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Original Article

SARS-CoV-2 mRNA vaccine-related myocarditis and pericarditis: An analysis of the Japanese Adverse Drug Event Report database

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ABSTRACT

Background: The association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines and myocarditis/pericarditis in the Japanese population has not been systematically investigated. This study was aimed at clarifying the association between SARS-CoV-2 mRNA vaccines (BNT162b2 and mRNA-1273) and myocarditis/pericarditis as well as influencing factors by using the Japanese Adverse Drug Event Report database.

Methods: Reporting odds ratios (RORs) and 95 % confidence intervals (95 % CIs) for the association between the vaccines and myocarditis/pericarditis were calculated using data from the database (April 2004–December 2023). Age, sex, onset time, and outcomes in symptomatic patients were evaluated.

Results: The total number of reports was 880,999 (myocarditis: 1846; pericarditis: 761). The adverse events associated with the vaccines included myocarditis (919 cases) and pericarditis (321 cases), with the ROR [95 % CIs] being significant for both (myocarditis: 30.51 [27.82–33.45], pericarditis: 21.99 [19.03–25.40]). Furthermore, the ROR [95 % CIs] of BNT162b2 and mRNA-1273 were 15.64 [14.15–17.28] and 54.23 [48.13–61.10], respectively, for myocarditis, and 15.78 [13.52–18.42] and 27.03 [21.58–33.87], respectively, for pericarditis. Furthermore, most cases were ≤30 years or male. The period from vaccination to onset was ≤8 days, corresponding to early failure type based on analysis using the Weibull distribution. Outcomes were recovery or remission for most cases; however, they were severe or caused death in some cases.

Conclusion: In the Japanese population, SARS-CoV-2 mRNA vaccination was significantly associated with the onset of myocarditis/pericarditis. The influencing factors included age of ≤30 years and male. Furthermore, although most adverse events occurred early after vaccination, overall outcomes were good.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the Coronaviridae family. The World Health Organization has designated infections associated with SARS-CoV-2 as Coronavirus disease 2019 (COVID-19) [1]. COVID-19 triggered a global pandemic ever since the first case of infection was reported in 2019. As of March 2024, it has affected 676,609,955 people worldwide, including 33,329,551 people in Japan [2]. In 2020, BNT162b2 (Pfizer BioNTech) and mRNA-1273 (Moderna) were developed as coronavirus modified uridine mRNA vaccines (SARS-CoV-2 mRNA vaccines). In Japan, vaccination with BNT162b2 and mRNA-1273 was started in February 2021 and May 2021, respectively. Both vaccines have been proven effective in suppressing the onset and exacerbation of COVID-19 [3,4], and the usefulness of SARS-CoV-2 mRNA vaccines has been demonstrated [5,6]. However, adverse events associated with SARS-CoV-2 mRNA vaccination, including myocarditis and pericarditis, have been reported across the world, some of which became severe [7–10]. To appropriately manage the risks, factors influencing the development of myocarditis and pericarditis after SARS-CoV-2 mRNA vaccination and related outcomes have been clarified based on large-scale medical database from countries around the world [11–13]. Additionally, in Japan, severe cases of cardiogenic shock or death associated with myocarditis after SARS-CoV-2 mRNA vaccination have been reported [14–21]. However,

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in Japan, there has been no systematic evaluation of the association between SARS-CoV-2 mRNA vaccines and myocarditis/pericarditis based on large-scale medical information database. One of the reasons is that vaccination history and medical information regarding adverse events are not centrally managed in Japan, making it difficult to perform analyses using large-scale medical data, unlike those in other countries.

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) manages the Japanese Adverse Drug Event Report (JADER), a large-scale database for spontaneous reporting of adverse events. The database includes information such as adverse events and outcomes associated with vaccination. Large-scale databases for spontaneous reporting of adverse events, including JADER, are effective resources for studies that systematically explore the association between drugs and adverse events, and they contribute to the accumulation of evidence for safe medication [22–24]. The prognoses of myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccines have been reported using European databases for spontaneous reporting of adverse events [25]. While it was believed that the association between SARS-CoV-2 mRNA vaccines and myocarditis/pericarditis in the Japanese population could be systematically elucidated using the JADER database, no such study was conducted. Therefore, in this study, we systematically evaluated the onset of myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccines, as well as factors influencing the onset of these conditions and outcomes by using the JADER database. We also compared the onset and related factors for myocarditis and pericarditis associated with BNT162b2 and mRNA-1273.

2. Methods

2.1. Study design

Data from the JADER database were downloaded from the website of PMDA in February 2024, and the specific data items extracted in this study consist of three tables: (1) case list table (demo); (2) drug information table (drug); (3) adverse reaction table (reac) in JADER. The number of adverse events aged 12 years or above was extracted from the data for April 2004 to December 2023.

2.2. Definition of drug exposure

The analyzed drugs were the SARS-CoV-2 BNT162b2 vaccine and the SARS-CoV-2 mRNA-1273 vaccine. In the JADER database, there are two types of adverse events, namely “narrow,” which is the descriptor used when the possibility is high, and “wide,” which is the descriptor used in all possibilities. In this study, to accurately identify adverse events, the target range was set to “narrow” [26]. The “narrow” was defined based on a report that is listed as “suspect drug” for “drug involvement” in the “drug information table (drug)".

2.3. Definition of adverse events

Terminology from the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [27] was used to extract adverse events. Adverse events were defined as “myocarditis” and “pericarditis” using preferred terms in MedDRA. We defined vaccine-induced myocarditis/pericarditis as adverse event reports within the “narrow” range. Furthermore, if myocarditis/pericarditis was not described in the adverse event report, we defined the adverse event as out of scope such as myocarditis/pericarditis.

2.4. Statistical analysis

The reporting odds ratio (ROR) and the corresponding 95 % confidence interval (95 % CI) for the association between SARS-CoV-2 mRNA vaccines and myocarditis/pericarditis were evaluated, and disproportionality analysis was performed [28]. ROR was calculated using the following formula based on the number of myocarditis or pericarditis reports (n11) and the number of other adverse events (n21) associated with SARS-CoV-2 mRNA vaccines, and the number of myocarditis or pericarditis (n12) and the number of other adverse events (n22) associated with other drugs [28].

$$\mathrm{ROR} = \frac{n11/n21}{n12/n22}$$

If the lower limit of the 95 % CI exceeded 1.0, the association was determined as statistically significant [28]. In addition, age, gender, and outcome were counted using reports. When the age, gender, and outcome were missing, the report was excluded from the analysis.

CzeekV PRO (INTAGE Healthcare Inc.) was used in the analysis of the JADER database. For the analysis of onset time, the scale parameter α and the shape parameter β were calculated using the Weibull distribution [29]. For the scale parameter, the time when a failure occurred in 63.2 % of the total was indicated as α [29]. In addition, concerning failure rate, if β was less than 1, it was determined as an early failure type where adverse events decrease with time; if β equaled 1, it was determined as a random failure type where adverse events occurred at a constant pace; and if β exceeded 1, it was determined as wear-out failure type where the incidence increased with time [29]. In addition, JMP® Pro 17.2.0 (JMP Statistical Discovery LLC) was used for statistical processing.

3. Results

3.1. Adverse event reporting

There was a total of 880,999 reports of adverse events (1846 reports of myocarditis and 761 reports of pericarditis). Adverse events associated with SARS-CoV-2 mRNA vaccines included 919 cases of myocarditis and 321 cases of pericarditis, with both demonstrating significant ROR [95 % CI] (myocarditis: 30.51 [27.82–33.45], pericarditis: 21.99 [19.03–25.40]). The number of myocarditis and pericarditis occurrences, and ROR (95 % CI) were analyzed by product, and it was found that there were 559 cases of myocarditis (ROR [95 % CI]: 15.64 [14.15–17.28]) and 234 cases of pericarditis (ROR [95 % CI]: 15.78 [13.52–18.42]) associated with BNT162b2, and 360 cases of myocarditis (ROR [95 % CI]: 54.23 [48.13–61.10]) and 87 cases of pericarditis (ROR [95 % CI]: 27.03 [21.58–33.87]) associated with mRNA-1273 (Table 1).

3.2. Relationship with age and sex

The onset of myocarditis and pericarditis was aggregated by age (Fig. 1). Based on the result, the majority of the cases of onset were in individuals aged ≤30 years, with myocarditis accounting for 68 % (625

Table 1
Reporting odds ratio (ROR) for myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccines.

		ROR (95 % CI)	number of reports (total)
Total SARS-CoV-2 mRNA vaccines	Myocarditis	30.51 (27.82–33.45)	919 (28,590)
	Pericarditis	21.99 (19.03–25.40)	321 (28,590)
BNT162b2	Myocarditis	15.64 (14.15–17.28)	559 (24,320)
	Pericarditis	15.78 (13.52–18.42)	234 (24,320)
mRNA-1273	Myocarditis	54.23 (48.13–61.10)	360 (4270)
	Pericarditis	27.03 (21.58–33.87)	87 (4270)

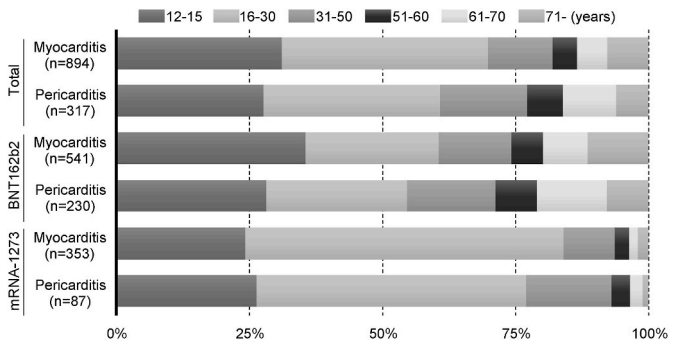

Fig. 1. Onset age of myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccines, BNT162b2 and mRNA-1273.

cases) and pericarditis for 60 % (193 cases). The onset rate in individuals aged ≤30 years was high, at 61 % (328 cases) for myocarditis and 54 % (126 cases) for pericarditis associated with BNT162b2 and 84 % (297 cases) for myocarditis and 77 % (67 cases) for pericarditis associated with mRNA-1273. As shown in Fig. 2, the majority of the cases of onset occurred in male patients (myocarditis: 78 % [713 cases], pericarditis: 74 % [238 cases]), at 73 % (402 cases) for myocarditis and 72 % (168 cases) for pericarditis associated with BNT162b2 and 87 % (311 cases) for myocarditis and 80 % (70 cases) for pericarditis associated with mRNA-1273.

3.3. Onset time

The number of reports of the onset times of myocarditis and pericarditis after vaccination is shown in Fig. 3. Time-to-event analysis using the Weibull distribution revealed α to be 7.36 (6.56–8.26) days for myocarditis and 5.89 (4.89–7.08) days for pericarditis (Table 2). In addition, β was <1, corresponding to early failure type (Figs. S1A and B). Furthermore, with regard to BNT162b2, α and β were 5.89 (95 % CI: 4.91–7.05) and 0.84 (95 % CI: 0.75–0.92), respectively, for myocarditis; the corresponding values for pericarditis were 6.41 (95 % CI 5.03–8.11) and 0.87 (95 % CI 0.75–0.99). Regarding mRNA-1273, α and β were 8.40 (95 % CI 7.23–9.72) and 0.81 (95 % CI 0.75–0.88), respectively, for myocarditis; the corresponding values for pericarditis were 5.22 (95 % CI 3.88–6.96) and 0.84 (95 % CI 0.71–0.98; Table 2, Figs. S1C–F). Based on the aforementioned findings, the onset of myocarditis was concentrated to ≤8 days, while the onset of pericarditis was concentrated to ≤6 days, with both corresponding to early failure type.

3.4. Outcome

After the onset of myocarditis and pericarditis, improvement (recovery or remission) was noted in 78 % (595 cases) and 87 % (222 cases) of cases, respectively (Fig. 4A, D). On the other hand, a severe outcome (sequela or non-recovery) after the onset of myocarditis and pericarditis was noted in 11 % (80 cases) and 8 % (20 cases) of cases, respectively; death was reported in 11 % (84 cases) and 5 % (13 cases), respectively. Similar tendencies were observed in the subgrouping analysis associated with BNT162b2 and mRNA-1273 (Fig. 4B, C, E, and F).

4. Discussion

In this study, it was shown that SARS-CoV-2 mRNA vaccination is significantly associated with myocarditis and pericarditis in the Japanese population. The Danish medical database revealed a hazard ratio of 1.90–5.35 for myocarditis and pericarditis in persons who received SARS-CoV-2 mRNA immunization compared to those who were not vaccinated [12]. According to an analysis combining a large-scale spontaneous reporting system in Europe and the vaccination tracking data of the European Centers for Disease Control and Prevention, the standardized morbidity for myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccination was 8.44–17.27 and 5.79–9.76 per one million people [25]. Furthermore, the results of a meta-analysis including a total of 42 studies indicated that there is no regional difference in the onset of myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccines in North America, Europe, and Asia [30]. Based on these results, it is thought that SARS-CoV-2 mRNA vaccines

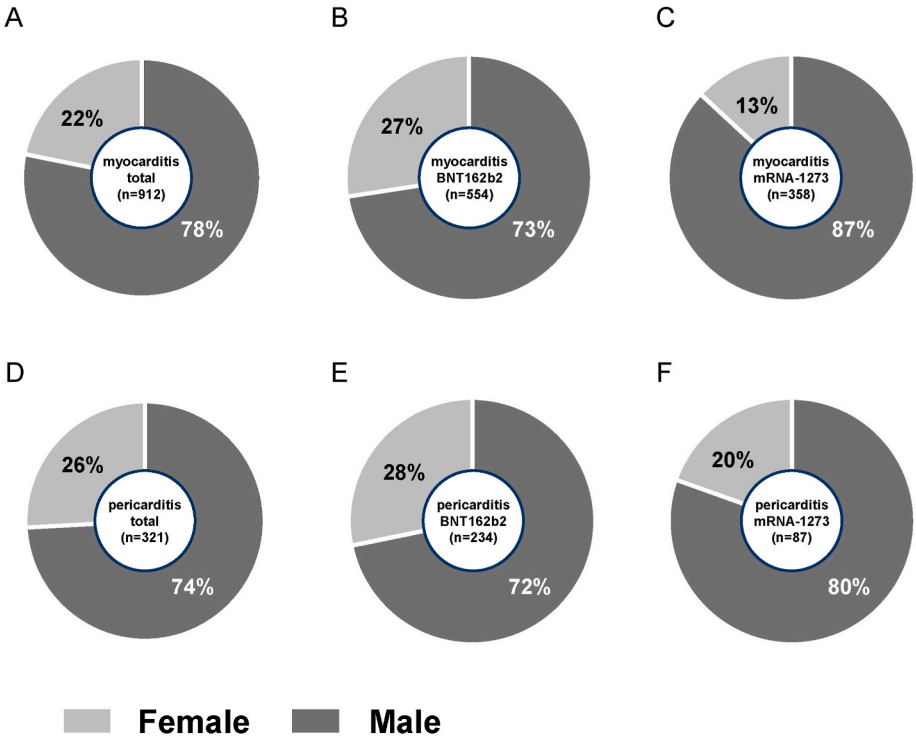

Fig. 2. Sex of myocarditis- and pericarditis-affected patients who received the (A, D) SARS-CoV-2 mRNA vaccines (B, E) BNT162b2 and (C, F) mRNA-1273.

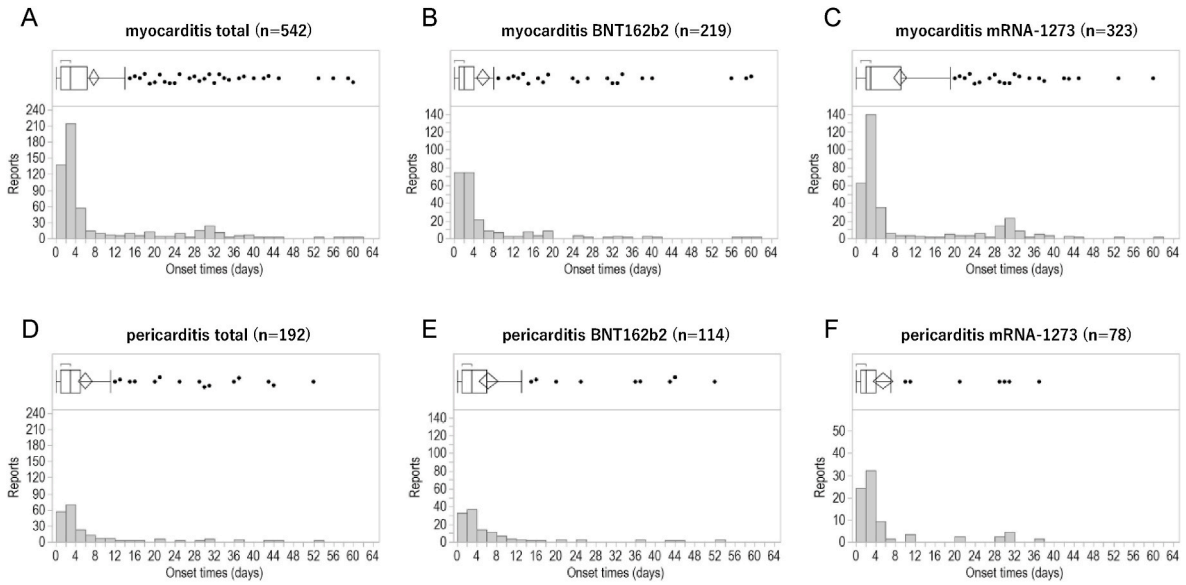

Fig. 3. Onset times of myocarditis and pericarditis associated with the (A, D) SARS-CoV-2 mRNA vaccines (B, E) BNT162b2 and (C, F) mRNA-1273.

Table 2
The Weibull parameters of myocarditis and pericarditis associated with SARS-CoV-2 mRNA vaccines.

Target drugs	Cardiotoxicity	Reports	α (95 % CI)	β (95 % CI)
Total SARS-CoV-2 mRNA vaccines	Myocarditis	542	7.36 (6.56–8.26)	0.81 (0.76–0.87)
	Pericarditis	192	5.89 (4.89–7.08)	0.85 (0.77–0.94)
BNT162b2	Myocarditis	219	5.89 (4.91–7.05)	0.84 (0.75–0.92)
	Pericarditis	114	6.41 (5.03–8.11)	0.87 (0.75–0.99)
mRNA-1273	Myocarditis	323	8.40 (7.23–9.72)	0.81 (0.75–0.88)
	Pericarditis	78	5.22 (3.88–6.96)	0.84 (0.71–0.98)

also pose a risk of myocarditis and pericarditis onset in the Japanese population.

In this study, the influencing factors for myocarditis and pericarditis included being 30 years or below of age and being male. The expression level of IgG and the percentage of CD4, which produces inflammatory substances, were higher in young people than in older people after SARS-CoV-2 mRNA vaccination [31]. Regardless of the etiology, IgG anti-cardiac autoantibodies [32] and inflammatory substances [33] are related to the onset of myocarditis. Individuals who have experienced myocarditis after SARS-CoV-2 mRNA vaccination exhibit higher expression of IgG anti-cardiac autoantibodies compared to those who have not developed the illness [34]. These facts suggest that vaccination may have increased IgG expression levels, thereby increasing the risk of myocarditis in young people compared with older people. With regard to sex differences, the expression of soluble suppression of tumorigenesis-2, which increases at the onset of myocarditis, was significantly increased in gonadectomized mice following the administration of testosterone, compared with estrogen [35]. Thus, testosterone was suggested to be involved in the onset of myocarditis. In addition, a study involving a mouse model of myocarditis accompanied by infection with coxsackievirus B3 showed that deleting interferon (IF) -γ expression suppresses the onset of myocarditis and that IF-γ expression is higher in male mice than in female mice [36]. These findings suggest that the risk of myocarditis may be higher in male individuals than in female individuals. Therefore, when inoculating individuals 30 years or below of age or male individuals with SARS-CoV-2 mRNA vaccines, it is necessary to pay attention to the onset of myocarditis and pericarditis.

Some studies abroad showed the relationship between the number of vaccinations and the occurrence of myocarditis/pericarditis: the expression level of IgG was higher after the second dose than the first dose [37]. Additionally, a cohort study in claims databases in the USA showed that the risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination was increased the second dose compared to the first dose [8]. Although we could not analyze the relationship between the number of vaccinations and the risk of myocarditis/pericarditis in the JADER database due to the difficulty in determining the timing of the dose, the possibility that the number of doses influences the occurrence of myocarditis and pericarditis cannot be eliminated from the Japanese population. Further investigations are necessary to reveal this point.

Based on the results of analysis using the Weibull distribution, the onset of myocarditis and pericarditis after vaccination corresponded to early failure type, with the onsets concentrated at $\leq$8 and $\leq$ 6 days after vaccination for myocarditis and pericarditis, respectively. In a cohort study based on a Canadian medical information database, 86.9 % of myocarditis or pericarditis after vaccination occurred within 7 days [13]. Considering the results of the present study and previous reports, it is necessary to pay particular attention to the onset of myocarditis and pericarditis within 7 days after SARS-CoV-2 mRNA vaccination.

In their retrospective studies, one study reported 129 mild cases and one case of death among 136 cases of myocarditis after vaccination [38], while other study reported no death in 105 cases of myocarditis [13]. In addition, based on an investigation of the outcomes for individuals who had developed myocarditis and pericarditis associated with BNT162b2 and mRNA-1273 vaccines using EudraVigilance, an adverse event spontaneous reporting database in Europe, a rate of death and sequela were reported as 0.55–0.91 % and 1.53–3.03 %, respectively [25]. The outcome of myocarditis and pericarditis in the Japanese population in this study was recovery or remission in 74–90 % of cases. However, the percentages of severe outcomes and death were found to be between 8–11 %, and 5–11 %, respectively. These rates were higher than those reported in other countries [25]. This suggests that it is important to be vigilant about the worsening of symptoms once the disease starts in the Japanese population.

Based on a cohort study that compared the onset of myocarditis and pericarditis associated with BNT162b2 and mRNA-1273 vaccines, the odds ratio of mRNA-1273 relative to BNT162b2 was 2.78 (95 % CI: 1.67–4.62) for myocarditis and 2.42 (95 % CI: 1.31–4.46) for

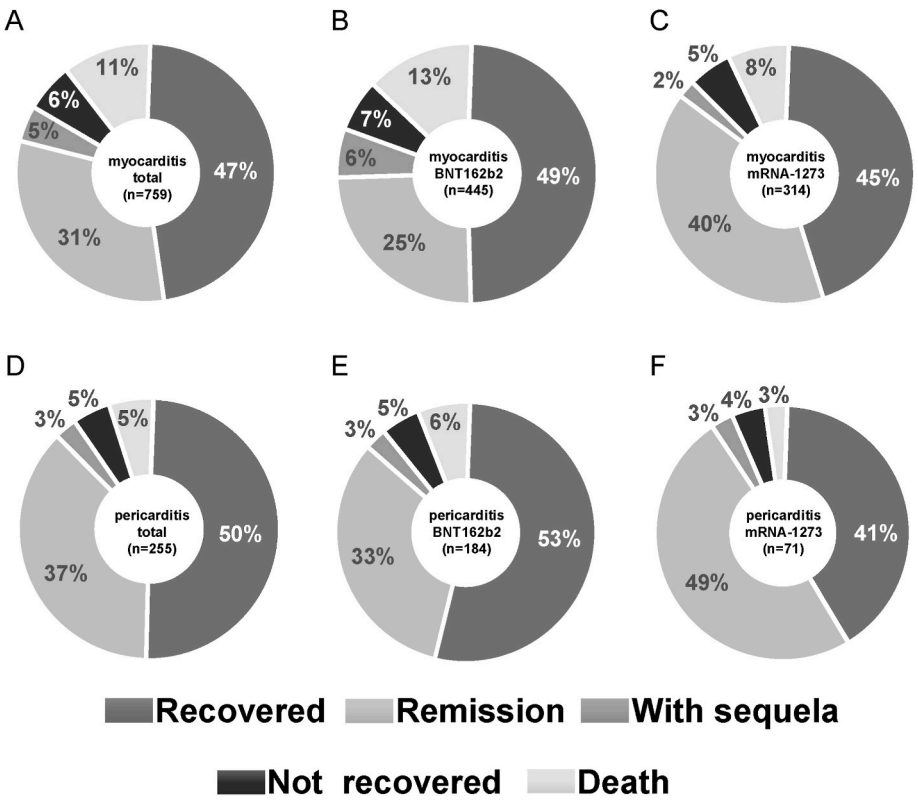

Fig. 4. Outcomes of myocarditis and pericarditis associated with the (A, D) SARS-CoV-2 mRNA vaccines (B, E) BNT162b2 and (C, F) mRNA-1273.

pericarditis, indicating an increased risk of myocarditis and pericarditis onset associated with mRNA-1273 [39]. Furthermore, in an analysis using EudraVigilance, the ROR of the onset of myocarditis and pericarditis associated with BNT162b2 and mRNA-1273 were reported to be 9.76 (95 % CI: 9.06–10.51) for mRNA-1273 and 5.79 (95 % CI: 5.56–6.01) for BNT162b2 [25]. In this study, the ROR of myocarditis and pericarditis was also higher for mRNA-1273 than for BNT162b2. According to the report, the amount of IgG expression following mRNA-1273 was notably more than that following BNT162b2 [40]. Therefore, it was suggested that the high ROR for myocarditis and pericarditis associated with mRNA-1273 is owing to the higher expression of IgG caused by mRNA-1273.

This study has several limitations. First, the ROR calculated based on adverse event reporting did not involve the use of a non-administered group as the control; thus, onset risk cannot be estimated. In addition, patient bias dependent on patient background including underlying diseases and reporting bias that occurs because of adverse events are not reported even if they develop, cannot be eliminated. Thus, it is believed that the results of this study using a database for spontaneous reporting of adverse events have high validity despite the presence of various biases; however, for true risk evaluation, prospective epidemiological studies and evaluations adjusted for background factors are desirable.

5. Conclusion

In the Japanese population, SARS-CoV-2 mRNA vaccination was significantly associated with the onset of myocarditis/pericarditis. The influencing factors included age of ≤30 years and male. Furthermore, most adverse events occurred early after vaccination. Hence, it is imperative to focus on Japanese males aged 30 or lower, specifically urging them to promptly seek medical assistance for inspection and treatment upon experiencing chest symptoms after vaccination.

Ethics approval

As the adverse events database is an anonymized open-access database, institutional review board approval and informed consent were not required according to the Ministry of Health, Labor, and Welfare's Ethical Guidelines for Medical and Health Research involving Human Subjects.

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Author contributions

KTaka, KTagu, and KM conceived and designed the study. KTaka carried out data collection. KTaka, KTagu, MS, YI, YO, YE, KTani, and KM oversaw data analysis. KTaka and KTagu drafted the manuscript. MS, YI, KTani, and KM reviewed and edited the manuscript. All authors contributed to the writing of the final manuscript and management or administration of the trial.

Declaration of competing interest

KM received grant support funding from Meiji Seika Pharma Co., Ltd. The other authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2024.07.025.

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