Research Article

Adverse Events Following COVID-19 Vaccination in Young Japanese People: A Case-Control Study of the Risk of Systemic Adverse Events by A Questionnaire Survey

Marie Suehiro[1], Shinya Okubo[2], Kensuke Nakajima[2], Kosuke Kanda[3], Masanobu Hayakawa[3], Shigeru Oiso[2], Tsutomu Kabashima[4], Hideaki Fujita[5], Yukio Ando[6], Takahiro Muro[1*]

[1]Division of Medical Informatics, Nagasaki International University, Japan

[2]Division of Pharmaceutical Health Care and Science, Nagasaki International University, Japan

[3]Division of Clinical Pharmaceutics, Nagasaki International University, Japan

[4]Division of Pharmaceutical Technology, Nagasaki International University, Japan

[5]Section of Functional Morphology, Nagasaki International University, Japan

[6]Division of Amyloidosis Research, Department of Pharmacy, Faculty of Pharmaceutical Sciences, Nagasaki International University, Japan

***Corresponding author:** Takahiro Muro, Division of Medical Informatics, Nagasaki International University, Japan.

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Summary

What is known and objective

Racial differences in adverse events following COVID-19 vaccines have not been sufficiently studied. Here, we aimed to study the adverse events of Moderna's intramuscular COVID-19 vaccine in young Japanese people.

Methods

A case-control study was conducted using a questionnaire survey. Risk factors were determined using a multivariable logistic regression model. We also compared the occurrence of systemic adverse events in three pairs (minor and adult; male and female; and occurrence and non-occurrence of adverse events after the first dose). Propensity matching was used to balance variables.

Results

We analysed 3,369 data points (1,877 after the first dose and 1,492 after the second dose) obtained from a questionnaire survey of 7,965 vaccinated individuals. Comparing the results of the first and second doses, the incidence of local adverse events did not change significantly; however, the incidence of systemic adverse events increased significantly ($p < 0.001$). Eighty-three percent of the participants complained of local adverse events, and 65% of participants complained of systemic adverse events. Anaphylaxis occurred in one female student (0.03%). Even when an adverse event occurred, most of the symptoms improved within 3 days. Female sex was associated with systemic adverse events after the first and second doses with odds ratios (ORs) (95% confidence interval, CI) of 2.49 (2.03–3.06), and 1.83 (1.28–2.61), respectively. Age (<20 years: minor) was associated with systemic adverse events after the first dose with an OR of 1.80 (1.44–2.24). The results of the analysis of six cohorts that were created using propensity score matching showed that the incidence of systemic adverse events at the first dose in females was significantly higher than that in males, and that of minors was significantly higher than that of adults.

What is new and conclusion.

The results of this study clarified, for the first time, the risk factors for several adverse events from the injection of Moderna's intramuscular COVID-19 vaccine in young Japanese people. This study suggests that women, minors who experienced adverse events after the first dose, those who experienced adverse events after the first dose, and those who had adverse events after the second dose, should be aware of adverse events.

What is known and objective

The COVID-19 crisis has been spreading worldwide, and the number of infected people is increasing due to the emergence of mutant strains. The COVID-19 vaccine is expected to be effective in preventing coronavirus infection and disease aggravation. In Japan, priority groups, such as healthcare workers and the older adults (aged 65 and over), were the first to be vaccinated. Workplace vaccinations began on 21 June 2021 at universities and businesses; university employees and students have also been vaccinated. In June 2021, in Japan, Moderna's intramuscular injection of the COVID-19 vaccine was used for vaccination in places associated with students and corresponding teaching staff. However, as of September 2021, the Comirnaty intramuscular injection vaccine had been used for healthcare workers and elderly people ahead of other COVID-19 vaccines.

Adverse events of the Comirnaty intramuscular injection vaccine in healthcare workers and elderly people and that of Moderna's intramuscular COVID-19 vaccine in the defence forces, who were prioritised for administration, are

currently being studied. However, adverse events associated with the intramuscular injection of Moderna's COVID-19 vaccine in young people have not yet been well studied in Japan [1,2]. In addition, racial differences in adverse events following coronavirus vaccines have not been sufficiently studied. We have already reported adverse events associated with the first dose of Moderna's intramuscular injection of its COVID-19 vaccine. In Japan, the intramuscular injection of Moderna's COVID-19 vaccine will continue to be used in large-scale inoculation venues such as universities and workplaces. Therefore, to clarify the adverse events following coronavirus vaccination in the young Japanese population, we conducted a questionnaire survey after the second dose for students, faculty, and staff who belong to an educational foundation, Kyushu Bunka Gakuen.

1. Methods

1.1. Design

A case-control study with a questionnaire survey was conducted.

1.2. Study population

The study population included people who were vaccinated with Moderna's intramuscular COVID-19 vaccine.

This vaccination drive included students attending educational facilities run by the educational foundation Kyushu Bunka Gakuen, universities, junior colleges, cooking training facilities, training facilities for dental hygienists, and high schools. In addition, the vaccination drive included those employed by local companies related to the educational foundation of Kyushu Bunka Gakuen.

1.3. Data collection

Information regarding early adverse events that occurred immediately after vaccination at the site was obtained from the medical records. To obtain information on the adverse events that occurred after leaving the site, we conducted a questionnaire survey on a website created for this survey using Google Forms. The Japanese Ethics Guidelines for Epidemiological Studies stipulate that the use of existing medical records in observational studies can be used without the consent of individual patients by disclosing information about the purpose and conduct of the study and guaranteeing the opportunity for refusal. An explanation of this study is provided on the website of the Nagasaki International University. Consent to participate in the study was obtained individually.

In addition to assessing adverse events related to vaccination, we obtained the following: type of adverse event, date of occurrence, period of occurrence, and medication/care. In addition, other attributes (age, sex, allergy history, and history of adverse events to previous medications) were also obtained. Fever was defined as an increase of more than 1 °C from the usual body temperature.

1.4. Statistical analysis

Patient demographics and answers to the questionnaire were summarised with frequencies and percentages for categorical data and median plus range for continuous data. We compared the patients who experienced adverse events (AE group) with those who did not experience adverse events (No-AE group) using the Wilcoxon ranked-sum test for continuous variables and Fisher's exact test for dichotomous variables. Differences were considered

significant at $p < 0.05$. The incidence was calculated for each adverse event, and Fisher's exact test was performed to compare the first and second doses. To estimate the risk factors of adverse events, we first evaluated the odds ratios (ORs), 95% confidence intervals (95% CIs), and p-values of each potential risk factor using unadjusted logistic regression models. Second, we determined the risk factors using a multivariable logistic regression model. Statistical significance was determined if the 95% CIs did not include 1.00 in logistic analyses. Candidate predictors were selected according to a literature review and clinical expertise. We selected six variables, including patient demographics (age, sex, allergy history, history of adverse events to past medications, history of local adverse events after the first dose of vaccination, and history of systemic adverse events after the first dose vaccination). Age, a continuous variable, was categorised as minor (<20 years) or adult.

Finally, we compared the occurrence of systemic adverse events in three pairs (minors and adults, male and female, and occurrence and non-occurrence of adverse events after the first vaccine dose). Propensity matching was used to balance variables [3,4]. One-to-one matching without replacement was completed using nearest neighbour matching within a calliper (0.2 of the standard deviation of the logit of the propensity score [5,6]). To estimate the propensity score, we fitted a logistic regression model using variables such as age (minor or adult), allergy history, and history of adverse events to past medications. The occurrence of local or systemic adverse events was also used to estimate propensity scores after the second inoculation. After matching the propensity scores, the statistical balance between the two groups was evaluated. A standardised difference (Std diff) of <0.1 suggests adequate variable balance [7]. For comparison of the categorical variables, the McNemar test was employed. All statistical analyses were performed using JMP Pro 16 (SAS Institute Inc., Cary, NC, USA).

2. Results

2.1. Adverse events at the vaccination site

In this vaccination program, 7,965 people (3,998 for the first dose and 3,967 for the first and second doses) were vaccinated. Adverse events occurring at the vaccination site (immediately or within 30 minutes after vaccination) are shown in (Table 1).

Adverse events	1st dose				2nd dose				Total			
	Number of people (N = 3,998)	(%)	sex female	sex male	Number of people (N = 3,967)	(%)	sex female	sex male	Number of people (N = 7,965)	(%)	sex female	sex male
Vagal syncope	5	0.13	4	1	2	0.05	2		7	0.001	2	
Hyperventilation syndrome	4	0.10	4		2	0.05	2		6	0.001	2	
Feeling sick	4	0.10	3	1	4	0.10	3	1	8	0.001	3	1
Suffocation	3	0.08	3		2	0.05	2		5	0.001	2	
Nausea	1	0.03	1		2	0.05	2		3	0.000	2	
Anaphylaxis	1	0.03	1						1	0.000		
Hyperventilation with involuntary movement	1	0.03	1						1	0.000		
Severe urticaria	1	0.03	1						1	0.000		
Total	20	0.5	18	2	12	0.3	11	1	32	0.004	11	1

Table 1: Adverse event at vaccination site (immeditaly after vaccination or within 30minutes after vaccination).

After the first dose, the proportion of individuals with adverse events at the vaccination site was 0.5%, and anaphylaxis occurred in one female student (0.03%). After the second dose, the proportion of individuals with adverse events at the vaccination site was 0.3%, and none of them had anaphylaxis.

2.2. Demographic characteristics of participants

Table 2 shows the demographic characteristics of participants of the questionnaire survey. After the first dose, we obtained data from 1,993 participants (response rate: 49.8%). A total of 1,877 subjects who agreed to participate in the present study were enrolled in the analysis. Female participants accounted for 66% of the study population, with a median age of 22 years. Twenty-four percent of the study population was younger than 20 years of age. In addition, after the second dose, we obtained data from 1,504 subjects who responded to the questionnaire survey (response rate: 38%). A total of 1,492 subjects who agreed to participate in the present study were enrolled in the analysis. Female participants accounted for 66% of the study population, with a median age of 21 years. Twenty-six percent of the study population was younger than 20 years of age.

Characteristic	1st dose		2nd dose		Total	
	Number of people (N = 1,877)	(%) [a]	Number of people (N = 1,492)	(%) [a]	Number of people (N = 3,369)	(%) [a]
Female	1242	66	992	66	2234	66
Age, median (range), y	22	(18-70)	21	(18-64)	22	(18-70)
Age (minor[b])	444	24	380	26	824	24
Allergy history	219	12	151	10	370	11
Adverse events history*	118	6	77	5	195	6

a) Data are expressed as No.(%) unless otherwise indicated.

b) minor : < 20 years old

* for past medication except corona virus vaccination

Table 2: Demographic Charecteristics of participents.

2.3. Adverse events after leaving the vaccination site

The incidence of each adverse event is presented in Table 3. Local and systemic adverse events were generally mild. After the first dose, 82% of the participants complained of local adverse events. Injection site pain was the most common local adverse event (71%). Systemic adverse events occurred in 48% of participants. The most common systemic adverse event was myalgia (34%), followed by general fatigue (31%). In contrast, after the second dose, 85% of the participants complained of local adverse events after the second dose. Injection site pain was the most common local adverse event (69%). Systemic adverse events occurred in 88% of participants. The most common adverse event was fever (81%), followed by general fatigue (75%). Comparing the results of the first and second doses, the incidence of all systemic adverse events increased significantly ($p < 0.001$). The incidence of local adverse events, such as swelling, thermal sensation, redness, and itching, also increased significantly ($p < 0.001$).

Adverse event	1st dose		2nd dose		Comparison of 1st and 2nd dose (P-value)[a)]	Total	
	Number of people (N = 1,877)	(%)	Number of people (N = 1,492)	(%)		Number of people (N = 3,369)	(%)
Local adverse events							
Any	1,533	82	1,275	85	0.003	2,808	83
Pain	1,334	71	1,027	69	0.161	2,361	70
Swelling	757	40	784	53	<0.001	1,541	46
Thermal sense	641	34	762	51	<0.001	1,403	42
Redness	476	25	636	43	<0.001	1,112	33
Itching	370	20	399	27	<0.001	769	23
Induration	312	17	264	18	0.434	576	17
Systemic adverse events							
Any	894	48	1,314	88	<0.001	2,208	66
Myalgia	632	34	754	51	<0.001	1,386	41
Fatigue	581	31	1,118	75	<0.001	1,699	50
Fever	416	22	1,216	82	<0.001	1,632	48
Headache	386	21	785	53	<0.001	1,171	35
Joint pain	119	6	498	33	<0.001	617	18
Chills	86	5	656	44	<0.001	742	22

a) Fisher's exact test

Table 3: Incidence of each adverse event.

Figure 1 shows the time of onset of AEs, Figure 2 shows the duration of AEs, and the type of treatment for AEs is shown in Figure 3. Injection site pain occurred from day 0 to day 1 and continued for 2 days. However, almost all symptoms improved without any treatment. Eleven percent of the participants used pain medication after the second dose. The symptoms improved within a few days for most adverse events. The onset of systemic adverse events, such as fever and malaise, often occurred the day after injection, and these adverse events resolved within a few days in most people. Systemic symptoms in many people improved with the administration of antipyretic analgesics, such as acetaminophen. After the first dose, 75% of those who developed symptoms did not undergo any treatment, and 17% were administered acetaminophen. General fatigue often occurred on the day of injection (94%) and continued for 2–3 days thereafter (66%). In contrast, after the second dose, for those who developed local adverse events, more than 86% did not undergo any treatment, and most showed improvement within 3 days. However, many people who developed systemic adverse events used drugs. In particular, 88% of people who developed fever used antipyretic analgesics, such as acetaminophen. However, most of the symptoms improved within 3 days, and few people visited a medical institution.

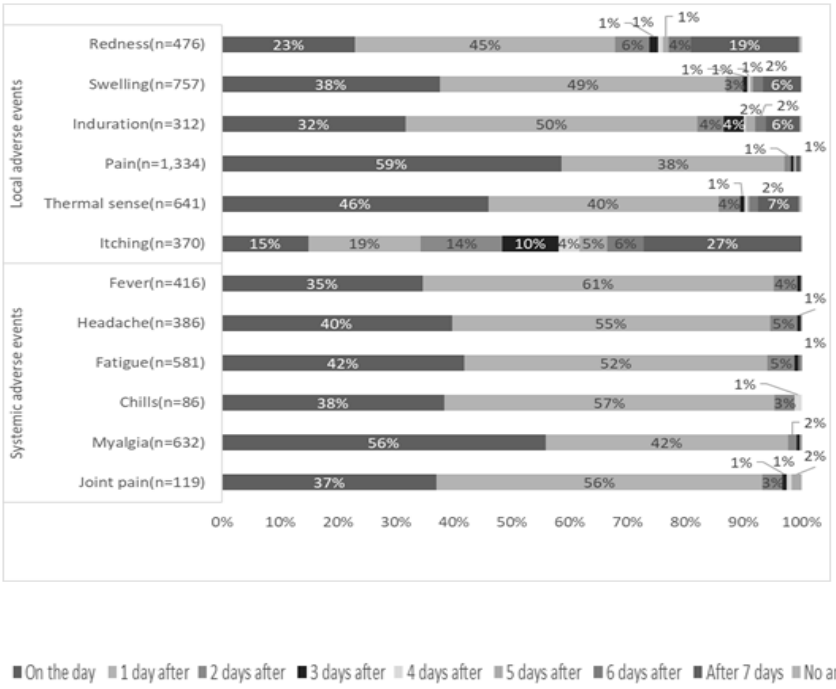

Figure 1a: Time of onset of adverse events after the first dose (days after vaccination).

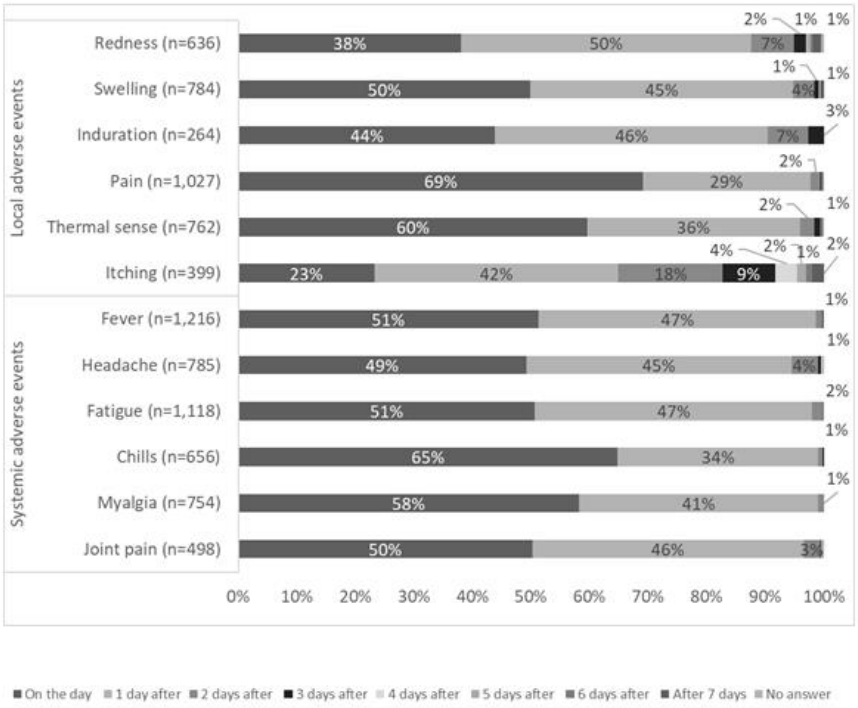

Figure 1b: Time of onset of adverse events after the second dose (days after vaccination).

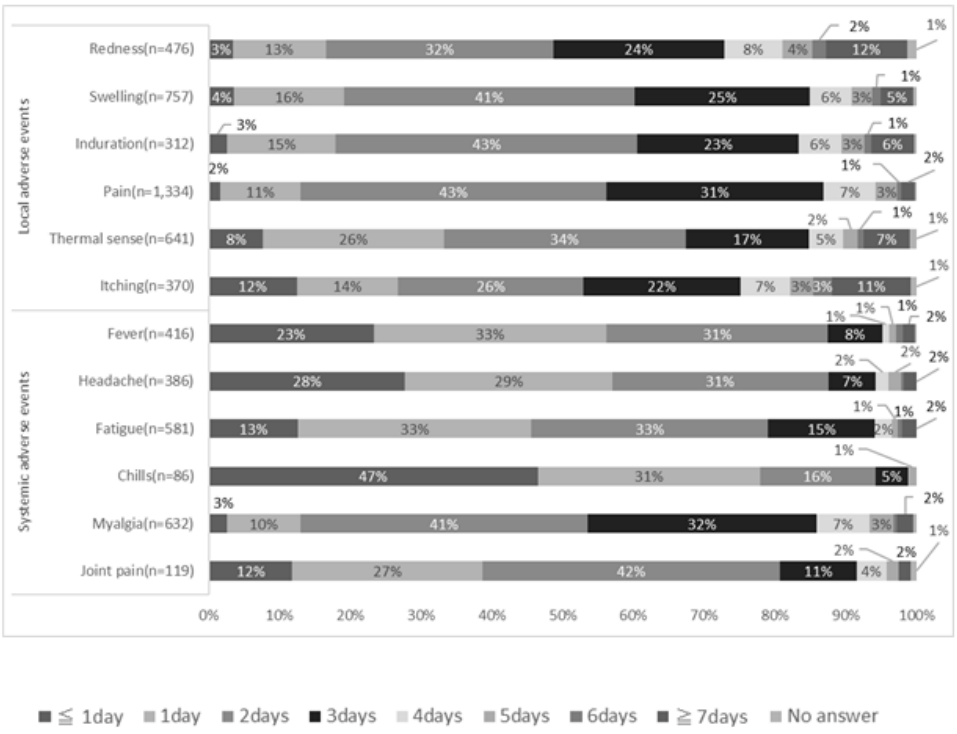

Figure 2a: Duration of adverse events after the first dose.

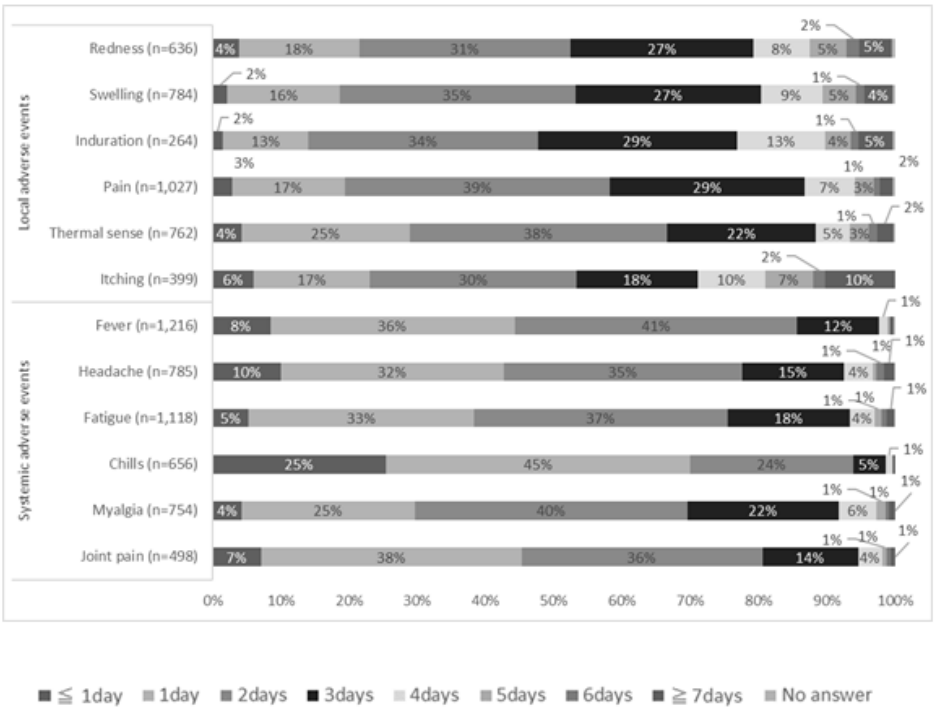

Figure 2b: Duration of adverse events after the second dose

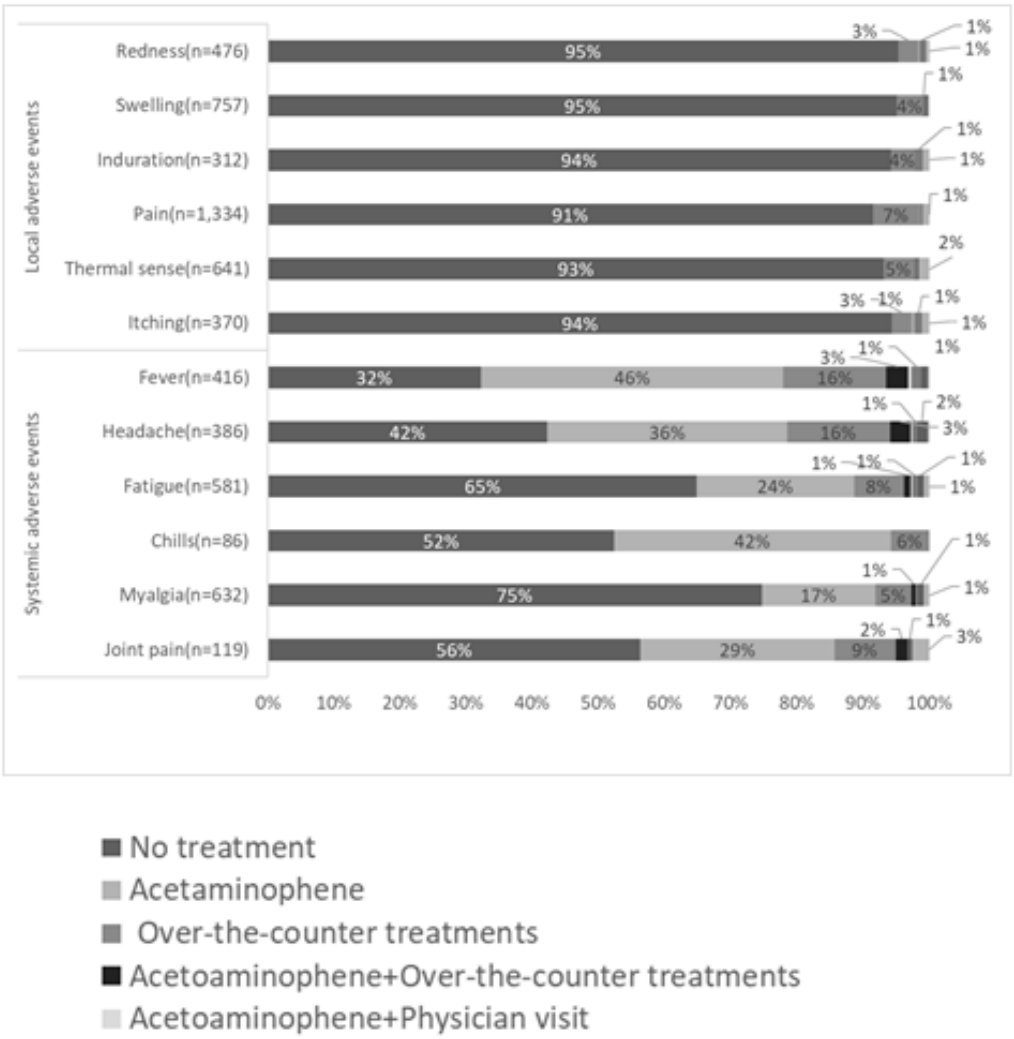

Figure 3a: Type of treatment for adverse events after the first dose.

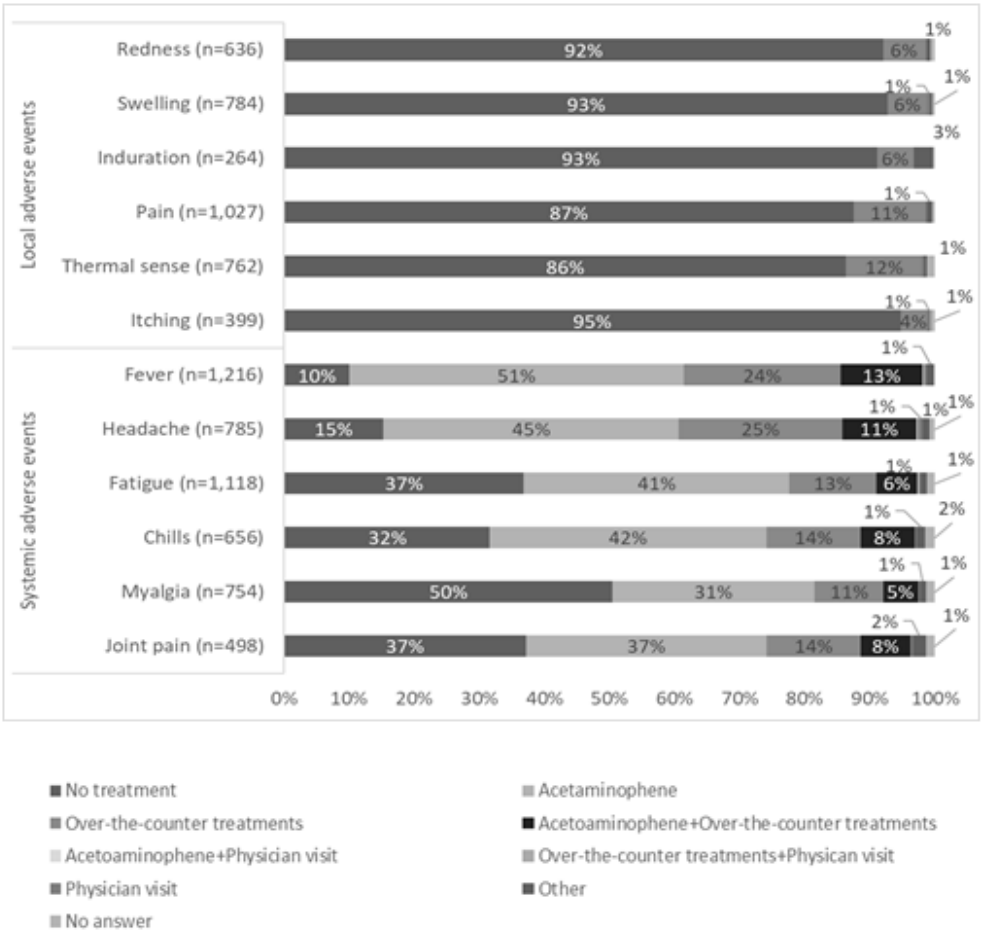

Figure 3b: Type of treatment for adverse events after the second dose.

2.4. Comparison of the AE and No-AE groups

The characteristics of the AE and no-AE groups are shown in Tables 4 and 5, respectively. Regarding local adverse events, the number of female participants in the AE group was significantly larger than that in the No-AE group ($p < 0.001$) both after the first and second doses. After the first dose, regarding systemic adverse events, the number of female participants and minors in the AE group was significantly higher than that in the No-AE group ($p < 0.001$) (Table 4). After the second dose, regarding systemic adverse events, the number of female participants and age in the AE group were significantly higher than those in the No-AE group ($p < 0.001$) (Table 5).

Local adverse events

Characteristic	AE group (N = 1,533)	No-AE group (N = 344)	P-Value[b)]
sex (female)	1068 (70%)	174 (51%)	<0.001
age, median, (range), y	22 (18-70)	26 (18-64)	<0.001
age (minor)[c)]	374 (24%)	70 (20%)	0.139
allergy history	194 (17%)	25 (7%)	0.003
adverse events history*	103 (7%)	15 (4%)	0.006

Systemic adverse events

Characteristic	AE group (N = 894)	No-AE group (N = 983)	P-Value[b)]
sex (female)	691 (77%)	551 (56%)	<0.001
age, median, (range), y	21 (18-70)	27 (18-64)	<0.001
age (minor)[c)]	267 (30%)	177 (18%)	<0.001
allergy history	125 (14%)	94 (10 %)	0.004
adverse events history *	71 (8%)	47 (5%)	0.111

a) Data are expressed as No.(%) unless otherwise indicated.

b) Wilcoxon's rank sum test was performed for continuous variables, and Fisher's exact test was performed for categorical variables.

c) minor : < 20 years old

Abbreviations: AE group, participants who experienced adverse events; No-AE group, participants who did not experience adverse events

* for past medication except corona virus vaccination

Table 4: Demographic and clinical charecteristics stratified by adverse evnent on 1st dose [a)]

Local adverse events

Characteristic	AE group (N = 1275)	No-AE group (N = 217)	P-Value[b)]
sex (female)	878 (69%)	113 (52%)	<0.001
age, median, (range), y	22 (18-64)	21 (18-64)	0.062
age (minor)[d)]	325 (25%)	57 (26%)	0.734
allergy history	135 (11%)	16 (7%)	0.180
adverse events history*	70 (5%)	7 (3%)	0.097

Systemic adverse events

Characteristic	AE group (N = 1314)	No-AE group (N = 178)	P-Value[b)]
sex (female)	909 (69%)	80 (45%)	<0.001
age, median, (range), y	22 (18-64)	30 (18-64)	<0.001
age (minor)[c)]	342 (26%)	38 (21%)	0.349
allergy history	139 (11%)	12 (7%)	0.144
adverse events history*	73 (6%)	3 (2%)	0.027

a) Data are expressed as No.(%) unless otherwise indicated.

b) Wilcoxon's rank sum test was performed for continuous variables, and Fisher's exact test was performed for categorical variables.

c) minor: < 20 years old

Abbreviations: AE group, participants who experienced adverse events; No-AE group, participants who did not experience adverse events

* for past medication except corona virus vaccination

Table 5: Demographic and clinical charecteristics stratified by adverse evnent on 2nd dose[a)]

2.5. Multivariable analysis of AE and No-AE groups

The results of the multivariable analysis of the AE and No-AE groups after the first dose are shown in Table 6. Local adverse events were associated with sex (female) and allergy history, with ORs (95% CI) of 2.15 (1.69–2.73) and 1.73 (1.10–2.74), respectively (Table 6a). Regarding local adverse events, induration and itching were associated with age (<20 years) (OR [95% CI]: 0.56 [0.40–0.78] and 0.62 [0.46–0.83], respectively), and injection site pain was associated with a history of adverse events with past medication OR (95% CI): 3.11 [1.12–8.65]. Systemic adverse events were associated with sex (female), age (<20 years), allergy history, and history of adverse events with past medications, with ORs (95% CI) of 2.49 (2.03–3.06), 1.80 (1.44–2.24), 1.39 (1.03–1.89), and 1.53 (1.02–2.29), respectively (Table 6b). Tables 7(a) and (b) show the results of the multivariable analysis after the second dose. Local adverse events were associated with sex (female) and first dose local adverse event, with ORs (95% CI) of 1.72 (1.60–2.93) and 18.41 (12.88–26.32), respectively. Systemic adverse events were associated with sex (female), first dose local adverse events, and first dose systemic adverse events, with ORs (95% CI) of 1.83 (1.28–2.61), 4.04 (2.83–5.76) and 2.96 (2.01–4.36), respectively.

a) Local adverse events

Adverse event	Characteristic		Adjusted OR(95%CI)	P-Value[a)]
Any	sex	male	1 [Reference]	
		female	2.15 (1.69-2.73)	<0.001
	allergy history	NO	1 [Reference]	
		Yes	1.73 (1.10-2.74)	0.018
Redness	sex	male	1 [Reference]	
		female	2.18 (1.68-2.83)	<0.001
	allergy history	NO	1 [Reference]	
		Yes	1.40 (1.01-1.94)	0.042
Swelling	sex	male	1 [Reference]	
		female	2.00 (1.60-2.51)	<0.001
	allergy history	NO	1 [Reference]	
		Yes	1.48 (1.08-2.05)	0.016
Induration	age (minor* or adult)	adult	1 [Reference]	
		minor	0.56 (0.40-0.78)	＜0.001
	allergy history	NO	1 [Reference]	
		Yes	1.56 (1.09-2.23)	0.015
Pain	sex	male	1 [Reference]	
		female	1.60 (1.17-2.20)	0.004
	Adverse events history**	NO	1 [Reference]	
		Yes	3.11 (1.12-8.65)	0.030
Thermal sense	sex	male	1 [Reference]	
		female	3.13 (2.44-4.01)	<0.001
	allergy history	NO	1 [Reference]	
		Yes	1.43 (1.04-1.97)	0.030
Itching	sex	male	1 [Reference]	
		female	2.96 (2.18-4.02)	＜0.001
	age (minor* or adult)	adult	1 [Reference]	
		minor	0.62 (0.46-0.83)	0.002

b)Systemic adverse events

Adverse event	Characteristic		Adjusted OR(95%CI)	P-Value[a)]
Any	sex	male	1 [Reference]	
		female	2.49 (2.03-3.06)	＜0.001
	age (minor* or adult)	adult	1 [Reference]	
		minor	1.80 (1.44-2.24)	＜0.001
	allergy history	NO	1 [Reference]	
		Yes	1.39 (1.03-1.89)	0.033
	Adverse events history**	NO	1 [Reference]	
		Yes	1.53 (1.02-2.29)	0.039
Fever	age (minor* or adult)	adult	1 [Reference]	
		minor	1.34 (1.05-1.72)	0.020
Headache	sex	male	1 [Reference]	
		female	1.88 (1.35-2.63)	＜0.001
	age (minor* or adult)	adult	1 [Reference]	
		minor	1.52 (1.13-2.03)	0.005
Fatigue	sex	male	1 [Reference]	
		female	1.64(1.19-2.27)	0.002
Chills	allergy history	NO	1 [Reference]	
		Yes	2.17 (1.25-3.78)	0.006
Myalgia	sex	male	1 [Reference]	
		female	1.47(1.05-2.06)	0.023

a) multivariate logistic analysis

*minor : < 20 years old

** for past medication except corona virus vaccination

Abbreviations: OR, odds ratio; CI, confidence Interval

Table 6: Summary AEs of characterisitics by logistics regression analysis 1st dose

a)Local adverse events

Adverse events	Characteristic		Adjusted OR (95%CI)	P-Value[a)]
Any	sex	male	1 [Reference]	
		female	1.75 (1.21-2.55)	0.003
	1st dose local adverse events	NO	1 [Reference]	
		Yes	18.57 (12.95-26.61)	＜0.001
Redness	sex	male	1 [Reference]	
		female	1.65 (1.28-2.12)	＜0.001
	age (minor* or adult)	adult	1 [Reference]	
		minor	0.48 (0.36-0.62)	＜0.001
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.56 (1.22-1.99)	＜0.001
Swelling	sex	male	1 [Reference]	
		female	1.44 (1.11-1.85)	0.006
	age (minor* or adult)	adult	1 [Reference]	
		minor	0.63 (0.48-0.82)	＜0.001
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.66 (1.30-2.13)	＜0.001
Induration	age (minor* or adult)	adult	1 [Reference]	
		minor	0.40 (0.27-0.58)	＜0.001
Pain	age (minor* or adult)	adult	1 [Reference]	
		minor	0.67 (0.48-0.92)	0.014
	1st dose local adverse events	NO	1 [Reference]	
		Yes	3.60 (2.39-5.39)	＜0.001
Thermal sense	sex	male	1 [Reference]	
		female	2.09 (1.63-2.70)	＜0.001
	age (minor* or adult)	adult	1 [Reference]	
		minor	0.71 (0.54-0.93)	0.013
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.33 (1.04-1.70)	0.021
Itching	sex	male	1 [Reference]	
		female	1.93 (1.45-2.57)	＜0.001
	age (minor* or adult)	adult	1 [Reference]	
		minor	0.50 (0.37-0.67)	＜0.001
	1st dose local adverse events	NO	1 [Reference]	
		Yes	0.61 (0.41-0.92)	0.017
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.32 (1.01-1.71)	0.040

b)Systemic adverse events

adverse events	Characteristic		Adjusted OR(95%CI)	P-Value[a)]
Any	sex	male	1 [Reference]	
		female	1.89 (1.32-2.70)	＜0.001
	1st dose local adverse events	NO	1 [Reference]	
		Yes	4.05 (2.83-5.79)	＜0.001
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	2.82 (1.91-4.16)	＜0.001
Headache	sex	male	1 [Reference]	
		female	2.48 (1.93-3.20)	＜0.001
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.50 (1.17-1.91)	0.001
Fatigue	sex	male	1 [Reference]	
		female	1.65 (1.18-2.31)	0.003
	1st dose local adverse events	NO	1 [Reference]	
		Yes	1.97 (1.33-2.92)	＜0.001
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.96 (1.40-2.73)	＜0.001
Chills	sex	male	1 [Reference]	
		female	1.41 (1.10-1.81)	0.006
	1st dose local adverse events	NO	1 [Reference]	
		Yes	1.40 (1.01-1.94)	0.043
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.31 (1.04-1.66)	0.025
Myalgia	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	2.52 (1.98-3.21)	＜0.001
Joint pain	sex	male	1 [Reference]	
		female	1.43 (1.10-1.86)	0.007
	age (minor* or adult)	adult	1 [Reference]	
		minor	0.50 (0.38-0.65)	＜0.001
	1st dose local adverse events	NO	1 [Reference]	
		Yes	1.45 (1.02-2.07)	0.038
	1st dose systemic adverse events	NO	1 [Reference]	
		Yes	1.52 (1.19-1.94)	＜0.001

a) multivariate logistic analysis

*minor : < 20 years old

Abbreviations: OR, odds ratio; CI, confidence Interval

Table 7: Summary adverse events of chareristics by logistic regression analysis on 2nd dose

a) After the 1st dose, sex association for systemic adverse events

	Pre-matching				Post-matching			
	female (N = 1242)	male (N = 635)	P value[a)]	Std diff	female (N = 628)	male (N = 628)	P value[a)]	Std diff
age (minor)	333 (27%)	111 (18%)	<0.001	0.223	111 (18%)	111 (18%)	1.000	0.000
allergy history	157 (13%)	62 (10%)	0.069	0.091	60 (10%)	60 (10%)	1.000	0.000
adverse events history*	85 (7%)	33 (5%)	0.191	0.069	33 (5%)	33 (5%)	1.000	0.000

b) After the 1st dose, minor association for systemic adverse events

	Pre-matching				Post-matching			
	minor (N = 444)	adult (N = 1420)	P value[a)]	Std diff	minor (N = 444)	adult (N = 444)	P value[a)]	Std diff
sex (female)	333 (75%)	903 (64%)	<0.001	0.249	333 (75%)	333 (75%)	1.000	0.000
allergy history	49 (11%)	167 (12%)	0.734	0.023	49 (11%)	49 (11%)	1.000	0.000
adverse events history*	24 (5%)	94 (7%)	0.434	0.051	24 (5%)	24 (5%)	1.000	0.000

c) After the 2nd dose, sex association for systemic adverse events

	Pre-matching				Post-matching			
	female (N = 989)	male (N = 503)	P value[a)]	Std diff	female (N = 458)	male (N = 458)	P value[a)]	Std diff
age (minor)	307 (31%)	75 (15%)	<0.001	0.386	79 (17%)	71 (16%)	0.532	0.047
allergy history	102 (10 %)	49 (10%)	0.786	0.019	44 (10%)	45 (10%)	1.000	0.007
adverse events history*	59 (6%)	18 (4%)	0.063	0.112	16 (3%)	17 (4%)	1.000	0.012
1st inoculation any local adverse event	845 (85%)	379 (75%)	<0.001	0.251	375 (82%)	375 (82%)	1.000	0.000
1st inoculation any systemic adverse event	646 (65%)	200 (40%)	<0.001	0.529	198 (43%)	197 (43%)	1.000	0.004

d) After the 2nd dose, minor association for systemic adverse events

	Pre-matching				Post-matching			
	minor (N = 380)	adult (N = 1087)	P value[a)]	Std diff	minor (N = 380)	adult (N = 380)	P value[a)]	Std diff
sex (female)	305 (80%)	669 (62%)	<0.001	0.421	304 (80%)	305 (80%)	1.000	0.000
allergy history	33 (9%)	117 (11%)	0.280	0.070	33 (9%)	33 (9%)	1.000	0.012
adverse events history*	19 (5%)	54 (5%)	1.000	0.001	16 (5%)	17 (5%)	1.000	0.000
1st inoculation any local adverse event	317 (83%)	890 (82%)	0.584	0.041	317 (83%)	318 (84%)	1.000	0.007
1st inoculation any systemic adverse event	264 (69%)	572 (53%)	<0.001	0.351	264 (69%)	264 (69%)	1.000	0.000

e) After the 2nd dose, any local adverse event association for systemic adverse events

	Pre-matching				Post-matching			
	1st dose local adverse event (N = 1222)	1st dose non local adverse event (N = 269)	P value[a)]	Std diff	1st dose local adverse event (N = 259)	1st dose non local adverse event (N = 259)	P value[a)]	Std diff
sex (female)	843 (69%)	146 (54%)	<0.001	0.306	142 (54%)	142 (54%)	1.000	0.008
age (minor)	317 (26%)	63 (25%)	0.584	0.058	63 (24%)	63 (24%)	1.000	0.009
allergy history	134 (11%)	17 (6%)	0.019	0.166	17 (7%)	17 (7%)	1.000	0.000
adverse events history*	66 (5%)	10 (4%)	0.287	0.081	9 (3%)	10 (4%)	1.000	0.021
1st inoculation any systemic adverse event	758 (62%)	88 (32%)	<0.001	0.614	87 (34%)	87 (34%)	1.000	0.000

f) After the 2nd dose, any systemic adverse event association for systemic adverse events

	Pre-matching				Post-matching			
	1st dose systemic adverse event (N = 846)	1st dose non systemic adverse event (N = 649)	P value[a)]	Std diff	1st dose systemic adverse event (N = 506)	1st dose non systemic adverse event (N = 506)	P value[a)]	Std diff
sex (female)	646 (76%)	343 (53%)	<0.001	0.507	320 (63%)	319 (63%)	1.000	0.004
age (minor[b)])	264 (32%)	116 (19%)	<0.001	0.314	108 (21%)	107 (21%)	1.000	0.005
allergy history	99 (12%)	52 (8%)	0.024	0.124	44 (9%)	45 (9%)	1.000	0.007
adverse events history*	56 (7%)	20 (3%)	0.002	0.165	16 (3%)	18 (4%)	0.862	0.022
1st inoculation any local adverse event	758 (90%)	464 (72%)	<0.001	0.470	438 (87%)	438 (87%)	1.000	0.000

a) Fisher's exact test was performed for categorical variables.

b) minor : < 20 years old

Abbreviations: Std diff, standardized difference

* for past medication except corona virus vaccination

Table 8: Pre-matching and post-matching summary statistics

2.6. McNemar analysis of each risk factor

Table 8 presents the cohorts created for each PSM. Because standardised differences <0.1 were obtained for all variables, the covariate balance in the matched cohort was considerably improved. Table 9 shows a comparison of the incidence of systemic adverse events after the first and second doses. After the first dose, female participants and minors had a significantly higher incidence of systemic adverse events which was significantly higher in female participants and minors. After the second dose, female participants and the occurrence of adverse events after the first dose had a significantly higher incidence of systemic adverse events. However, there were no significant differences between minors and adults.

a) 1st dose

Group matched by each propensity score	Systemic adverse events N (%)[a)]	P value[b)]
Sex		
female	342 (54%)	<0.001
male	203 (68%)	
Age		
minor	267 (60%)	<0.001
adult	186 (42%)	

a) Data are expressed as No. (%).

b) McNemar test

b) 2nd dose

Group matched by each propensity score	Systemic adverse events N (%)[a)]	P value[b)]
Sex		
female	404 (88%)	0.022
male	382 (83%)	
Age		
minor	342 (90%)	0.701
adult	345 (91%)	
Local adverse events after 1st dose		
Yes	230 (89%)	<0.001
No	180 (69%)	
Systemic adverse events after 1st dose		
Yes	474 (94%)	<0.001
No	432 (85%)	

a) Data are expressed as No. (%).

b) McNemar test

Table 9: Comparisons of systemic adverse events between groups matched by each propensity score.

2.7. What is new and Conclusion

The results of this study clarified, for the first time, the risk factors for several adverse events from the intramuscular injection of Moderna's COVID-19 vaccine in young Japanese people. Moderna's intramuscular COVID-19 vaccine efficacy after the second dose was 94.1% in preventing COVID-19 among those without evidence of previous SARS-CoV-2 infection [8,9] Currently, this vaccine requires two doses to be fully effective, with the second dose having a higher frequency of adverse events [1,2,8-10]. In this study, which compared the occurrence of adverse events after the first and second doses, the results showed that the second dose had an increase in all systemic adverse events and in many local adverse events. This is consistent with the results of other reports [8,9]. In a previous study, we reported that minors aged <20 years were at greater risk of systemic adverse events from Moderna's intramuscular injection of the COVID-19 vaccine after the first dose [11] However, the same results were not observed for the second dose. According to a report by the Japanese Defence Forces, local pain incidence tends to be higher in older people [1] However, other adverse events decrease with increasing age. In comparison with the Comirnaty intramuscular injection, there is less tendency for the incidence to decrease due to older age [1]. Based on the results of our multivariable logistic analysis, being a minor was found to be an independent influencing factor for systemic adverse events as well as fever after the first dose of Moderna's intramuscular injection COVID-19 vaccine, but minors were not shown to be independent influencing factors for systemic adverse events and fever. In contrast, adults were more likely to have local adverse events, such as redness, induration, and itching, after the second dose. Second, the results of this study show that female sex is a major risk factor for many adverse events, except for local pain and induration. Previous reports showed that women are more likely to develop anaphylaxis immediately after vaccination than men [12]. Similarly, in the present study, more women than men had symptoms immediately after vaccination. The reasons why female participants have stronger immunity and a higher incidence of autoimmune diseases are not clear. However, sex hormones, such as oestrogen, contribute to the development and activity of the immune system, accounting for differences in gender-related immune responses [13]. The ratio of naive B cells before vaccination and the ratio of activated CD8-positive T cells after vaccination are detected as immunological features that positively correlate with the increase in antibody titre after vaccination [14]. The results of this study showed that female participants had a higher incidence of adverse events. According to a study by the Chiba University in Japan, the older the age, the lower the antibody titre, and it has been reported that women of all ages have higher antibody titres [15] Furthermore, from the results of the multivariable analysis, it was reported that the female sex is a factor that tends to increase antibody titres after vaccination, and that older age is also a factor because antibody titres do not easily increase [14]. The relationship between antibody titres and side reactions was not investigated in the present study. This may need to be analysed in detail in the future. In this study, to obtain information on AEs that occurred after leaving the vaccination site, we conducted a questionnaire survey on a website. Therefore, the existence of a reporting bias cannot be completely ruled out. This is one of the limitations of the present study.

This study suggested that women, minors who experienced adverse events after the first dose, those who experienced adverse events after the first dose, and those who had adverse events after the second dose, should be aware of adverse events. However, even if an adverse event occurs, most of the symptoms improve within 3 days,

and the adverse events can be appropriately managed by taking antipyretic analgesics such as acetaminophen. The COVID-19 vaccine has also been shown to be effective against mutant strains, such as the delta strain [16]. COVID-19 has a higher risk of severe effects than post-vaccination adverse events, and vaccination is now recommended for patients with heart disease and pregnant women [17,18] The population does not need to be overly afraid of adverse events, and it is recommended that those at high risk make as many advanced preparations as possible, such as having antipyretic analgesics at hand, food for several days, and taking a few days off after vaccination. It is important to note that people must be vaccinated.

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