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DIA

ORIGINAL RESEARCH

Risks of Myocarditis and Pericarditis Following Vaccination with SARS-CoV-2 mRNA Vaccines in Japan: An Analysis of Spontaneous Reports of Suspected Adverse Events

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Abstract

Objective To identify the risks of myocarditis or pericarditis after vaccination with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines in Japan.

Methods We conducted an observed-to-expected analysis (OE analysis) of spontaneous reports of suspected adverse events from pharmaceutical companies, calculating rate ratios with myocarditis and pericarditis after the vaccination of the mRNA vaccines Comirnaty (BNT162b2) and Spikevax (mRNA-1273) and expected rate of myocarditis and pericarditis in the population before the COVID-19 pandemic. These reports dated from 17/2/2021 to 14/11/2021 and from 22/5/2021 to 14/11/2021 for Comirnaty and Spikevax, respectively. The observed-to-expected ratios (OE ratios) for each vaccine were estimated by age groups and sex.

Results We identified 281 and 195 cases of myocarditis or pericarditis for Comirnaty and Spikevax, respectively, which were administrated 163,059,502 and 31,768,352 doses for Comirnaty and Spikevax until the 14th of November 2021, respectively. The OE ratios were statistically significantly higher in adolescent and young adult males in their age of teens and twenties after the second dose in a two-dose series [Comirnaty in teens male: 6.15 (95% CI, 2.26–21.98), Comirnaty in twenties male: 2.86 (95% CI, 1.13–8.38), Spikevax in teens male: 41.59 (95% CI, 5.64–43,281.94), Spikevax in twenties male: 16.84 (95%CI, 6.77–57.49)].

Conclusions Risks of myocarditis and pericarditis following SARS-CoV-2 mRNA vaccines in Japan seems to be significantly elevated for adolescent and young adult males.

Keywords COVID-19 · Myocarditis · Pericarditis · mRNA Vaccines · Observed-to-expected analysis

Introduction

In Japan, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines Comirnaty and Spikevax (previously known as COVID-19 Vaccine Moderna]) were approved for marketing on 14/2/2021 and 21/5/2021, respectively, while vaccination started on 17/2/2021 and 22/5/2021, respectively. Vaccine safety surveillance in Japan is performed by the Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) under the Immunization act[1] and the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices[2]. Medical institutions report suspected adverse events following immunization (AEFIs) adverse in accordance with the

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Immunization act. The PMDA organizes this information and codes the events using the latest version of MedDRA PT. Pharmaceutical companies report suspected adverse reaction events after coding them in MedDRA PT in accordance with the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices. The reason for using MedDRA is that PMDA is a member of the International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use (ICH). The ICH specifies the use of MedDRA to make information on drug safety available in a manner that is comparable to other countries. Among the many AEFIs described, the number of myocarditis or pericarditis cases reported by pharmaceutical companies gradually increased since the first account on 31/3/2021 along with a progressive increase of reporting odds ratios (ROR) of myocarditis for the two vaccines [as of 27 June 2021: Comirnaty (myocarditis:1.91), Spikevax (myocarditis:4.46)]. At the same time, the number of case reports of myocarditis or pericarditis following vaccination in Japan as well as several scientific reports from other countries have also been rising [3]. For example, Matta et al. in the United States summarized case reports on the development of myocarditis after mRNA vaccination in a systematic review and meta-analysis [4]. They collected case reports published between January 1, 2020 and July 17, 2021 and pooled the individual data of 69 patients. In this paper, they reported that 88.5% of patients presented with symptoms after the second dose of mRNA vaccine, were hospitalized a median of 3 days after vaccination, the median age of onset was 21 years, and the majority of patients were male. In addition, a systematic review of myocarditis and pericarditis after mRNA vaccination was conducted by Lane et al. [5] using spontaneous reports and literature from the UK, US, and Europe. In this paper, 62.24% (n = 11 331) of the sexes of those who had myocarditis and pericarditis after mRNA vaccination were reported to be male. In the U.K. and the U.S., more cases were reported in vaccinated persons younger than 40 years of age. (59.7% and 47.3%, respectively), while age trends were less clear in the EU. It was also noted that more cases were reported after the second dose. In these contexts, as of July 7th 2021, the medical package inserts in Japan of both Comirnaty and Spikevax were updated, and particularly the IMPORTANT PRECAUTIONS and OTHER PRECAUTIONS sections were revised. A cautionary statement regarding myocarditis and pericarditis was included in the IMPORTANT PRECAUTIONS section, while the statement "although the causality is unknown, cases of myocarditis and pericarditis have been reported overseas following inoculation with coronavirus modified uridine RNA vaccine (SARS-CoV-2)" was added to the OTHER PRECAUTIONS section.

Myocarditis and pericarditis are very rare diseases. Myocarditis and Pericarditis are inflammatory heart diseases. When inflammation induced by some cause affects myocardium, the condition is diagnosed as myocarditis, whereas when inflammation affects epicardium, the condition is diagnosed as pericarditis. The clinical diagnosis of myocarditis is made on imaging findings which suggest inflammation of myocardium. Imaging modality for diagnosis includes echo-cardiogram, cardiac MRI, and myocardial scintigram. Definitive diagnosis of myocarditis is confirmed by pathological findings of inflammation in myocardium. Endomyocardial biopsy or autopsy is needed to perform pathological diagnosis [2]. The clinical diagnosis of myocarditis is made on imaging findings which suggest inflammation of epicardium. Imaging modality for diagnosis includes electrocardiogram, echo-cardiogram and cardiac MRI. Definitive diagnosis of pericarditis is confirmed by pathological findings of inflammation in myocardium. Pericardial biopsy or autopsy is needed to perform pathological diagnosis [2]. Before the COVID-19 pandemic, they were recognized as illnesses generally occurring after viral and bacterial infections as well as exposure to radiation and drugs, while it was not known whether such diseases could be caused by vaccines. Their diagnosis is complicated by the fact that clinical symptoms and most laboratory findings are non-specific and a differential diagnosis would be needed to distinguish them from other conditions. The prognosis is mostly good, however, some very severe cases with rapid progression may occur [6].

Although the biological mechanisms involved in the development of myocarditis or pericarditis following vaccination against SARS-CoV-2 have not been yet elucidated [7], warnings and regulations about myocarditis and pericarditis have already been issued for mRNA vaccines in several countries [8–11]. For example, Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for the evaluation of drug safety in the European Medicines Agency (EMA), conducted a detailed review of myocarditis in the European Economic Area (EEA) in 145 cases after vaccination of Comirnaty and 19 cases after Spikevax, as well as 138 cases of pericarditis after the use of Comirnaty and a review of reports of 19 cases that developed after the use of Spikevax in the EEA. As of May 31, 2021, approximately 177 million doses of Comirnaty and 20 million doses of Spikevax had been administered in the EEA. As a result, they concluded that on July 9, 2021, myocarditis and pericarditis could occur in very rare cases after vaccination with Comirnaty and Spikevax. They listed myocarditis and pericarditis as a new adverse reaction in the product information for these vaccines, and recommended that a warning be provided to raise awareness among health care professionals[8]. Nevertheless, so far no population-based study to assess this relation in Japan due to the lack of precise data about the incidence of myocarditis and pericarditis in non-vaccinated individuals and the inability of the system to

connect spontaneous reports of adverse events with health care data of vaccinated persons. In addition, it is also unclear whether there are ethnic differences in myocarditis and pericarditis after SARS-CoV-2 mRNA vaccination.

Therefore, this study aims to fill this knowledge gap and identify the relation between the occurrence of myocarditis or pericarditis and SARS-CoV-2 vaccination in Japan.

Methods

Data Source of Observed Cases

To identify the number of cases of myocarditis and pericarditis after vaccination, we used the documents published by the Joint Committee on Adverse Events of Vaccines and Drug Safety of Pharmaceutical Affairs and Food Safety of the Ministry of Health, Labour, and Welfare in Japan [12]. These documents cover all adverse events reported in Japan. The number of cases used in this study is based on spontaneous reports received from pharmaceutical companies between the 17th of February 2021 and 14th of November 2021. The number of vaccinations (Table 1) was also obtained from the published documents of the Joint Committee.

Definition of Background Rate: Incidence in the General Population

The incidence of myocarditis and pericarditis in the general population before the COVID-19 pandemic could be found in the documents published by the Joint committee [12], and was calculated using the National Database of Health Insurance Claims and Specific Health Check-ups of Japan (NDB) and the data of population estimates in the Portal Site of Official Statistics of Japan run by the Ministry of Internal Affairs and Communication [13]. To define the number of myocarditis and pericarditis cases as numerator of the background rate, NDB was used, while to calculate the denominator, the data of the estimated population in the Portal Site was used because of limited data availability. NDB is a national database run by the government, which contains national health insurance claims data and specific health check data. Almost all 127 million Japanese citizens belong to this health insurance system, thus this database covers almost all Japanese population. To calculate the incidence, personal identifier (ID0 variable[1]), date, age group, sex, diagnosis codes according to the International Classification of Diseases (ICD-10) were extracted from NDB. In order to identify a more accurate the number of case, suspected diagnosis codes were excluded. The incidence of myocarditis and pericarditis was classified in two groups, i.e., narrow and broad. The "narrow" group was defined by the diagnosis of acute myocarditis or acute pericarditis, while the "broad" group dealt with the diagnosis of myocarditis or pericarditis with the exception of those induced by radiation and neoplasm as well as chronic conditions.

Definition of the Outcome: Observed Cases

The outcome of myocarditis and pericarditis among vaccinated individuals was defined according to the MedDRA code Ver24.1 system as follows: Myocarditis (10028606/Myocarditis, 10014961/Eosinophilic myocarditis, 10083635/Giant cell myocarditis, 10064539/Autoimmune myocarditis, and 10082606/Immune-mediated myocarditis) and Pericarditis (10034484/Pericarditis, 10079058/Autoimmune pericarditis, and 10059361/Pleuropericarditis). When at least one of these codes occurred in a spontaneous report, it was counted as a case of myocarditis or pericarditis. The incidence of myocarditis is combined with that of pericarditis because the two diseases are very similar inflammatory conditions that can coexist. In fact, some case reports contained these two events at the same time and making it difficult to conclude whether the inflammation was limited only to the myocardium or pericardium. When myocarditis and pericarditis appear in a same spontaneous report, we counted as one case.

Statistical Method: OE Analysis

To assess the relation between SARS-CoV-2 vaccination and myocarditis or pericarditis, we used an observed-to-expected analysis (OE analysis). In this analysis, we calculated rate ratios with the observed rates of myocarditis and pericarditis after the vaccination of SARS-CoV-2 vaccines and the expected rate, which is the incidence of myocarditis and pericarditis in the general population before the COVID-19 pandemic calculated with Japanese Health insurance claims data NDB. According to the guidelines on good pharmacovigilance of the European Medicines Agency, this type of analysis is useful for population-based vaccination programs that require immediate decisions on safety concerns. Furthermore, it is also useful for the evaluation of signals in case of lack of reliable epidemiological data [14]. The formula for calculating the OE ratio and Poisson confidential interval (risk$\alpha = 5\%$), which was used in this study, is shown below:

$$\widehat{OE\ ratio} = \frac{Observedcases(a)}{Personyearpar100,000(c_1)} \Big/ \frac{Expectedcases(b)}{Personyearpar100,000(c_2)}$$

[1] Referred by preprint article: Shinichiro K, Tatsuya N, Tomoya M, et al. National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB): Outline and patient-matching technique. bioRxiv 2018. https://doi.org/10.1101/280008

Table 1 Number of vaccinations using COVID-19 mRNA vaccines in Japan (From 17th of February 2021 to 14th of November 2021)

Comirnaty		12–19	20–29	30–39	40–49	50–59	60–69
1st dose	Male	2,872,854	2,852,280	3,703,367	5,419,628	5,702,254	6,129,070
	Female	2,790,385	3,391,311	4,402,039	6,393,544	6,581,720	6,745,140
	Unknown	1927	4831	6471	9397	10,070	10,428
	Total	5,665,166	6,248,422	8,111,877	11,822,569	12,294,044	12,884,638
2nd dose	Male	2,555,822	2,561,369	3,408,923	5,151,780	5,534,662	6,067,439
	Female	2,473,955	3,082,276	4,088,289	6,089,327	6,363,346	6,655,197
	Unknown	2514	4542	6168	9453	10,174	10,464
	Total	5,032,291	5,648,187	7,503,380	11,250,560	11,908,182	12,733,100
Spikevax							
1st dose	Male	501,258	1,989,181	1,926,608	2,189,300	1,819,728	691,930
	Female	477,527	1,588,792	1,290,674	1,453,561	1,171,070	466,933
	Unknown	3330	4061	1674	2242	1939	524
	Total	982,115	3,582,034	3,218,956	3,645,103	2,992,737	1,159,387
2nd dose	Male	458,685	1,925,424	1,861,732	2,113,447	1,761,575	675,965
	Female	445,505	1,539,243	1,243,384	1,398,770	1,131,493	455,309
	Unknown	2482	4000	1588	2096	1857	511
	Total	906,672	3,468,667	3,106,704	3,514,313	2,894,925	1,131,785

Comirnaty		70–79	80–89	90–99	100-	Unknown	Total
1st dose	Male	6,792,838	3,395,698	564,385	8597	58	37,441,029
	Female	8,019,904	5,203,963	1,607,207	63,818	95	45,199,126
	Unknown	9301	5903	2131	91	393,981	454,531
	Total	14,822,043	8,605,564	2,173,723	72,506	394,134	83,094,686
2nd dose	Male	6,772,200	3,382,574	559,964	8433	54	36,003,220
	Female	7,988,112	5,180,448	1,593,399	62,779	102	43,577,230
	Unknown	9349	5930	2,163	91	323,518	384,366
	Total	14,769,661	8,568,952	2,155,526	71,303	323,674	79,964,816
Spikevax							
1st dose	Male	245,727	38,780	3054	17	24	9,405,607
	Female	199,408	43,401	5758	94	33	6,697,251
	Unknown	16	3	2	0	56,471	70,262
	Total	445,151	82,184	8814	111	56,528	16,173,120
2nd dose	Male	242,382	38,113	2971	19	17	9,080,330
	Female	196,324	42,491	5586	85	17	6,458,207
	Unknown	16	2	2	0	44,134	56,688
	Total	438,722	80,606	8559	104	44,168	15,595,225

$c_1 = c_2$ =number of vaccine × Risk window $(day)/365.2425/100,000$

b = backgroud rate (Person year par $100,000$) × c_2

The ratios were estimated by age group every 10 years from 10–19 to 80 + years and based on sex. A 14-day risk window was selected for the estimation. The general population incidence of the narrow definition was used, and subjects whose date of onset of adverse events was not

$$\widehat{OE\,ratio}\,CI = \left(\frac{c_2}{c_1}\right)\left(\frac{a}{b+1}\right)\frac{1}{F_{\alpha/2,2(b+1),2a}}to\left(\frac{c_2}{c_1}\right)\left(\frac{a+1}{b}\right)F_{\alpha/2,2(a+1),2b}$$

reported were excluded. Different analyses were performed based on the number of doses, which were distinguished in three groups: 1st dose, 2nd dose, and 1st + 2nd doses.

This statistical analysis was conducted with Microsoft Office Excel 2016 and performed between November 15 and December 2, 2021.

Sensitivity Analysis

The estimated ratios are uncertain due to the number observed, diagnostic certainty of adverse events, exposure levels, and incidence in the general population [14]. We therefore performed sensitivity analyses calculating OE ratios in different condition from OE analysis at the levels of the risk window, definition of incidence in the general population, and number of observations.

This sensitivity analysis follows the same methodology as the main analysis described in the previous section, except for the following changes in the analysis conditions. We applied the risk window at 7, 14, and 21 days for Comirnaty, and 7, 14, and 28 days for Spikevax considering the interval between two injections and the time of onset of myocarditis or pericarditis after vaccination that we observed from the spontaneous reports. We also performed analyses with the broad definition of incidence in the general population. In addition, we performed analyses including subjects who did not have the day of occurrence of the adverse event. Finally, we performed 72 sets of analyses (Table2) including the main analysis.

Microsoft Office Excel 2016 was used for the analyses, which was performed between November 15 and December 2, 2021.

All analyses in this study were performed as a public health obligation and not as a research activity.

Results

Descriptive Data

The number of vaccinations in Japan with both vaccines from 17th of February 2021 until the 14th of November 2021 corresponded to 163,059,502 (1st dose: 83,094,686, 2nd dose: 79,964,816) and 31,768,352 doses (1st dose: 16,173,120, 2nd dose: 15,595,225) for Comirnaty and Spikevax, respectively (Table 1). Comirnaty comprised 83.7% of mRNA vaccines vaccinated in Japan during this period. Those vaccinated with Comirnaty were older and more likely to be female than those vaccinated with Spikevax. We identified 281 cases of myocarditis or pericarditis for Comirnaty and 195 cases for Spikevax among the spontaneous reports dating between the 17th of February 2021 and 14th of November 2021 (Table 3). As for the proportion of sex among the cases, it was higher for males than females for both vaccines (Comirnaty: 61.9%, Spikevax: 88.2%). For male age groups, adolescents and young adults, especially in the 12–19 and 20–29 age groups, exhibited more cases than other generations for both vaccines. As for the date of the onset of cases, the majority of cases occurred up to day 7 for both vaccines.

OE Analysis

Table 4 and Figs. 1 and 2 illustrate the main results of the OE analyses. For the two vaccines, the lower 95% confidential interval (CI) of the OE ratios were higher than 1 in males in 10–19 years (OE ratio: Comirnaty 6.15 [2.26–21.98], Spikevax 41.59 [5.64–43,281.94]) and 20–29 years (OE ratio: Comirnaty 2.86 [1.13–8.38], Spikevax 16.84 [6.77–57.49]) at the 2nd dose analysis. At the 1st + 2nd doses analysis, it was higher than 1 in males in 10–19 years (OE ratio: 20.53 [4.70–295.10]) and 20–29 years (OE ratio: 8.81 [4.59–19.00]) for Spikevax, but only in 10–19 years (OE ratio: 3.62 [1.73–8.36]) for Comirnaty. Compared to males, there is nothing in the lower 95% confidential intervals of the OE ratios which is greater than 1 in females for all 3 analyses and in males for the 1st dose analysis. As age decreased, the estimated OE ratios generally increased for both vaccines in both sexes.

Sensitivity Analyses

Table 5 shows the summary of results for sensitivity analyses comparing principal analyse. The details of the results of the sensitivity analyses are showed in Appendix 1–11. The ranges of OE ratios in each condition of sensitivity analyses were generally similar to those of the main analyses; the lower values of the CI of the OE ratios were higher than 1 in young males for both vaccines, especially at the 2nd dose for all testing conditions. While a trend toward higher OE ratios with shorter risk window was observed in comparing between the principal analysis and the sensitivity analysis, and in some of the analysis conditions with a 7-day risk window, there were cases in which the lower CI of the OE ratio exceeded 1 in males in 30–39 years for both vaccines, the patterns in differences between the two vaccines and relationships between age or sex and OE ratios did not significantly differ between the main and sensitivity analyses.

Discussion

The conducted OE analysis showed a statistical relation between vaccination and occurrence of myocarditis and pericarditis, especially in adolescent and young adult males with the second dose of either Comirnaty or Spikevax.

Table 2 Condition of 72 sets of OE analyse

	Definition of myocarditis/ Pericarditis	Risk window (day)*	Cases with unknown onset data	Dose number	Table
Principal anlyse	Narrow	14	Not include	1st + 2nd dose	Table 4
	Narrow	14	Not include	1st dose	
	Narrow	14	Not include	2nd dose	
Sensitivity analyse	Narrow	14	Include	1st + 2nd dose	Appendix 1
	Narrow	14	Include	1st dose	
	Narrow	14	Include	2nd dose	
	Broad	14	Not include	1st + 2nd dose	Appendix 2
	Broad	14	Not include	1st dose	
	Broad	14	Not include	2nd dose	
	Broad	14	Include	1st + 2nd dose	Appendix 3
	Broad	14	Include	1st dose	
	Broad	14	Include	2nd dose	
	Narrow	21 or 28	Not include	1st + 2nd dose	Appendix 4
	Narrow	21 or 28	Not include	1st dose	
	Narrow	21 or 28	Not include	2nd dose	
	Narrow	21 or 28	Include	1st + 2nd dose	Appendix 5
	Narrow	21 or 28	Include	1st dose	
	Narrow	21 or 28	Include	2nd dose	
	Broad	21 or 28	Not include	1st + 2nd dose	Appendix 6
	Broad	21 or 28	Not include	1st dose	
	Broad	21 or 28	Not include	2nd dose	
	Broad	21 or 28	Include	1st + 2nd dose	Appendix 7
	Broad	21 or 28	Include	1st dose	
	Broad	21 or 28	Include	2nd dose	
	Narrow	7	Not include	1st + 2nd dose	Appendix 8
	Narrow	7	Not include	1st dose	
	Narrow	7	Not include	2nd dose	
	Narrow	7	Include	1st + 2nd dose	Appendix 9
	Narrow	7	Include	1st dose	
	Narrow	7	Include	2nd dose	
	Broad	7	Not include	1st + 2nd dose	Appendix 10
	Broad	7	Not include	1st dose	
	Broad	7	Not include	2nd dose	
	Broad	7	Include	1st + 2nd dose	Appendix 11
	Broad	7	Include	1st dose	
	Broad	7	Include	2nd dose	

*Risk window: 21 days for Comirnaty, 28 days for Spikevax

Practical Implication

In other countries, the following measures against myocarditis and pericarditis have been taken. In the U.S. package inserts for both Comirnaty and Spikevax, myocarditis is listed in section "6.2 Post-Authorization Experience" as an adverse reaction that was identified after marketing [15, 16]. In addition, the package insert of Spikevax notes that some observational studies using post-marketing data have shown that the risk of myocarditis may be higher in males under 40 years at the second dose of Spikevax compared to other approved mRNA vaccines for Covid-19[16]. Furthermore, the package inserts in the U.K. and Europe, as of May 2022, list myocarditis as an very rare adverse reaction (< 1/10,0000) in "4.8 Undesirable effects" for both Comirnaty and Spikevax. Furthermore, in the package inserts for both Comirnaty and Spikevax [17–20]in the U.S., the U.K., and the EU, the section "5 WARNINGS AND PRECAUTIONS" or "4.4 Special warnings and precautions for use" lists that cases of post-vaccination myocarditis are more

Table 3 Description of case characteristics

	Comirnaty (n = 281)			Spikevax (n = 195)		
	Male	Female	Unknown	Male	Female	Unknown
	174	104	3	172	23	0
Age group						
12–19	43	12	2	41	3	0
20–29	38	5	0	97	4	0
30–39	20	9	1	13	6	0
40–49	15	12	0	14	6	0
50–59	12	16	0	3	3	0
60–69	15	14	0	2	1	0
70–79	17	11	0	0	0	0
80 or more	10	16	0	0	0	0
Unknown	4	9	0	2	0	0
Day of onset						
0	23	14	0	16	5	0
1	39	16	0	45	1	0
2	21	5	1	39	2	0
3	8	7	0	30	0	0
4	9	3	0	11	5	0
5	4	3	0	5	1	0
6	2	1	0	0	0	0
7	7	0	0	1	0	0
8 ~ 14	12	8	0	2	2	0
15 ~ 21	4	6	0	3	2	0
22 ~ 28	0	3	0	2	0	0
29 ~ 60	2	1	0	2	1	0
61 ~ 90	0	1	0	0	0	0
Unknown	43	36	2	16	4	0
Doses						
1st dose	71	63	2	28	9	0
2nd dose	103	41	1	144	14	0

frequently reported in young males and after the second dose of vaccination. In addition to the OE analysis results, we compared the results of studies and measures taken in other countries [4–7, 15–20], whose results showed a similar tendency in the age and sex of individuals with a the risk of myocarditis or pericarditis after the vaccination, and we determined that myocarditis and pericarditis are risks that require attention after mRNA vaccination in Japan because of the report of severe cases of these diseases leading to cardiogenic shock, cardiac tamponade, or sudden death. On the basis of this evaluation, as of December the 3rd 2021, the package inserts of both Comirnaty and Spikevax were further updated to list myocarditis and pericarditis as "SERIOUS ADVERSE REACTIONS", and also the Ministry of Health, Labour and Welfare (MHLW) imposed an obligation for the medical institutions to report adverse reactions as myocarditis and pericarditis. Furthermore, in the IMPORTANT PRECAUTIONS section, the sentence "Although the causal relationship with this vaccine is unknown, cases of myocarditis and pericarditis have been reported following inoculation with this vaccine" was replaced by "Myocarditis, pericarditis may occur" To the Clinically Significant Adverse Reactions section, myocarditis and pericarditis were also added. In the OTHER PRECAUTIONS section, the sentence "Although the causal relationship is unknown" was removed, and the information that myocarditis and pericarditis occur especially following the second inoculation of the vaccine was added.

We performed an OE analysis to identify the relation between mRNA vaccines against COVID-19 and myocarditis or pericarditis because of the following reasons: (1) Post-vaccination myocarditis and pericarditis have been attracting attention in Japan and abroad, and the accumulation of cases including several serious cases have been observed in Japan; (2) The Reporting OR was also calculated to be high, although we have the limitation of using individual

Table 4 Results of the observed-to-expected analysis—Principal analyses (Risk window: 14 days; Definition of back ground incidence: narrow; Subjects: excluded those whose date of onset of adverse events is unknown)

	Male						Female					
	Comirnaty			Spikevax			Comirnaty			Spikevax		
1st + 2nd dose	Observed case	O/E ratio	95%CI	Observed case	O/E ratio	95%CI	Observed case	O/E ratio	95%CI	Observed case	O/E ratio	95%CI
10–19 years	35	3.62	**[1.73–8.36]**	35	20.53	**[4.70–295.10]**	8	1.72	[0.48–7.18]	3	3.69	[0.25–4710.74]
20–29 years	26	1.85	[0.93–3.84]	90	8.81	**[4.59–19.00]**	2	0.32	[0.03–1.80]	3	0.99	[0.13–7.40]
30–39 years	11	0.75	[0.31–1.76]	12	1.53	[0.57–4.45]	4	0.51	[0.11–1.97]	4	1.72	[0.26–19.06]
40–49 years	12	0.56	[0.25–1.20]	8	0.92	[0.31–2.75]	8	0.64	[0.23–1.67]	3	1.05	[0.14–9.43]
50–59 years	10	0.4	[0.17–0.87]	2	0.25	[0.03–1.30]	9	0.68	[0.26–1.71]	2	0.85	[0.06–11.69]
60–69 years	9	0.27	[0.11–0.58]	2	0.54	[0.05–4.14]	9	0.53	[0.21–1.27]	1	0.86	[0.01–67.48]
70–79 years	13	0.23	[0.12–0.43]	0	–	–	8	0.26	[0.10–0.58]	0	–	–
80 + years	7	0.17	[0.07–0.39]	0	–	–	9	0.26	[0.11–0.56]	0	–	–
1st dose	Observed case	O/E ratio	95% CI	Observed case	O/E ratio	95% CI	Observed case	O/E ratio	95% CI	Observed case	O/E ratio	95% CI
10–19 years	7	1.37	[0.37–5.46]	1	1.12	[0.01–2013.77]	5	2.03	[0.35–21.34]	0	–	–
20–29 years	7	0.95	[0.29–3.16]	6	1.16	[0.30–4.82]	2	0.61	[0.05–5.35]	1	0.65	[0.01–19.76]
30–39 years	3	0.39	[0.07–1.68]	2	0.5	[0.05–3.87]	4	0.99	[0.19–5.33]	3	2.54	[0.22–133.20]
40–49 years	5	0.46	[0.12–1.45]	1	0.23	[0.00–2.28]	4	0.62	[0.13–2.62]	2	1.36	[0.08–80.52]
50–59 years	4	0.32	[0.08–1.04]	1	0.25	[0.01–2.52]	4	0.59	[0.13–2.40]	0	–	–
60–69 years	5	0.3	[0.09–0.85]	0	–	–	6	0.7	[0.20–2.26]	1	1.69	[0.02–3046.18]
70–79 years	9	0.32	[0.13–0.71]	0	–	–	5	0.32	[0.09–0.94]	0	–	–
80 + years	5	0.25	[0.07–0.68]	0	–	–	6	0.35	[0.11–0.93]	0	–	–
2nd dose	Observed case	O/E ratio	95% CI	Observed case	O/E ratio	95% CI	Observed case	O/E ratio	95% CI	Observed case	O/E ratio	95% CI
10–19 years	28	6.15	**[2.26–21.98]**	34	41.59	**[5.64–43,281.94]**	3	1.38	[0.16–16.47]	3	7.64	※2
20–29 years	19	2.86	**[1.13–8.38]**	84	16.84	**[6.77–57.49]**	0	–	–	2	1.35	[0.08–79.68]
30–39 years	8	1.14	[0.36–3.69]	10	2.6	[0.73–12.72]	0	–	–	1	0.88	[0.01–68.91]
40–49 years	7	0.67	[0.22–1.96]	7	1.64	[0.42–7.64]	4	0.65	[0.14–2.75]	1	0.71	[0.01–55.67]
50–59 years	6	0.49	[0.15–1.42]	1	0.26	[0.01–2.84]	5	0.76	[0.19–2.89]	2	1.72	[0.10–101.51]
60–69 years	4	0.24	[0.06–0.75]	2	1.09	[0.08–24.10]	3	0.36	[0.06–1.48]	0	–	–
70–79 years	4	0.14	[0.04–0.41]	0	–	–	3	0.2	[0.04–0.69]	0	–	–
80 + years	2	0.1	[0.01–0.41]	0	–	–	3	0.18	[0.03–0.61]	0	–	–

Bold values mean that the lower 95% confidential interval (CI) of the OE ratios were higher than 1

※1…does not include the cases for which sex is unknown

※2…not possible to calculate because the number of expected cases is very small

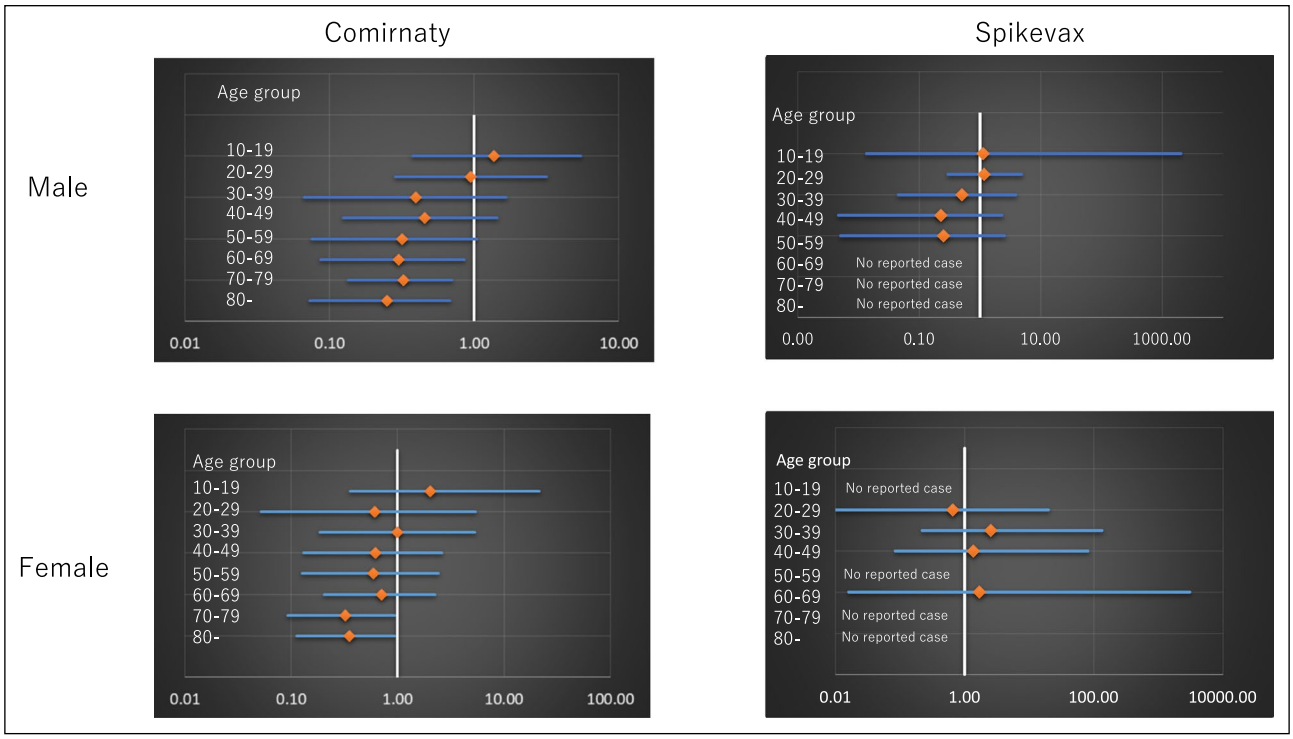

Figure 1 OE ratios of myocarditis and pericarditis of receipt of 1st dose of Comirnaty and Spikevax by age group and gender.

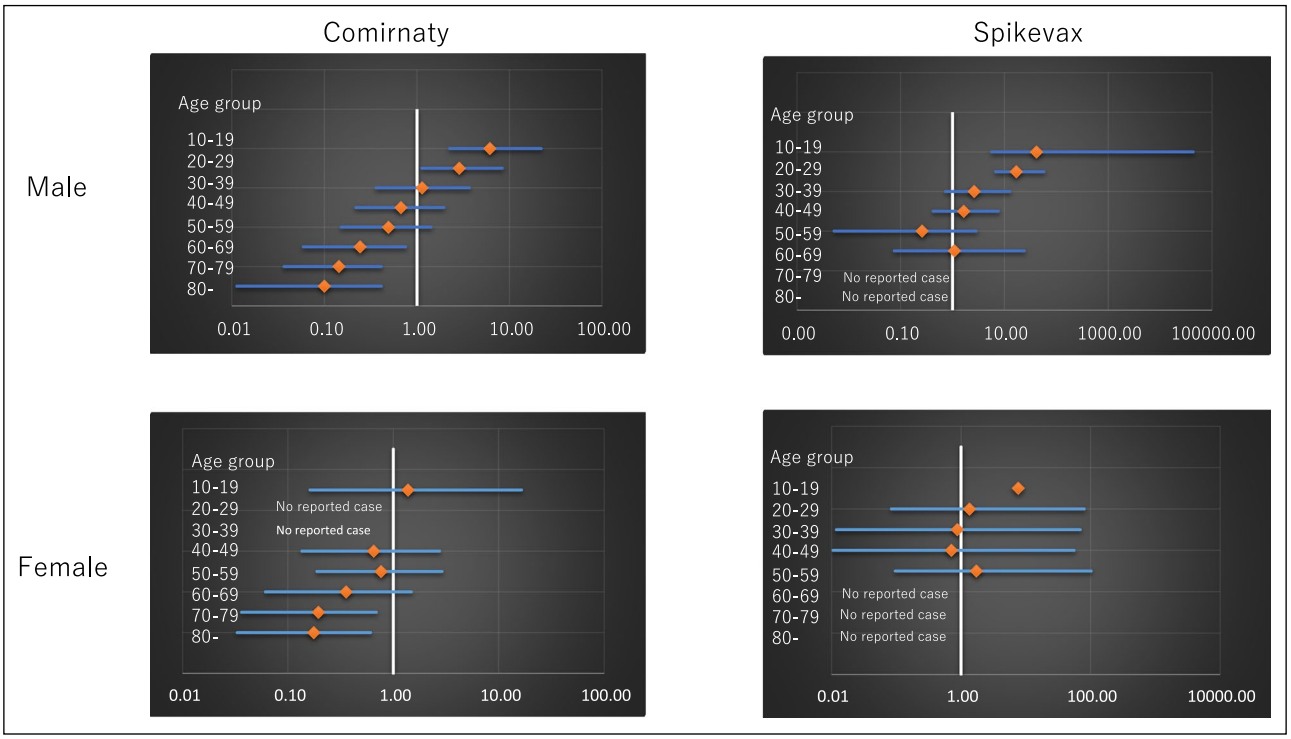

Figure 2 OE ratios of myocarditis and pericarditis of receipt of 2nd dose of Comirnaty and Spikevax by age group and gender.

Table 5 Summary of results for sensitivity analyses comparing principal analyse

	Definition of myocarditis/Pericarditis	Risk window (day)*	Cases with unknown onset data	Dose number	Age group and gender whose lower CI of OE ratio is greater than 1		Details of result in
					Comirnaty	Spikevax	
Principal anlyse	Narrow	14	Not include	1st + 2nd dose	Male:10–19	Male:10–19,20–29	Table 4
	Narrow	14	Not include	1st dose	None	None	
	Narrow	14	Not include	2nd dose	Male:10–19,20–29	Male:10–19,20–29	
Sensitivity analyse	Narrow	14	Include	1st + 2nd dose	Male:10–19,20–29	Male:10–19,20–29	Appendix 1
	Narrow	14	Include	1st dose	None	None	
	Narrow	14	Include	2nd dose	Male:10–19,20–29	Male:10–19,20–29	
	Broad	14	Not include	1st + 2nd dose	Male:10–19	Male:10–19,20–29	Appendix 2
	Broad	14	Not include	1st dose	None	None	
	Broad	14	Not include	2nd dose	Male:10–19	Male:10–19,20–29	
	Broad	14	Include	1st + 2nd dose	Male:10–19	Male:10–19,20–29	Appendix 3
	Broad	14	Include	1st dose	None	None	
	Broad	14	Include	2nd dose	Male:10–19,20–29	Male:10–19,20–29	
	Narrow	21 or 28	Not include	1st + 2nd dose	Male:10–19	Male:10–19,20–29	Appendix 4
	Narrow	21 or 28	Not include	1st dose	None	None	
	Narrow	21 or 28	Not include	2nd dose	Male:10–19	Male:10–19,20–29	
	Narrow	21 or 28	Include	1st + 2nd dose	Male:10–19,20–29	Male:10–19,20–29	Appendix 5
	Narrow	21 or 28	Include	1st dose	None	None	
	Narrow	21 or 28	Include	2nd dose	Male:10–19,20–29	Male:10–19,20–29	
	Broad	21 or 28	Not include	1st + 2nd dose	None	Male:10–19,20–29	Appendix 6
	Broad	21 or 28	Not include	1st dose	None	None	
	Broad	21 or 28	Not include	2nd dose	Male:10–19	Male:10–19,20–29	
	Broad	21 or 28	Include	1st + 2nd dose	None	Male:10–19,20–29	Appendix 7
	Broad	21 or 28	Include	1st dose	None	None	
	Broad	21 or 28	Include	2nd dose	Male:10–19	Male:10–19,20–29	
	Narrow	7	Not include	1st + 2nd dose	Male:10–19,20–29	Male:10–19,20–29	Appendix 8
	Narrow	7	Not include	1st dose	None	None	
	Narrow	7	Not include	2nd dose	Male:10–19,20–29	Male:20–29,30–39	
	Narrow	7	Include	1st + 2nd dose	Male:10–19,20–29,30–39	Male:10–19,20–29	Appendix 9
	Narrow	7	Include	1st dose	None	None	
	Narrow	7	Include	2nd dose	Male:10–19,20–29,30–39	Male:20–29,30–39	
	Broad	7	Not include	1st + 2nd dose	Male:10–19,20–29	Male:10–19,20–29	Appendix 10
	Broad	7	Not include	1st dose	None	None	
	Broad	7	Not include	2nd dose	Male:10–19,20–29	Male:10–19,20–29	
	Broad	7	Include	1st + 2nd dose	Male:10–19,20–29	Male:10–19,20–29	Appendix 11
	Broad	7	Include	1st dose	None	None	
	Broad	7	Include	2nd dose	Male:10–19,20–29	Male:10–19,20–29	

*Risk window: 21 days for Comirnaty, 28 days for Spikevax

data among vaccinated people. Under the Immunisation Act, we have the Adverse Drug Reaction reporting system (clause 12). All reports of death and serious cases and some adverse events of special interest (anaphylaxis and others), which are send to PMDA, were investigated and causality between vaccination and each event was discussed based on opinions from clinical experts. As a result of the causality assessment by experts, almost all cases were concluded to be unassessable or unclassified. In general, the reasons for the difficulty in assessing the causality of vaccination and AEFI are as follows: (1) Vaccines are often administered to healthy individuals, and background information on underlying diseases is lacking, (2) There are few events that can be explained based on the pharmacological effects of the vaccine itself, and in many cases it is difficult to evaluate the causality of events that occur after vaccination based on pharmacological mechanisms, (3) It is not possible to distinguish drug adverse events from accidental events or complications and events induced by concomitant medications. In addition to the above, the following factors are specific to cases of myocarditis and pericarditis: these diseases are very rare and have not been known to be caused by any vaccines.

Comparison with the Situation of Other Countries

The reported rates of myocarditis and pericarditis after the second dose of mRNA COVID-19 vaccines were 3.2 and 1.3 cases per million doses in Japan for Comirnaty, respectively. 13.2 and 2.7 cases for Spikevax, respectively (as of June 12, 2022). In the U.S., this reporting rate is 3.7 cases per million doses of vaccination, which is calculated based on all number of vaccinations using Comirnaty and Spikevax combined [21]. Although the reporting rate in Japan is not comparable to that in the U.S. due to differences in the method of collecting adverse reaction reports after vaccination, we cannot conclude that the reporting rate in Japan is more extreme than that in the U.S. This is the reason for the bias in our analysis. We judge it unlikely that this reporting rate situation has a significant influence on our results as a bias in our analysis.

Furthermore, when we compare the calculated OE rations to overseas situations, our results are consistent with the results of analyses or reports by EMA, CDC, and Public Health Ontario at the subgroup level that presents a significant risk of myocarditis or pericarditis [8–10]. A group of FDA has effectuated an OE analysis of myocarditis and pericarditis after vaccination of Comirnaty and Spikevax using several health care insurance claim database [22]. Table 6 shows comparison of results of OE analysis between FDA study and ours. Despite differences in the age categories used in the analysis, there were similarities in that young men were at higher risk of post-vaccine myocarditis and pericarditis for both vaccines compared to other sexes and age groups. In contrast, the results of a case–control study by the EPI-PHARE team in France, which was effectuated using a single database of the national health insurance, differed from our and other analyses. The results of the study conducted in France showed that the risk of myocarditis occurred not only in young males but also young females, who exhibited a statistically significant risk (OR at the second dose after up to 7 days of vaccination: Comirnaty 11.4 [95%CI: 4.5–28.6], Spikevax 40.6 [95%CI: 9.9–166.4]) [23]. For this study, the health insurance data from the total population were used when they detected cases of myocarditis or pericarditis after vaccination. Their case detection therefore seems to be more comprehensive than that of our study. This explains why it is possible to have more cases of myocarditis or pericarditis after the vaccination in Japan than those detected in the spontaneous reports of suspected adverse events. This factor may be the reason for the difference between the French study and our analysis. On the other hand, considering that our analysis is based on a large sample size of approximately 200 million doses of mRNA vaccine, we are awaiting the results of further analysis in the immediate future.

Limitations and Strengths of This Analyses

It should be noted that this study has some limitations. Firstly, our analysis is based on several different databases, with different definitions between the observed cases, which are identified in spontaneous reports of suspected adverse events, and the expected cases in the general population, which are identified in the NDB. At the moment, we do not have an infrastructure for the evaluation of myocarditis/pericarditis cases of both vaccinated and non-vaccinated individuals using a single database. Secondly, we did not use a criterion that can specify the level of diagnostic precision when we identified the cases. We only considered the diagnosis code for the definition of the observed and expected cases, and we were unable to evaluate the clinical presentations and the results of diagnostic tests in more detail. This is responsible for some diagnostic uncertainty. However, when calculating the expected cases in the NDB, the accuracy of the data was ensured as far as possible by removing the suspected disease codes and using a unique Patient-Matching Technique[2] to remove duplicates. Thirdly, as we used spontaneous reports, there is a possibility of underestimation of the incidence of adverse events. To overcome these concerns and verify the robustness of the main analysis, we performed the sensitivity analyses under many analysis conditions. We believe that this study is the best possible estimation considering the present data collection system in Japan.

Despite these limitations, this study has the following strengths. Our analysis is the first large SARS-CoV-2 mRNA vaccine analysis of approximately 200 million doses for east Asian population. While some medicines have shown ethnic differences in efficacy and safety between Japanese and the others, we can show that this new modality of mRNA vaccines have no ethnic differences between Japan and overseas in terms of safety against myocarditis and pericarditis, comparing to the analysis in North America and the EU. In addition, it is very meaningful that the pharmacoepidemiologic assessment was conducted as a complement to the limiting factors of individual case assessment, and was used as one of the factors to decide whether or not to take a regulatory action in a timely manner. Since there are several limitations to the interpretation of the OE analysis, it would be desirable to use a single database for further evaluation, but this will require infrastructure development and a tremendous amount of time to create it. In the tense situation

[2] Referred by preprint article: Shinichiro K, Tatsuya N, Tomoya M, et al. National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB): Outline and patient-matching technique. bioRxiv 2018. https://doi.org/10.1101/280008

Table 6 Comparison of results of OE analysis

Japan					Wong et al. [22]					
Number of vaccine doses					Number of vaccine doses					
Comirnaty			Spikevax				Comirnaty		Spikevax	
163,059,502			31,768,353		DP2		159,435		84,586	
					DP3		262,536		47,301	
					DP4		209,473		37,285	
	Comirnaty		Spikevax				Comirnaty		Spikevax	
Male	O/E ratio	95%CI	O/E ratio	95%CI	Male		O/E ratio	95%CI	O/E ratio	95%CI
10–19 years	4.42	**[2.11–10.36]**	25.08	**[5.65–359.03]**	18–25 years	DP2	10.74	**[5.36–19.21]**	9.07	**[2.95–21.17]**
20–29 years	3.18	**[1.62–6.80]**	10.82	**[5.38–25.05]**		DP3	9.69	**[5.74–15.31]**	9.97	**[4.78–18.33]**
30–39 years	1.45	[0.69–3.14]	1.50	[0.53–4.56]		DP4	4.80	**[2.30–8.82]**	13.30	**[7.27–22.31]**
40–49 years	0.54	[0.24–1.14]	1.21	[0.46–3.32]	26–35 years	DP2	3.85	**[1.25–8.97]**	4.06	[0.84–11.85]
50–59 years	0.38	[0.17–0.78]	0.32	[0.06–1.30]		DP3	4.30	**[1.96–8.16]**	4.89	**[1.80–10.65]**
60–69 years	0.31	[0.15–0.60]	0.45	[0.04–3.17]		DP4	3.88	**[2.00–6.77]**	4.14	**[1.67–8.54]**
70–79 years	0.18	[0.09–0.33]	–	–	36–45 years	DP2	1.70	[0.35–4.97]	1.97	[0.24–7.11]
80 + years	0.11	[0.04–0.25]	–	–		DP3	2.28	[0.84–4.97]	3.27	**[1.37–8.10]**
						DP4	0.82	[0.17–2.40]	2.90	**[1.07–6.32]**
					46–55 years	DP2	0.85	[0.13–3.09]	1.39	[0.17–5.01]
						DP3	1.18	[0.32–3.02]	0.89	[0.11–3.23]
						DP4	1.32	[0.43–3.09]	0.44	[0.01–2.46]
					56–64 years	DP2	1.08	[0.22–3.15]	0.52	[0.01–2.88]
						DP3	1.11	[0.36–2.58]	0.90	[0.18–2.62]
						DP4	1.20	[0.39–2.79]	1.44	[0.39–3.69]
	Comirnaty		Spikevax				Comirnaty		Spikevax	
Female	O/E ratio	95%CI	O/E ratio	95%CI	Female		O/E ratio	95%CI	O/E ratio	95%CI
10–19 years	1.77	[0.57–6.22]	3.03	[0.23–3869.53]	18–25 years	DP2	3.78	[0.46–13.66]	10.83	**[2.23–31.64]**
20–29 years	0.54	[0.12–2.11]	0.83	[0.12–5.42]		DP3	4.47	**[1.22–11.45]**	4.21	[0.51–15.21]
30–39 years	0.78	[0.27–2.20]	1.96	[0.42–12.13]		DP4	9.28	**[4.24–17.62]**	2.06	[0.05–11.48]
40–49 years	0.52	[0.21–1.24]	0.51	[0.05–3.92]	26–35 years	DP2	1.33	[0.03–7.40]	2.56	[0.06–14.25]
50–59 years	0.53	[0.24–1.11]	0.74	[0.11–4.38]		DP3	0.93	[0.02–5.19]	0.00	[0.00–6.05]
60–69 years	0.48	[0.23–0.93]	0.50	[0.01–9.56]		DP4	0.69	[0.02–3.85]	1.34	[0.00–7.47]
70–79 years	0.15	[0.06–0.32]	–	–	36–45 years	DP2	4.26	**[1.56–9.27]**	0.00	[0.00–4.69]
80 + years	0.17	[0.08–0.32]	–	–		DP3	1.01	[0.12–3.65]	0.00	[0.00–3.09]
						DP4	2.22	[0.72–5.18]	0.00	[0.00–3.01]
					46–55 years	DP2	1.66	[0.34–4.86]	1.83	[0.22–6.60]
						DP3	0.35	[0.01–1.93]	3.16	**[1.16–6.88]**
						DP4	2.67	**[1.07–5.50]**	0.66	[0.02–3.36]
					56–64 years	DP2	3.67	**[1.58–7.23]**	0.67	[0.02–3.72]
						DP3	1.43	[0.47–3.35]	1.54	[0.42–3.94]
						DP4	1.72	[0.56–4.01]	1.05	[0.13–3.80]

Bold values mean that the lower 95% confidential interval (CI) of the OE ratios were higher than 1.

[Conditions of analysis]

Wong et al.: 1st + 2nd dose, risk windows 7 days, Calculating OE ratios in 3 database (DP2,DP3 and DP4)

Japan: 1st + 2nd dose, Risk window 7 days, Definition of background incidence: broad, Subjects: included those whose date of onset of adverse events is unknown

of the COVID-19 pandemic, rapidity is also critical in risk management of vaccines, and this our OE analysis is the best that can be achieved at present in Japan.

Conclusion

In conclusion, a large-scale study was conducted that confirmed a statistically significant association between the development of myocarditis or pericarditis and the two available mRNA vaccines against SARS-CoV-2 in adolescent and young adult males in Japan. However, considering the vaccine effectiveness, the efficacy in preventing severe disease and the frequency of theses adverse events, the benefit-risk ratio for the risk of myocarditis and pericarditis identified in this study remains positive.

Author Contributions

HK, SF, RM, YA, YK, TH, YS, TN, TI, YN, TY, and YS handled, analyzed, and double checked the data; SK, MK, NK, SH, TI, and HK wrote the manuscript. All authors read and approved the final version.

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Declarations

Conflict of Interest

All authors declared no competing interests.

Ethical Approval

Not applicable in waiver of the ethics committee of PMDA, approved by the Ethics Committee of Nara Medical University (No. 2831. 2020/10/30).

Other Declarations

The views expressed in the discussion part of this article are those of the authors and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

Consent to Participate

All authors declare to consent to participate in the research.

Consent for Publication

All authors declare to consent the publication of the article.

Supplementary Information

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