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Deciphering deaths associated with severe serious adverse events following SARS-CoV-2 vaccination: A retrospective cohort study

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Introduction

Mass vaccination played an essential role in developing herd immunity for and preventing severe outcomes from coronavirus disease 2019 (COVID-19) [1,2]. As of December 2022, more than 13 billion doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been administered worldwide [3].

A recent study indicated a lower mortality rate in the vaccinated population than in unvaccinated controls [4]. In addition, researchers found no significant association between the first doses of SARS-CoV-2 vaccines and non-COVID-19-related mortality [5]. Nevertheless, reports of deaths occurring within close temporal proximity to vaccinations have continued. Attempts have been made to determine the causality [6–8] or comorbidities associated with these deaths [8,9], albeit with limited success.

Vis-à-vis specific adverse events (AEs), thrombosis with thrombocytopenia syndrome after viral vector–based vaccination was shown to have a fatality rate of 31.6–35.9 %, with women and patients with intracranial hemorrhage or severe thrombocytopenia having an excess risk of death [10,11]. Additionally, myocarditis after mRNA-based vaccine administration was shown to have an 11.8–17.7 % fatality rate, especially in men following the second dose [12,13].

Despite mounting evidence on disease-specific mortality following SARS-CoV-2 vaccination, only a few studies have systematically analyzed the risk factors and case fatality rate (CFR) in patients already experiencing serious AEs (SAEs). This information is important for clinicians because some AEs may require timely medical attention to avoid poor outcomes.

Hence, our study aimed to (1) identify differences in patient-specific and external factors in patients with severe SAEs who died within 42 days of SARS-CoV-2 vaccine administration versus those who survived beyond 42 days; (2) evaluate how vaccine dose, vaccine mechanism, comorbidities, age, and sex may affect survival in patients with severe SAEs; and (3) explore the CFR in different types of severe SAEs. We believe that our study is the first to elucidate mortality in this group of patients.

Methods

Study design

We conducted a retrospective cohort study of physician- or self-reported severe SAEs temporally associated with SARS-CoV-2 vaccination in Gyeonggi Province, South Korea from February 26, 2021, to March 15, 2022. We assessed patient-specific and external factors contributing to mortality within 42 days of the last vaccination and the etiologies of severe SAEs that resulted in fatal outcomes.

In South Korea, four vaccines were approved in 2021: viral vector-based ChAdOx1-S/nCoV-19 (Oxford–AstraZeneca) and Ad.26. COV2.S (Janssen) vaccines and mRNA-based BNT162b2 (Pfizer-BioNTech), and mRNA-1273 (Moderna) vaccines [14].

Gyeonggi Province is one of the largest local government bodies in

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South Korea, inhabited by approximately 13 million people, which is almost one-third of the nation's population. As of March 2022, 85.9 % of its residents had been fully vaccinated, and 86.8 % had been vaccinated at least once against SARS-CoV-2.

Data collection

Passive surveillance on AEs following immunization

As part of a government-led passive surveillance program, patients and physicians were asked to report relevant AEs following immunization (AEFIs) to local government authorities using a post-marketing survey of SARS-CoV-2 vaccines. The Korean government motivated both physicians and patients with expert feedback and monetary compensation in case of a possible association between the reported AEs and the vaccine. Additionally, to overcome the shortcomings of passive surveillance, Gyeonggi Province periodically monitored reporting rates in all hospitals at the provincial level and issued updated educational resources to in-hospital infection control centers to aid in the prompt reporting of cases.

The Gyeonggi Infectious Disease Control Center (GIDCC) dealt with all reported individual cases of AEFIs following SARS-CoV-2 vaccination by reviewing electronic medical records from hospitals and drug utilization review records provided by the Korean Health Insurance Review and Assessment Service. It also interviewed patients or primary caregivers and engaged in discussions with relevant medical personnel to arrive at a diagnosis.

Definition of cases

The reported severe SAEs were defined as death; events that were life-threatening, required admission to the intensive care unit (ICU), or were associated with permanent sequelae; or AEs of special interest (AESIs; e.g., anaphylaxis, thrombotic thrombocytopenia syndrome, myocarditis, and Guillain–Barré syndrome) temporally associated with vaccine administration.

Severe SAEs were defined as those "resulting in substantial morbidity and mortality," including admissions to the ICU, life-threatening symptoms, mortality, or severe damage. For brevity, however, the term "severe SAE" used throughout the manuscript implies that substantial morbidity or mortality occurred. Non-SAEs included systemic reactions, such as a fever, chills, malaise, myalgia, and a headache, and local reactions at the injection site, such as pain, swelling, and redness.

Cohort and longitudinal follow-up

From a total of 38,828,691 SARS-CoV-2 vaccine doses administered from February 26, 2021, to March 15, 2022, 105,409 AEs were reported. Overall, 687 patients had severe SAEs temporally associated with SARS-CoV-2 vaccination. Of note, the causality between SARS-CoV-2 vaccines and the reported SAEs is still under investigation. The cases were excluded from the study if they did not require ICU admission, were not life-threatening or fatal, and were not associated with long-term sequelae (N = 23) (Supplementary Material 1). In total, 664 cases of severe SAEs resulted in significant morbidity or mortality. All severe SAEs were followed up, first by the local community health center responsible for the participants' residential district and subsequently by the GIDCC.

Consequently, for survival analysis, the patients were grouped into two groups: the "death" group, which included 291 deaths that occurred during the follow-up period within 42 days of vaccination, or the

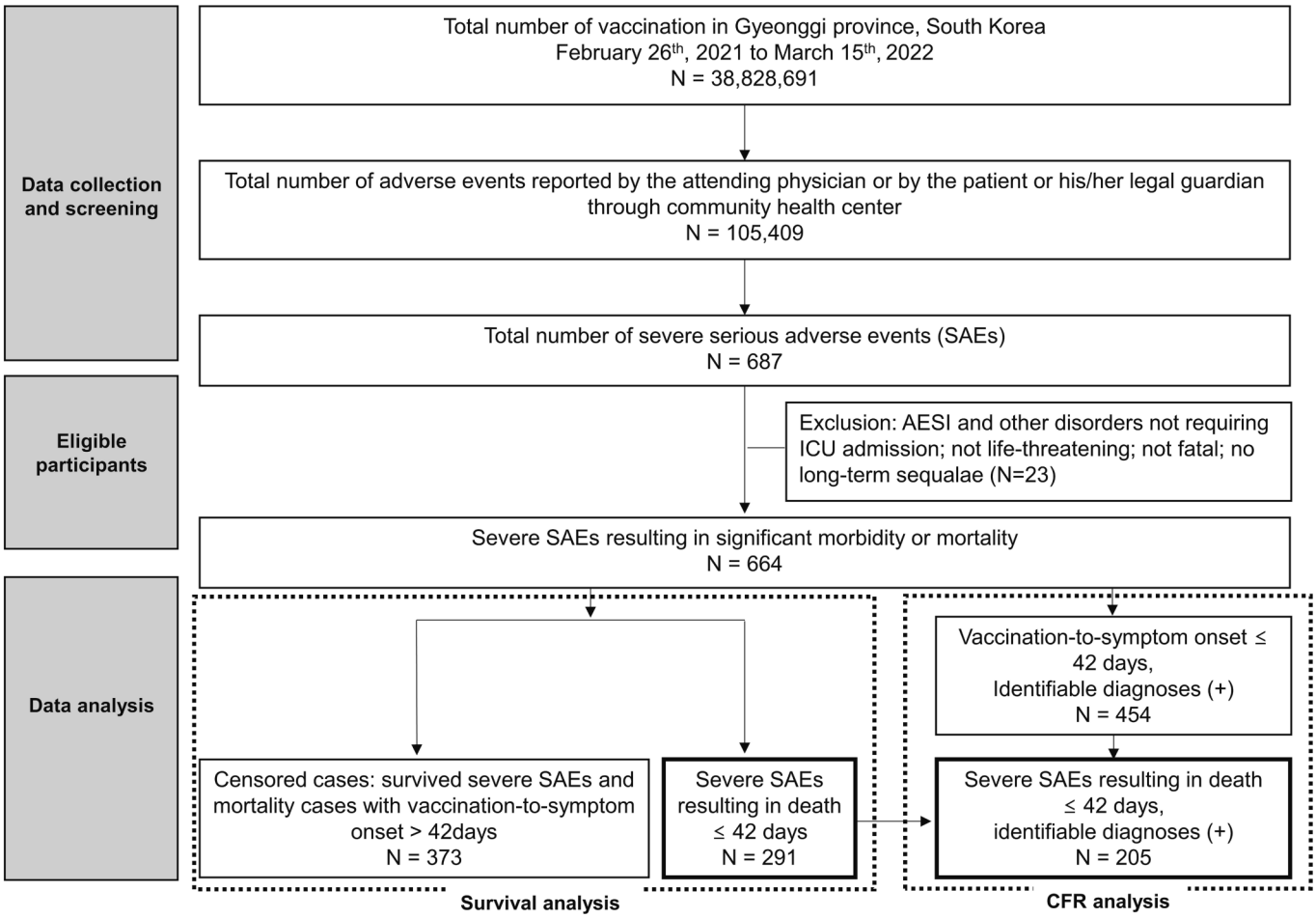

Fig. 1. Flow chart of study participants and cohort selection.

"censored" group, which included 373 patients who survived beyond 42 days from vaccination.

For analyzing etiologies leading to fatal outcomes within 42 days of vaccination, we determined that 540 cases occurred within 42 days post-vaccination, of which 454 had identifiable diagnoses. Of 291 cases of severe SAEs resulting in mortality within 42 days, 205 had identifiable diagnoses (Fig. 1).

Covariates

A set of risk factors suspected to be associated with mortality following SARS-CoV-2 vaccination was selected: age, sex, vaccine mechanism (mRNA-based or viral vector–based), number of doses received (first, second, or booster shot), vaccination site (community health center, nursing hospital and facility, medical institution, or vaccination center), and relevant comorbidities.

The Charlson comorbidity index (CCI), a weighted scoring system that reliably predicts 10-year mortality in a multimorbid patient, was used as a quantitative proxy to reflect the comorbidity burden [15]. Conditions covered by the CCI include the following: myocardial infarction, congestive heart failure, peripheral vascular disease, a cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive lung disease or asthma, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, presence of paraplegia or hemiplegia, moderate-to-severe chronic kidney disease, a solid tumor, a hematological malignancy (leukemia or lymphoma), and a human immunodeficiency virus infection or acquired immune deficiency syndrome.

Furthermore, the obtained CCI score was dichotomized into two groups using a cut-off value of 2 (low, ≤2; high, >2) for statistical analyses [16,17]. We used the age-unadjusted CCI in subsequent statistical analyses to avoid redundancy.

Diagnostic classification of severe SAEs

The core clinical diagnoses were classified according to the International Classification of Diseases 10th Revision (ICD-10) and ICD-10 Clinical Modification classification schemes and were subsequently grouped into the following etiological categories: certain infectious and parasitic diseases (A00-B99, U07.1, and U07.2); neoplasms (C00-D48); diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89); endocrine, nutritional, and metabolic diseases (E00-E88); mental and behavioral disorders (F00-F99); diseases of the nervous system (G00-G98); diseases of the circulatory system (I00-I99); diseases of the respiratory system (J00-J98 and U04); diseases of the digestive system (K00-K92); diseases of the musculoskeletal and connective tissue (M00-M99); diseases of the genitourinary system (N00-N98); symptoms and signs not classified elsewhere (R00-R99); injury, poisoning, and other consequences of external causes (S00-T98); and external causes of morbidity and mortality (V01-Y98). When death was reported as a severe SAE without a definite diagnosis, it was categorized as a severe SAE without an identifiable diagnosis.

Standard protocol approval, registration, and patient consent

The Korean Public Institutional Review Board granted an exemption for review for this study because it involved the analysis of de-identified data already obtained through the epidemiological investigation, presented a minimal risk to the participants, and met the needs of the current public health interest (identifier: P01-202204-01-006). Consent for checking the medical records and the possible usage of participant data for future public health research was obtained at the time of the epidemiological investigation. All methods were conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Statistical analyses

In this study, descriptive statistics were determined according to data attributes. Continuous data are presented as medians and interquartile ranges (IQRs), whereas categorical data are presented as absolute and relative frequencies (N [%]).

Comparisons between the death and censored groups in terms of baseline characteristics were analyzed using Student's *t*-test or the

Table 1
Baseline characteristics of patients experiencing severe serious adverse events (SAE) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination.

	Total (N = 664)	Survival status		*P*
		Censored (N = 373)	Death (N = 291)	
Age, median (IQR), y	68 (56, 79)	67 (54, 78)	69 (57, 81)	0.020[a]
Sex, N (%)				0.131
Female	253 (38.1)	152 (40.8)	101 (34.7)	
Male	411 (61.9)	221 (59.3)	190 (65.3)	
Number of doses received, N (%)				<0.001
1	307 (46.2)	177 (47.5)	130 (44.7)	
2	239 (36.0)	151 (40.5)	88 (30.2)	
3	118 (17.8)	45 (12.1)	73 (25.1)	
Vaccine mechanism, N (%)[c]				0.588
mRNA-based	434 (65.4)	240 (64.3)	194 (66.7)	
Viral vector–based	230 (34.6)	133 (35.7)	97 (33.3)	
Vaccination site, N (%)[c]				0.001
Community health center	20 (3.0)	11 (3.0)	9 (3.1)	
Nursing hospital and facility	39 (5.9)	12 (3.2)	27 (9.3)	
Medical institution	422 (63.6)	232 (62.2)	190 (65.3)	
Vaccination center	183 (27.6)	118 (31.6)	65 (22.3)	
Age-unadjusted CCI, N (%)[d]				0.267
≤2	355 (53.5)	207 (55.5)	148 (50.9)	
>2	309 (46.5)	166 (44.5)	143 (49.1)	
Comorbidities, N (%)				
Hypertension	339 (51.6)	184 (49.9)	155 (53.8)	0.354
Diabetes mellitus	230 (35.0)	124 (33.6)	106 (36.8)	0.441
Dyslipidemia	142 (21.6)	65 (17.6)	77 (26.7)	0.007
Ischemic heart disease	67 (10.2)	30 (8.1)	37 (12.9)	0.064
Arrhythmia	47 (7.2)	27 (7.3)	20 (6.9)	0.975
Atrial fibrillation	35 (5.3)	17 (4.6)	18 (6.2)	0.449
Stroke	81 (12.0)	40 (11.7)	41 (12.5)	0.833
Major depressive disorder	5 (0.8)	3 (0.8)	2 (0.7)	>0.999
Bipolar disorder	5 (0.8)	2 (0.5)	3 (1.0)	0.658
Dementia	80 (12.2)	36 (9.8)	44 (15.3)	0.043
Epilepsy	13 (2.0)	7 (1.9)	6 (2.1)	>0.999
Hyperthyroidism	2 (0.3)	2 (0.5)	0 (0)	0.507
Hypothyroidism	18 (2.7)	8 (2.1)	10 (3.4)	0.438
Cancer	34 (5.1)	18 (4.8)	16 (5.5)	0.832
Asthma	24 (3.6)	9 (2.4)	15 (5.2)	0.095
Parkinson's disease	11 (1.7)	5 (1.3)	6 (2.1)	0.547[b]
Benign prostatic hyperplasia	29 (4.4)	19 (5.1)	10 (3.4)	0.398
Chronic liver disease	15 (2.3)	9 (2.4)	6 (2.1)	0.969
Heart failure	15 (2.3)	7 (1.9)	8 (2.8)	0.626
Chronic kidney disease	39 (5.9)	22 (5.9)	17 (5.8)	>0.99

Note: Age is presented as the median (IQR). Otherwise, categorical variables are presented as N (%).
Abbreviations: IQR, interquartile range; CCI, Charlson Comorbidity Index.
[a]Mann–Whitney *U* test was used for analyses.
[b]Fisher's exact test was used for analyses.
[c]Vaccine product/mechanism with the closest temporal proximity to the adverse event and the corresponding vaccination site was chosen for analyses.
[d]Age-unadjusted CCI was formulated to exclude age so as to assess the pure effects of comorbidities and avoid redundancy with age as an independent variable.

Mann–Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables (Table 1).

Kaplan–Meier curves were drawn to represent the cumulative probability of death during the 42-day follow-up period (Fig. 2), and the mean survival time was calculated. We performed univariable and multivariable Cox proportional hazards regression analyses on the associations of age, sex, the CCI, the number of doses received, the vaccine mechanism, and the vaccination site with mortality in patients with severe SAEs (Table 2).

The CFR of severe SAEs with fatal outcomes was calculated as the number of total deaths due to severe SAEs divided by the total number of confirmed severe SAE cases, which was then multiplied by 100.

Statistical analyses were performed using IBM SPSS Statistics (version 24.0; IBM, Armonk, NY, USA) and Rex (version 3.6.0; RexSoft Inc., Seoul, Korea). The Kaplan–Meier and forest plots were drawn using the R statistical software program (version 4.1.2; R Core Team 2021).

Results

Baseline characteristics of patients with severe SAEs following SARS-CoV-2 vaccination

Among the 664 individuals who experienced severe SAEs following SARS-CoV-2 vaccination, the median age was 68 years (IQR: 56–79 years). A total of 61.9 % were men, and 65.4 % had received mRNA-based vaccines during their latest vaccination before the onset of the AEs. The largest proportion of patients only received the initial dose of the vaccine before the onset of the AEs (46.2 %). Most patients were vaccinated at medical institutions (63.6 %) or vaccination centers (27.6 %).

The death group was significantly older than the censored group (median age 69 and 67 years, respectively; $p = 0.020$). The distribution of vaccine mechanisms did not differ between the two groups. However, in terms of vaccine doses received before the onset of severe SAEs, the death group had significantly more patients who completed the third (booster) shot than the censored group (25.1 % and 12.1 %, respectively; $p < 0.001$). In addition, the death group was more likely to be vaccinated at nursing hospitals and facilities than the censored group (9.3 % and 3.2 %, respectively; $p = 0.001$). In contrast, the censored group was more likely to be vaccinated in vaccination centers than the death group (31.6 % and 22.3 %, respectively; $p = 0.001$). In terms of individual comorbidities, the death group had a larger proportion of patients with dyslipidemia (26.7 %) and dementia (15.3 %) than the censored group (dyslipidemia, 17.6 % and dementia, 9.8 %; $p = 0.007$ and $p = 0.043$, respectively; Table 1).

Patient-specific and external factors impacting mortality in patients with severe SAEs following SARS-CoV-2 vaccination

The overall mean survival time was 27.120 days (95 % confidence interval [CI], 25.825–28.415). In the univariable analysis, there was no statistically significant difference by sex or vaccine mechanism. However, patients who received the third dose had a higher risk of mortality than those who only received the first dose (crude hazard ratio [cHR], 1.955; 95 % CI, 1.465–2.608). Patients who were vaccinated at nursing hospitals and facilities were associated with a higher risk of mortality than those vaccinated at medical institutions (cHR, 2.158; 95 % CI, 1.466–3.177). Additionally, patients with a higher CCI (>2) were associated with a higher risk of mortality (cHR, 1.275; 95 % CI, 1.013–1.604). Finally, older age was associated with a slightly higher risk of mortality (cHR, 1.012; 95 % CI, 1.005–1.019).

In contrast to the univariable analysis, in the multivariable analysis, the number of vaccine doses received and the CCI were not associated with the risk of mortality in a statistically significant manner. Nevertheless, the vaccine mechanism, the vaccination site, and age were significantly associated with the risk of mortality in the multivariable analysis.

The viral vector-based vaccines were associated with a lower risk of mortality than the mRNA vaccines (adjusted HR (aHR), 0.648; 95 % CI, 0.461–0.913). Patients vaccinated at vaccination centers were associated with a lower risk of mortality (aHR, 0.579; 95 % CI, 0.409–0.819), whereas those vaccinated at nursing hospitals and facilities were associated with a higher risk of mortality (aHR, 2.087; 95 % CI, 1.366–3.187) when compared with patients vaccinated at medical institutions. Older age showed a slightly higher risk of mortality in the multivariable analysis (aHR, 1.014; 95 % CI, 1.005–1.023) (Table 2, Fig. 2).

Etiologies of severe SAEs with fatal outcome following SARS-CoV-2 vaccination: Frequency of death and CFR

For the 205 patients with identifiable diagnoses (Fig. 1), the overall CFR was 45.2 %. Diseases of the circulatory system (N = 110), respiratory system (N = 41), and digestive system (N = 12) were the most common etiologies of severe SAEs with fatal outcomes. Diseases of the circulatory system, the most common etiology, had a relatively low CFR (39.1 %). Meanwhile, other common etiologies of severe SAEs with fatal outcomes had a relatively high CFR (respiratory system, 69.5 %; digestive system, 66.7 %).

Conversely, severe SAEs with fatal outcomes had a high CFR, albeit at a low frequency. Although only six patients had fatal outcomes,

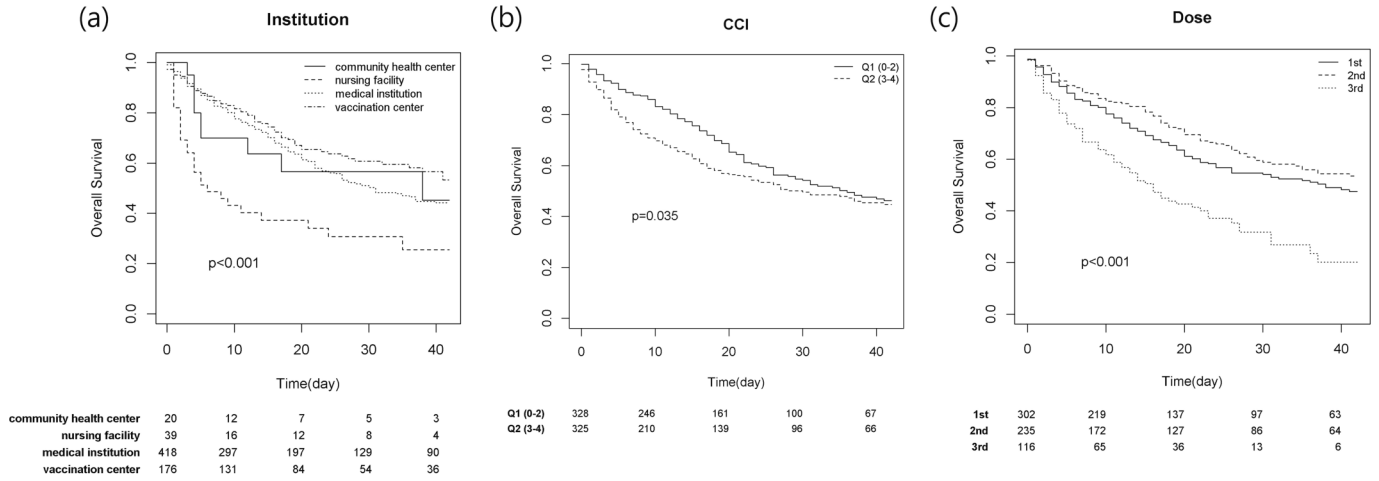

Fig. 2. Survival curves for patients with severe serious adverse events (SAEs). Kaplan–Meier plots drawn (a) by vaccination site, (b) by the dichotomized age-unadjusted Charlson comorbidity index (CCI), and (C) by the number of doses received before AE onset.

Table 2
Patient-specific and external factors associated with mortality in patients with severe serious adverse events following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination.

		Univariable analysis			Multivariable analysis		
		HR	(95 % CI)	*p-value*	HR	(95 % CI)	*p-value*
Sex	Female	1.000			1.000		
	Male	1.202	(0.944–1.530)	0.136	1.195	(0.933–1.530)	0.158
Vaccine mechanism[a]	mRNA-based	1.000			1.000		
	Viral vector–based	0.901	(0.706–1.149)	0.400	0.648	(0.461–0.913)	0.013
N of doses received	1st	1.000			1.000		
	2nd	0.798	(0.609–1.047)	0.103	0.805	(0.610–1.062)	0.125
	3rd	1.955	(1.465–2.608)	<0.001	1.417	(0.978–2.053)	0.065
Vaccination site	Medical institution	1.000			1.000		
	Nursing hospital and facility	2.158	(1.466–3.177)	<0.001	2.087	(1.366–3.187)	0.001
	Vaccination center	0.834	(0.648–1.075)	0.161	0.579	(0.409–0.819)	0.002
	Community health center	1.046	(0.556–1.971)	0.889	1.294	(0.680–2.463)	0.433
CCI, age-unadjusted	≤2	1.000					
	>2	1.275	(1.013–1.604)	0.039			
Age		1.012	(1.005–1.019)	0.001	1.014	(1.005–1.023)	0.002

Abbreviations: HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index.
[a]Mechanism of the vaccine with the closest temporal proximity to the adverse event was chosen for analyses.

neoplastic disorders had the highest CFR (85.7 %). Similarly, endocrine, nutritional, and metabolic diseases; diseases of the musculoskeletal and connective tissue; and diseases of the genitourinary system had a relatively high CFR (60.0 %, 58.3 %, and 56.3 %, respectively) while having a relatively low frequency of death (N = 3, N = 7, and N = 9, respectively).

Notably, neurological diseases had a low frequency of death (N = 3) and the lowest CFR (13.6 %; Fig. 3).

Discussion

We performed a retrospective cohort study involving 687 cases of reported severe SAEs that resulted in significant morbidity or mortality following SARS-CoV-2 vaccination. The key findings of this study were as follows: among patients with severe SAEs, (1) the viral vector-based vaccines were associated with a lower risk of mortality than the mRNA-based vaccines; (2) vaccinations performed at nursing hospitals and facilities were associated with a higher risk of mortality, whereas vaccinations performed at government-supported vaccination centers were associated with a lower risk; (3) age, but not CCI, was associated with a slightly increased risk of mortality; and (4) the CFR was variable according to different etiologies of severe SAEs, and an apparent mismatch was found between the frequency and CFRs. We believe our study is the first to provide a comprehensive insight into the fatality rate of individual AE etiologies and the potential risk factors for mortality in patients with severe SAEs following SARS-CoV-2 vaccination.

First, our findings suggest that patients vaccinated with viral vector-based vaccines have better survival outcomes than those vaccinated with mRNA-based vaccines. Notably, this finding was significant after adjusting for the number of doses received, the vaccination site, age, sex, and the CCI. A large proportion of AEFIs may primarily be explained by an excessive and unwanted immune response occasionally triggered by molecular mimicry [18]. Therefore, to understand the differences in survival outcomes following mRNA-based and viral vector-based

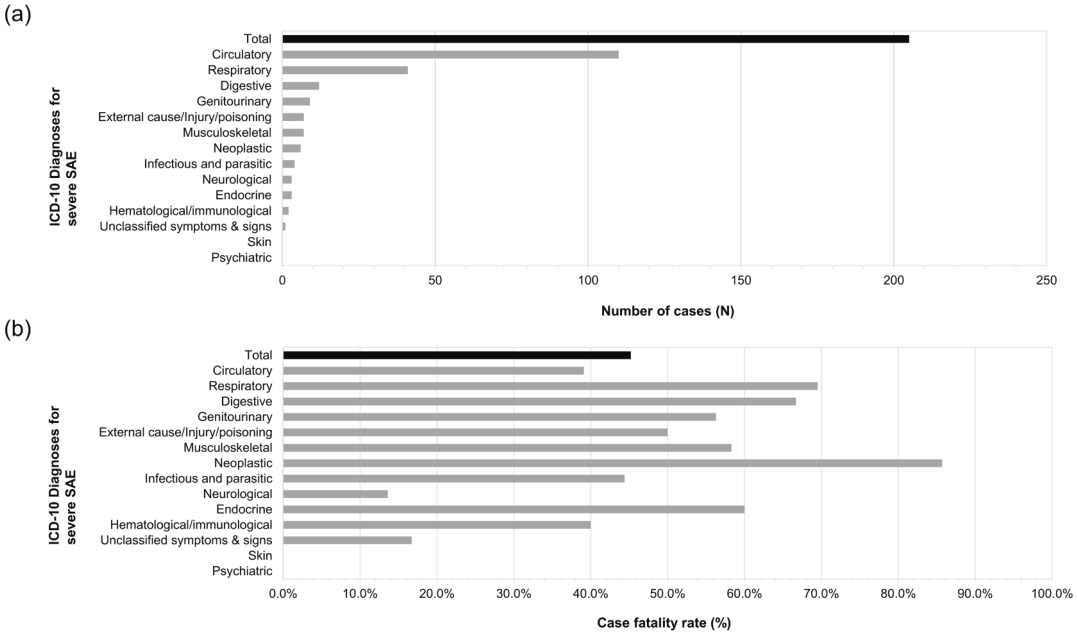

Fig. 3. Frequency of fatal outcomes and case fatality rates of severe serious adverse events (SAEs). (a) Each bar corresponds to the number of mortalities classified per the etiologic classification based on the International Classification of Diseases 10th Revision (ICD-10) diagnoses. (b) Each bar corresponds to the case fatality rate (%) per the etiologic classification based on ICD-10 diagnoses.

vaccination, the differences in their immunological traits must be recognized. Some distinguishing features of the working mechanisms of mRNA-based and vector-based vaccines are as follows: (1) mRNA-based vaccines have a different build-up of immunity, with primarily pathogen-agnostic innate immunity responsible for a lower level of protection from the first dose and primarily adaptive immunity and a significantly higher level of protection from multiple doses [19]; (2) the level of neutralizing antibody formation after multiple doses of mRNA-based vaccines exceeds that of viral vector-based vaccines [20]; and (3) the $CD8^+$ T-cell response is significantly higher following two or more doses of mRNA-based vaccines than following viral vector-based vaccines [21]. Furthermore, previous studies have shown that the homologous dosing of viral vector–based vaccines is associated with the least immunogenicity, whereas the homologous or heterologous mRNA-based booster shot is associated with higher immunogenicity [22]. These features collectively implicate both a stronger and broader immune response with multiple doses of mRNA-based vaccines than with viral vector-based vaccines, potentially increasing the probability of immunological complications.

Patients with severe SAEs who were vaccinated at designated government-supported community vaccination centers had better survival outcomes. Conversely, patients with severe SAEs vaccinated at nursing hospitals and facilities had an increased risk of mortality over 42 days. Despite our efforts to adjust for patient-specific factors, this finding may be attributable to an incomplete adjustment of general health and nutritional statuses among patients visiting different vaccination sites. Owing to their better functional status, vaccination center users may also have shown more active healthcare-seeking behaviors and had higher chances of receiving prompt medical care when necessary. To a lesser extent, better tertiary center accessibility among vaccination center users may have contributed to better survival outcomes. At the height of the COVID-19 pandemic, the South Korean government designated over 200 nationwide vaccine centers operated by teams of doctors, nurses, and an administrative workforce to boost the vaccine administration rate in densely populated metropolitan areas [23]. These vaccination centers served as mass vaccine distribution hubs for ambulatory populations. To orchestrate a large recipient load, standardized protocols were implemented and monitored by local public health authorities. Furthermore, expert oversight and quality checks were regularly provided by medical professionals from tertiary care centers bound to their respective city jurisdictions. These tight connections between vaccination centers and tertiary referral centers may have contributed to faster administrative processing and referrals, timely medical interventions, and, consequently, a lower mortality risk.

Age, but not the CCI, was associated with a slightly increased risk of mortality, despite both age and the CCI being associated with COVID-19–related mortality [24]. However, the risk factor associations of these variables have not been thoroughly examined in the literature. Our results suggest that age is associated with an approximately 1 % increase in the risk of mortality following a severe SAE. Nevertheless, the clinical significance or the public health implications of this finding remain uncertain, since the protective benefit from vaccination may outweigh the risk of mortality following a severe SAE. Multimorbidity has been associated with an increased incidence of AESIs regardless of vaccination status [25]. However, in our study, mortality following severe SAEs was not significantly associated with the weighted CCI. Despite concerns regarding comorbidities being associated with mortality following SARS-CoV-2 vaccination [9], patient-specific factors may not have much influence on the fatal outcomes of patients with severe SAEs than previously anticipated. Nevertheless, these patient-specific factors may still contribute significantly at the level of individual AESIs, warranting in-depth investigations for separate diagnoses.

Diseases of the circulatory system were the most common causes of severe SAEs with fatal outcomes. However, the CFR of this category was lower than anticipated (39.1 %), implying that diseases of the circulatory system were monitored and treated relatively well. This may be due to the acuteness of symptoms and the reputation built through media exposure. The most critical severe SAE with a fatal outcome in our study was neoplasms, which had a CFR of 85.7 %. The most commonly reported neoplasm was acute myeloid leukemia. Interpretation of these data, however, requires caution because the temporal link does not equate to causality. Studies to unveil an association between vaccination and these little-known potential AEs need to be conducted concomitantly for optimal clinical utility. Overall, the CFR was variable among the etiologies of severe SAEs, and an apparent mismatch was found between the frequency of death and the CFR. Concerning the vaccine mechanism, the overall CFR was similar between mRNA-based and viral vector-based vaccines (43.4 % vs. 48.7 %), but remarkable differences arose for circulatory diseases (35.3 % vs. 47.3 %; Supplementary Material 2).

Finally, 86 patients with unidentifiable diagnoses died within 42 days from the last vaccination in our study, and the diagnoses were inconclusive in 17 patients, even with autopsies. These patients experienced sudden death due to unclear causes and were labelled arbitrarily with sudden cardiac death, acute respiratory failure, or unclassified. This result does not imply causality and further research should be conducted to address this issue appropriately. We have included a demographic summary of these patients in Supplementary Material 3.

This study had several limitations that must be acknowledged. First, this was an observational study that inherently discovered only associations and not causations. However, we believe that the temporal association suggested in our study may provide valuable insights into causality assessments. Second, passive surveillance is vulnerable to under-reporting bias. However, to increase sensitivity, we undertook efforts to overcome this limitation, as described in the Methods section, and a robust follow-up was performed of each patient with severe SAEs to ensure that only a negligible amount of bias was driven by dropout. Third, the number of deaths associated with SARS-CoV-2 infection during the follow-up period was not entirely accounted for. Nationwide time-series correlation studies investigating SARS-CoV-2 infection, vaccination, and deaths following severe SAEs may aid in revealing temporal associations. Fourth, the denominator for the CFR in our study was patients with severe SAEs and not the total population. Therefore, caution must be taken when generalizing these data to the public. Population-based studies on the incidence and mortality rates following severe SAEs may be warranted. Finally, we did not account for the differences in immunogenicity and reactogenicity between homologous and heterologous vaccination strategies [26,27]. A follow-up study is underway to investigate the differential effects of sequential dosing schemes on mortality in patients with severe SAEs.

In conclusion, we found that older people receiving mRNA-based vaccines in nursing hospitals and facilities who reportedly develop severe SAEs with a high CFR (e.g., neoplastic, respiratory, and digestive disorders) may have an increased risk of 42-day mortality. Timely government-led public surveillance and guidance in these groups of vaccine recipients who develop severe SAEs should be implemented to avoid unnecessary fatalities.

Author contributions

J.H. and M.C.S. contributed to the acquisition and analysis of the data and drafted a substantial portion of the manuscript, tables, and figures. S.P. contributed to the conception and design of the study and drafted a substantial portion of the tables and figures. H.K., T.K., N.K., D. K.K., K.B., K.J.L., and E.L. contributed to the acquisition and verification of the data; B.S.H. contributed to the design of the study and interpretation of data; and J.Y., J.M.S., and K.P. contributed to the conception and design of the study, interpretation of the data, and revision of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100446.

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