinfection patients had higher probability of mortality (Fig. 2).

Table 2 Risk factors associated with reinfection.

Variables	Univariable CSH					Multivariable CSH				
	HR[a]	95% CI			P-value	aHR[a]	95% CI			P-value
Gender (male vs female)	0.83	0.81	–	0.85	<0.001	0.79	0.77	–	0.81	<0.001
Age group (vs 50–64 years)										
7–17	2.75	2.62	–	2.89	<0.001	2.72	2.57	–	2.88	<0.001
18–49	2.08	1.99	–	2.17	<0.001	2.22	2.12	–	2.31	<0.001
65–74	1.47	1.38	–	1.56	<0.001	1.39	1.31	–	1.49	<0.001
75+	2.20	2.05	–	2.36	<0.001	1.93	1.79	–	2.07	<0.001
Living in municipalities[b] **(yes vs no)**	0.90	0.87	–	0.93	<0.001	0.90	0.87	–	0.93	<0.001
CCI score (vs 0)										
1	1.20	1.11	–	1.29	<0.001	1.49	1.37	–	1.61	<0.001
2	1.33	1.19	–	1.48	<0.001	1.73	1.54	–	1.94	<0.001
3	1.70	1.37	–	2.10	<0.001	2.10	1.69	–	2.62	<0.001
4+	1.91	1.91	–	2.67	<0.001	2.88	2.42	–	3.43	<0.001
Vaccination status (vs none/one dose)										
Two doses	0.64	0.66	–	0.70	<0.001	0.68	0.65	–	0.71	<0.001
Booster	0.68	0.62	–	0.67	<0.001	0.81	0.78	–	0.85	<0.001

[a] Hazard ratios were matched by index date.
[b] Municipalities include: Taipei City, New Taipei City, Taoyuan City, Taichung City, Tainan City and Kaohsiung City.
Abbreviation: CSH, cause-specific hazard function; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index.

Table 3 All-cause mortality within 30 days among reinfection and non-reinfection patients.

Variables	Univariable Cox regression model					Multivariable Cox regression model				
	HR[a]	95% CI			P-value	aHR[a]	95% CI			P-value
Reinfection (yes vs no)	2.42	2.05	–	2.87	<0.001	4.29	3.00	–	6.12	<0.001
Gender (male vs female)	1.54	1.29	–	1.83	<0.001	1.90	1.36	–	2.64	<0.001
Age group (vs 50–64 years)										
7–17	0.02	0.00	–	0.13	<0.001	0.01	0.00	–	0.05	<0.001
18–49	0.13	0.09	–	0.21	<0.001	0.18	0.11	–	0.30	<0.001
65–74	4.21	2.84	–	6.25	<0.001	4.09	2.45	–	6.84	<0.001
75+	20.90	14.09	–	31.00	<0.001	20.96	12.48	–	35.20	<0.001
Living in municipalities[b] (yes vs no)	0.81	0.67		0.99	0.035	0.88	0.60	–	1.29	0.507
CCI score (vs 0)										
1	7.14	5.16	–	9.88	<0.001	2.30	1.31	–	4.02	0.004
2	18.69	11.70	–	29.86	<0.001	3.28	1.65	–	6.52	0.001
3	20.51	8.12	–	51.77	<0.001	2.51	0.55	–	11.40	0.235
4+	36.35	17.98	–	73.50	<0.001	10.10	3.41	–	29.92	<0.001
Vaccination status (vs none/one dose)										
Two doses	0.24	0.18	–	0.31	<0.001	0.31	0.18	–	0.52	<0.001
Booster	0.16	0.13	–	0.20	<0.001	0.12	0.08	–	0.18	<0.001

[a] Hazard ratios were matched by index date.
[b] Municipalities include: Taipei City, New Taipei City, Taoyuan City, Taichung City, Tainan City and Kaohsiung City.
Abbreviation: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index.

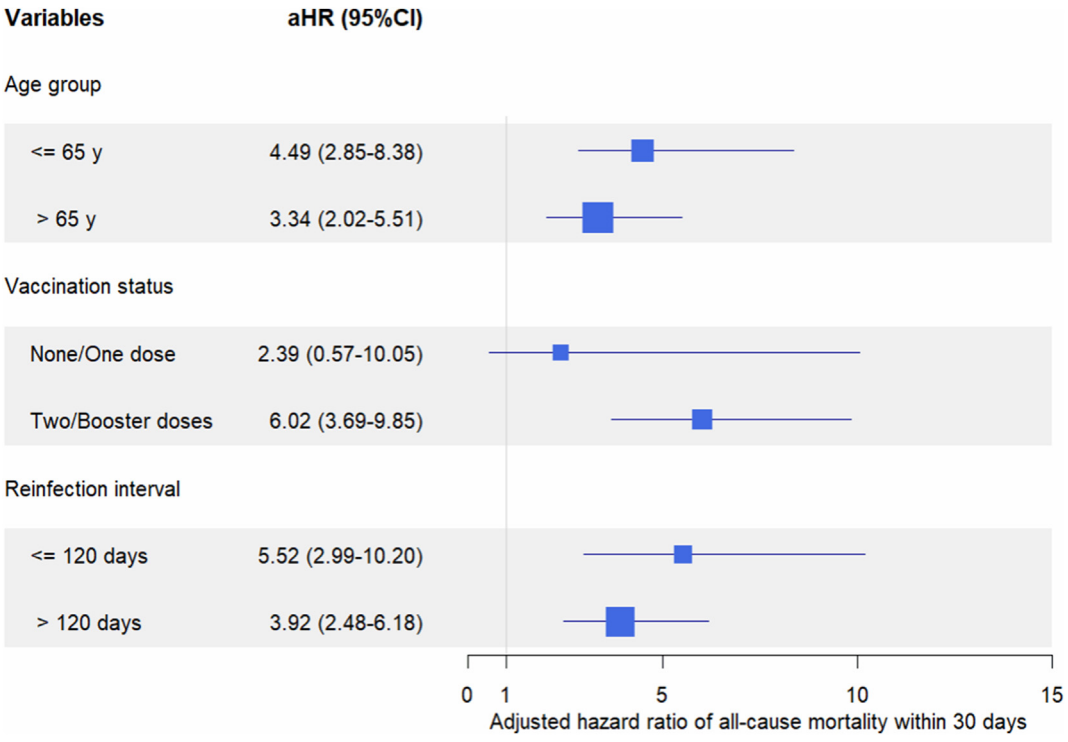

Figure 2. Subgroup analyses: Adjusted hazard ratios of all-cause mortality within 30 days comparing reinfection patients to non-reinfection patients.
Note: Hazard ratios were adjusted for age, gender, living area, CCI score and vaccine status.

Discussion

In this nationwide population-level study, we found that COVID-19 patients with younger age, female gender, higher CCI and not fully-vaccinated were more likely to acquire reinfection. Compare to non-reinfection patients, reinfection patients had a significantly increased risk of all-cause mortality within 30 days.

The results showed that variables associated with COVID-19 reinfection differed in terms of risk factors and mortality.

Specifically, younger age and female gender were more likely to experience repeated infections, but among reinfection patients, they had lower mortality rates. In contrast, while older age and male patients were less likely to get reinfection, they had a higher risk of mortality. On the other hand, patients with underlying diseases or not fully-vaccinated not only had higher probability of reinfection but also had an increased risk of mortality. It is important to note that during the study period, individuals under 18 years old had not yet received the booster vaccination. Although this could potentially introduce bias in the univariable analyses, we had adjusted for vaccination status in the multivariable regression analyses and revealed that patients under 18 years old had an increased risk of reinfection; however, they exhibited a lower likelihood of all-cause mortality. The possible reasons for the observed lower likelihood of reinfection among patients living in municipalities include factors such as higher health awareness, better adherence to preventive measures, living environment conditions, and potential differences in herd immunity levels or underreporting probabilities. Further research is needed to comprehensively understand the underlying mechanisms and potential factors that may contribute to this observation.

Our study found similar risk factors for reinfection as previous research, including younger age,[31,32] female gender,[6,33] and not fully-vaccination[32,34]; however, there is still no clear consensus on whether reinfection leads to more severe disease or not.[5] Some studies suggested that reinfection patients tend to have milder outcomes, regardless of hospitalization, acute diseases, or mortality, compared with patients without reinfection.[6—9] While, another study recruiting participants from a cohort of US Department of Veteran Affairs claimed that those with reinfection were at significant risk of mortality, hospitalization, as well as acute and postacute sequelae.[10] It should be noted that these studies were conducted during different phases of the epidemic and reinfection patients were infected by different combinations of variants (e.g., Alpha-Delta or Delta-Omicron or Omicron—Omicron). Neither of the above studies specifically explored the distinct effect of variant sublineages, nor focus on Omicron—Omicron reinfection. In addition, the number of reinfections surged dramatically during Omicron era,[6,34,35] it remains unclear how the immune response varies when exposed to different combinations of the Omicron variant with other variants, or when infected with two different sublineages of Omicron. In this study, which concentrated on Omicron—Omicron infections, we observed that reinfection patients were at a significant higher risk of mortality.

One potential bias in this study was the possibility of underreporting of reinfection cases, especially in patients with mild or asymptomatic infections, who may not seek medical attention or get tested, leading to an underestimation of the true incidence of reinfection and mortality rate. This is a common restriction in epidemiological studies of infectious diseases, and since testing and reporting behavior is unmeasurable and non-adjustable in our study, it is difficult to quantify the extent of underreporting. One approach to addressing this bias would be conducting a population-based survey to periodically test primary infection patients and measure their severity after reinfection. However, this would be a costly and time-consuming process, and it may not be feasible in the context of our study. Another possible bias resulted from the "Inpatient admission screening" policy in Taiwan, which required COVID-19 testing before hospitalization.[36] As a result, patients with severe conditions and had admission demand may have more tests and more likely to detect their reinfection. However, the adjustment for comorbidity status using CCI in survival analyses could mitigate the potential impact of the inpatient admission screening policy on our results.

There were some limitations in this study: First, we only included data from the first and second episodes of reinfection patients, excluding the relatively rare event of third or fourth reinfection during this study period. A previous study had demonstrated that the risk of morality increased in a gradual pattern depending on the frequency of infections.[10] Second, although we excluded immunocompromised patients in this study, specifically HIV patients with opportunistic infections, to mitigate potential confounding effects, not all patients with compromised immune status could be clearly distinguished based on the available data. We acknowledge that some uncertainty may still exist in this study. Third, we lacked information on whether patients received antiviral therapy, which may affect their survival probability. However, the antiviral use was determined according to age and comorbidities status, rather than reinfection, and both of them had been adjusted for in this study. Forth, we did not assess the impact of different types of COVID-19 vaccination, such as various platforms, regimens, brands, and the inoculation of homologous or heterologous booster doses. The complexity of these factors and the potential risk of dividing participants into small subgroups led us to refrain from specific evaluations. Fifth, there was limited availability of genome sequencing results of SARS-CoV-2 for patients, as only a small subset (0.05%) of the overall patient population underwent sequencing for surveillance purposes in Taiwan, which limited our ability to thoroughly investigate the impact of SARS-CoV-2 variants. However, based on data from the surveillance,[37] we knew that in April 2022, the dominant sub-lineage was Omicron BA.2, accounting for 73.8% of the sequenced cases. By September, the dominant sub-lineage had shifted to Omicron BA.5, which remained the predominant until the end of 2022. Therefore, patients in our study who experienced reinfection likely had their first episode during the Omicron BA.2 epidemic and their second episode during the era of Omicron BA.5.

To our knowledge, this is the first nationwide population-based study to explore COVID-19 reinfection characteristics and mortality concentrated in Omicron era. Our findings indicate that patients with COVID-19 reinfection were associated with higher mortality. These results emphasize the importance of monitoring the impact of COVID-19 on people with underlying diseases to inform effective prevention and treatment strategies. Furthermore, it underscores the importance of vaccination as a key strategy for reducing the risk of both reinfection and mortality from COVID-19.

Declaration of competing interest

The authors declare no conflicts of interest in this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.10.013.