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Original Article

Adverse reactions to the first and second doses of Pfizer-BioNTech COVID-19 vaccine among healthcare workers

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ABSTRACT

Introduction: In the current coronavirus infection 2019 (COVID-19) pandemic, the messenger RNA vaccines have been shown to help protect high-risk groups from COVID-19. Among healthcare workers vaccinated with Pfizer-BioNTech COVID-19 vaccine, a survey was conducted to analyze the relationship between the incidence and severity of adverse reactions after vaccination.

Methods: We conducted a prospective self-reported survey of adverse reactions among healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®) in Japan. After the first and second dose of vaccine, local and systemic reactions for 8 days after vaccination were reported by volunteer participants using a website. After receiving vaccination, 374 respondents participated in this matched-pair study.

Results: Both the incidence and severity of adverse reactions tended to be higher after the second vaccine dose than after the first dose. However, the incidence and numeric rating scale (NRS) score of muscle and skin pain were nearly the same after the first and second doses. In a comparison by sex, women had significantly higher incidence and NRS scores for adverse reactions such as headache, skin pain, erythema, and itching. The results also showed that younger age groups had higher incidence rates and NRS scores for all adverse reactions investigated, except for muscle pain, compared with older age groups.

Conclusion: Some adverse reactions to the Pfizer-BioNTech Comirnaty® COVID-19 vaccine showed gender and age differences. However, generally speaking, all side reactions disappear within a week. Therefore, these side reactions are not a significant concern in recommending vaccination.

1. Introduction

The pandemic of coronavirus infection 2019 (COVID-19), which has spread to countries worldwide since the beginning of 2020, shows no sign of resolution as of the beginning of 2022. The messenger RNA (mRNA) vaccines, such as the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®) and Moderna mRNA-1273 COVID-19 vaccine (Spikevax®), have received emergency authorization for clinical use and have been shown to help protect high-risk groups from COVID-19 infection. Since February 2021, healthcare workers in Japan have been given first priority for vaccination with the Comirnaty® vaccine. The target population was then expanded to people aged 65 years and over. Large-scale vaccination is currently underway for all citizens over the age of 12 in the national plan of Japan. However, in Japan as well as other countries, vaccination tends to be avoided by young people. As a result, younger people who become infected can spread the infection and thereby constitute an important factor in perpetuating the pandemic. Because the vaccination campaign began very quickly, a lack of accurate information regarding adverse reactions is also linked to the tendency of younger people to refrain from vaccination.

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The prevalence and spread of COVID-19 vary greatly among ethnic groups, and the effects of and adverse reactions to the COVID-19 vaccines may also differ among ethnic groups [1–8]. There are few detailed reports from Japan regarding the actual symptoms and frequency of vaccine adverse effects [9,10]. Additionally, no reports have compared or examined data for the same vaccinee after repeated inoculations. Therefore, it is important to more accurately evaluate the changes and characteristics of adverse reactions by comparing the incidence and severity of adverse reactions after each vaccination in the same vaccinee. During mass COVID-19 vaccination conducted at the Kyoto Prefectural University of Medicine Hospital, we administered a survey regarding adverse reactions occurring after the first and second vaccinations, and examined the relationship between the incidence and severity of adverse reactions after COVID-19 vaccination according to sex and age.

2. Materials and methods

2.1. Study design and participants

During the 4 months from March 8 to July 9, 2021, medical workers, medical students, and nursing students involved in healthcare at the Hospital of Kyoto Prefectural University of Medicine were vaccinated with the Comirnaty®. A total of 4,503 individuals were vaccinated with the first dose, and 4,473 received a second dose. According to the manufacturer's recommendations for administration of the vaccine, one frozen multidose vial was thawed at room temperature, diluted with 1.8 mL saline, and dispensed into six doses of 0.3 mL each in one 1-mL syringe per inoculation. Two injections were administered intramuscularly at intervals of 21 days ± 2 days in the deltoid muscle of the upper arm using a 25G needle. The study participants were individuals aged 18 years or older who were vaccinated and who voluntarily agreed to participate in the survey. Individuals who agreed to participate in the study were asked to report daily regarding the presence and severity of any adverse reactions (local reactions such as muscle pain, erythema, skin pain, itching, and headache; systemic reactions such as fever, general fatigue, chills, joint pain, and diarrhea) for a total of 8 days from the date of vaccination to day 7 after injection. Reporting was conducted via a website using a computer or mobile terminal. A 10-step numeric rating scale (NRS) was used (zero was set to indicate no reaction). For fever, the actual body temperature measurement was categorized using the NRS (score of 4 or higher indicated a body temperature of 37 °C or higher).

2.2. Sample size calculation and statistical analysis

After receiving the first dose, 595 (13.2%) participants voluntarily responded to the survey, with 584 valid surveys. After receiving the second dose, 442 (9.9%) participants responded to the survey, with 438 valid surveys (Table 1). The incidence of vaccine adverse reactions is presented as number and percentage or mean and standard deviation. We used the χ^2-test to compare the incidence of various side effects between the first and second doses. Paired *t*-tests were used for NRS comparison of adverse reactions using matched paired data for the first and second dose, the unpaired *t*-test was used for NRS comparisons by sex, analysis of variance (ANOVA) was applied for NRS comparisons by age group, and repeated measures ANOVA was used for NRS comparisons by time-course. With a significant difference at $p < 0.05$ in ANOVA, the Student–Newman–Keuls multiple comparisons test was added as a post-hoc test for intergroup NRS comparison. R version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) and Rstudio (ver. 1.4, Integrated Development for R. Rstudio, PBC, Boston, MA, USA) were used for the Cochran–Armitage trend test to evaluate the linear trend between the incidence of adverse reactions among age groups. Python version 3.8 (Python Software Foundation, https://www.python.org) with the Seaborn visualization library version 0.11.2 (https://seaborn.pydata.org/#) was used for linear regression analysis, graphing, and kernel density estimation (KDE) plots; InStat (GraphPad Software, San Diego, CA, USA) and Microsoft Excel for Mac ver. 16.53 (Microsoft Co., Redmond, WA, USA) was also used for statistical analysis.

Table 1
Characteristics of participants vaccinated with Pfizer-BioNTech Comirnaty® COVID-19 vaccine at Kyoto Prefectural University of Medicine Hospital.

characteristics	after 1st dose	after 2nd dose
Vaccinated, n	4,503	4,473
Survey participants, n (%)	595 (13.2)	442 (9.9)
Valid answer, n (%)	584 (13.0)	438 (9.8)
sex: male, female, n (%)	237 (40.6), 347 (59.4)	169 (38.6), 269 (61.4)
age: mean ± SD	40.08 ± 13.23	41.90 ± 12.76
Generations, n (%)		
18–19	18 (3.1)	11 (2.5)
20–29	144 (24.7)	88 (20.0)
30–39	113 (19.3)	80 (18.3)
40–49	144 (24.7)	118 (26.9)
50–59	125 (21.4)	105 (24.0)
60–69	37 (6.3)	35 (8.0)
70–74	3 (0.5)	1 (0.2)
Occupation, n (%)		
doctors	185 (31.7)	133 (30.4)
nurses	140 (24.0)	117 (26.7)
other medical workers	83 (14.2)	63 (14.4)
students	96 (16.4)	58 (13.2)
non-medical staff and others	80 (13.7)	67 (15.3)

SD, standard deviation.

3. Results

3.1. Study population

We analyzed adverse reactions after receipt of the first and second doses of the Comirnaty® as paired data for 374 participants who completed our survey (Table 2). The 374 participants comprised doctors, nurses, other medical workers, students, and non-medical staff. Among them, there was a slightly higher proportion of female respondents (39.8% men, 60.2% women), but there were no statistically significant differences in the average age between men and women ($p = 0.935$). The 374 respondents in the paired data ranged in age from 18 to 74 years old. Participants were divided into five age groups: 18–29 (76, 20.3%), 30–39 (69, 18.4%), 40–49 (101, 27.0%), 50–59 (96, 25.7%),

Table 2
Characteristics of study participants (matched pairs) vaccinated with Pfizer-BioNTech Comirnaty® COVID-19 vaccine.

age, generation	sex		total
	male	female	
age: mean ± SD	42.38 ± 13.35	42.49 ± 12.30	42.44 ± 12.71
n (%)	149 (39.8)	225 (60.2)	374 (100.0)
generations, n (%)			
18–19	5 (3.4)	5 (2.2)	10 (2.7)
20–29	28 (18.8)	38 (16.9)	66 (17.6)
30–39	27 (18.1)	42 (18.7)	69 (18.4)
40–49	38 (25.5)	63 (28.0)	101 (27.0)
50–59	33 (22.1)	63 (28.0)	96 (25.7)
60–69	17 (11.4)	14 (6.2)	31 (8.3)
70–74	1 (0.7)	0 (0.0)	1 (0.3)
Occupation, n (%)			
Doctors	84 (56.4)	36 (16.0)	120 (32.1)
Nurses	3 (2.0)	91 (40.4)	94 (25.1)
other medical workers	17 (11.4)	36 (16.0)	53 (14.2)
Students	24 (16.1)	23 (10.2)	47 (12.6)
non-medical staff and others	21 (14.1)	39 (17.3)	60 (16.0)

SD, standard deviation.

and 60–74 years old (32, 8.6%). There was no significant difference in the proportion of men and women in each age group from 18 to 74 years ($p = 0.375$) (Table 2).

3.2. Incidence and NRS of adverse reactions between first and second vaccination

For the 10 types of adverse reaction investigated in this study, the time-course of incidence and severity (NRS) was examined for up to 8 days after inoculation, including the day of vaccination (day 0) (Fig. 1a and b). For the first dose, the incidence of muscle pain exceeded 70%–90% on days 0 and 1. The incidence of general fatigue, skin pain, and headache were approximately 10%–30% and peaked on day 1. For the second dose, the incidence of most adverse reactions, including fever, general fatigue, chills, headache, joint pain, and erythema, and diarrhea, also increased and peaked on day 1. This indicated a general tendency for a higher incidence and NRS score for most adverse reactions after the second dose, with longer duration and greater severity than reactions after the first dose (Fig. 1a and b). For example, the NRS score for general fatigue, headache, muscle pain, erythema, and itching showed a significant increase on the day after receiving the second dose of vaccine, and these increases continued for several days after day 2 ($p <$ 0.001 to 0.01) (Fig. 1b).

3.3. Sex differences in the incidence and NRS of adverse reactions

For headache, skin pain, erythema, and itching, the incidence and NRS values in women after the second dose were significantly higher for several days than those in men ($p < 0.05$) (Fig. 2a and b). For incidence of fever after the first dose, there was no significant increase and no difference by sex (Supplementary Fig. S1a). The degree of fever was slightly higher in women on day 0 ($p = 0.024$) and day 1 ($p = 0.015$), but this was not a large difference (Supplementary Fig. S1b). After the second dose, significant increases in the incidence and NRS scores of fever in women were observed on days 1 and 2 ($p < 0.05$) (Supplementary Figs. S1a and S1b). Regarding incidence of general fatigue, chills, muscle pain and joint pain, significantly higher incidences were detected in women than men on day 1 and/or day 2 ($p < 0.05$) (Supplementary Fig. S1a). Regarding muscle pain, NRS scores were significantly higher in women than in men for 3–6 days after the first and second injections ($p < 0.05$) (Supplementary Fig. S1b).

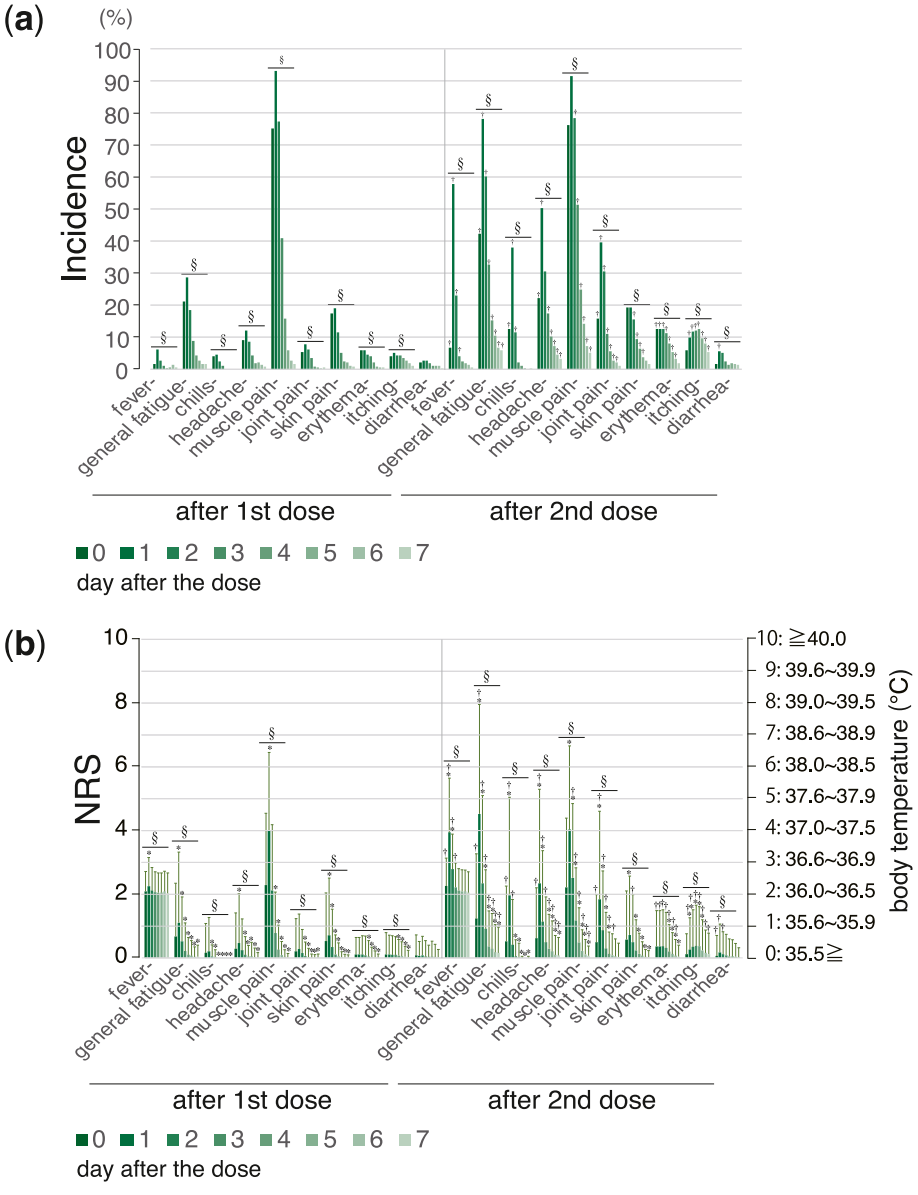

Fig. 1. The incidence and numeric rating scale (NRS) scores of frequent adverse reactions after the first and second doses of Pfizer-BioNTech Comirnaty® COVID-19 vaccine. (**a**) Incidence of frequent adverse reactions. †p < 0.05 vs. 1st dose using χ2-test. §p < 0.05 from day 0 to day 7 after vaccination using χ2-test. (**b**) NRS scores for frequent adverse reactions. †p < 0.05 vs. 1st dose, paired *t*-test. §p < 0.05 vs. NRS scores on days 0–7, repeated measures ANOVA. *p < 0.05 vs. NRS scores on day 0. Student–Newman–Keuls multiple comparisons test.

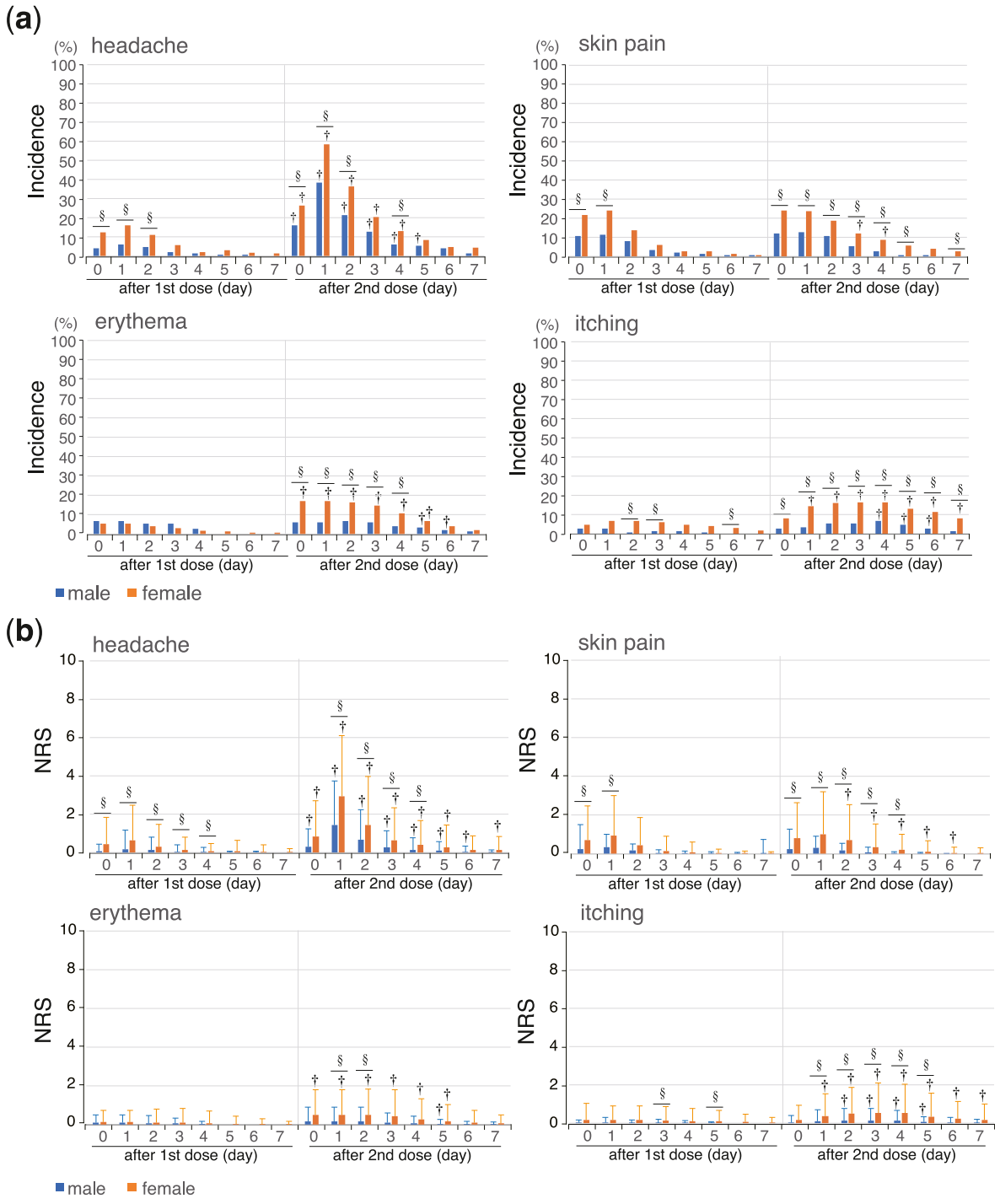

Fig. 2. Comparison of incidence and numeric rating scale (NRS) scores by sex. Four adverse reactions (headache, skin pain, erythema, and itching) after the first and second doses of Pfizer-BioNTech Comirnaty® COVID-19 vaccine. (**a**) Incidence of four adverse reactions. †$p < 0.05$ *vs.* 1st shot using χ^2-test §$p < 0.05$ between men and women using χ^2-test. (**b**) NRS scores of four adverse reactions. †p < 0.05 vs. 1st shot using paired *t*-test. §p < 0.05 between men and women using unpaired *t*-test.

3.4. Age differences in the incidence and NRS of adverse reactions

We investigated the incidence of adverse reactions by age group (Fig. 3 and Supplementary Fig. S2a). Muscle pain, general fatigue, headache, fever, joint pain, and chills were the most frequent adverse reactions overall; except for muscle pain, the incidence of these reactions was significantly higher after the second dose than after the first dose in all age groups ($p < 0.05$). In the comparison of the incidence of adverse reactions among age groups, after the 1st dose, a statistically significant difference was detected in fever at day 1, general fatigue from day 0 to day 4, chills from day 1 to day 2, and muscle pain from day 0 to day 1 ($p < 0.05$) (Fig. 3). After the 2nd dose, a statistically significant difference among age groups was detected in fever on day 1, general fatigue on day 0, headache from day 0 to day 1, muscle pain on day 1, skin pain from day 5 to day 6, and itching on day 6 ($p < 0.05$) (Fig. 3 and Supplementary Fig. S2a). In the adverse reactions that showed statistically significant differences in the age group comparison, the younger age cohorts generally tended to show a higher incidence than the older age groups.

We used the Cochran–Armitage trend test to analyze the linear trend

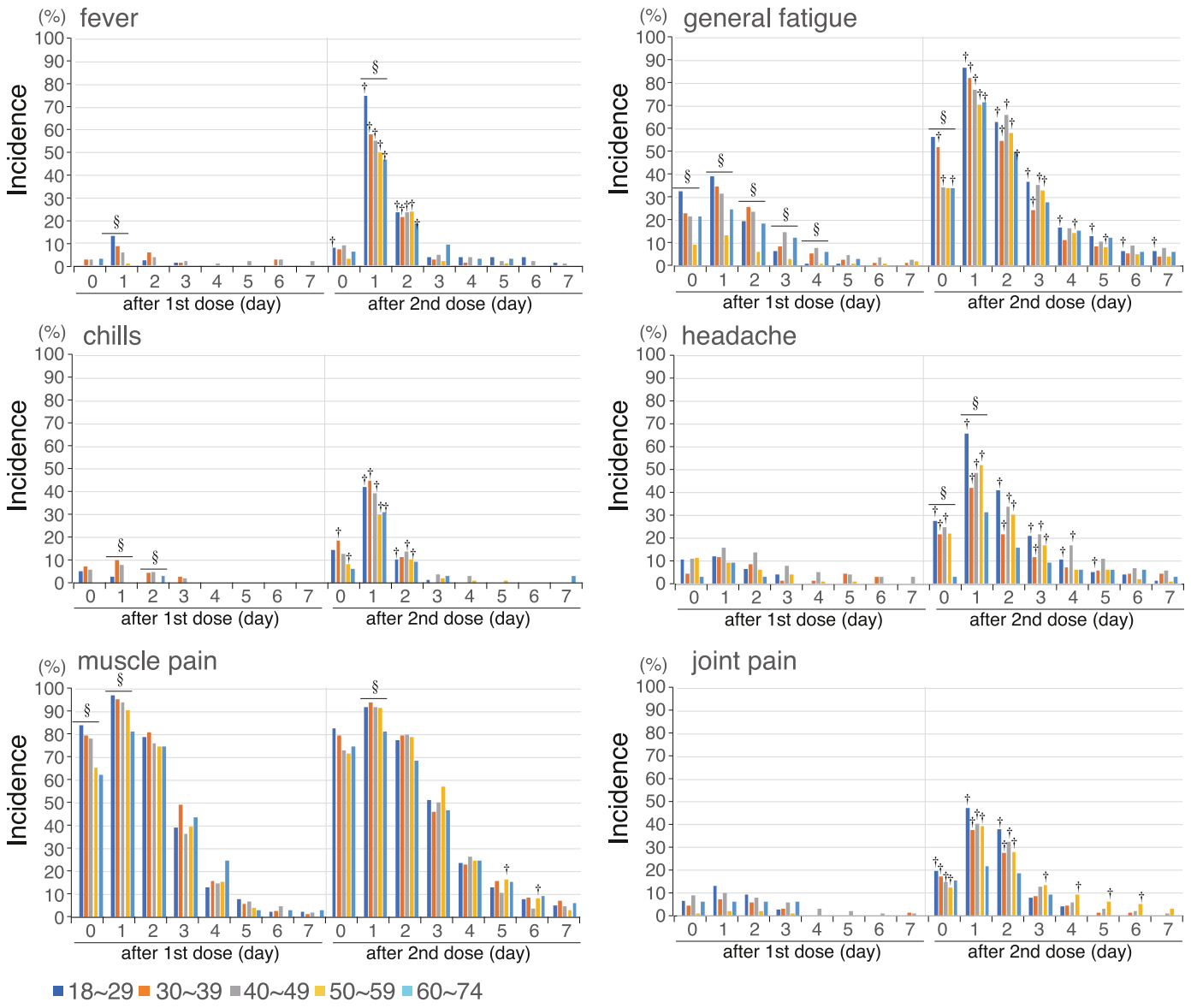

Fig. 3. Comparison of incidence and numeric rating scale (NRS) scores by age. Six major adverse reactions (fever, general fatigue, chills, headache, muscle pain, and joint pain) after the first and second doses of Pfizer-BioNTech Comirnaty® COVID-19 vaccine. †$p < 0.05$ vs. 1st shot using χ^2-test. §$p < 0.05$ among age groups using χ^2 test.

between age groups and the incidence of adverse reactions on day 1 (Table 3). The incidence of fever and general fatigue was more elevated in younger age groups after the first and second doses, with statistical significance. The same linear trend was observed for muscle and joint pain only after the first dose, and for headache only after the second dose.

Next, we compared NRS values for adverse reactions among age groups (Fig. 4 and Supplementary S2b). The NRS scores for fever, general fatigue, and headache were significantly higher in younger age groups than those in older participants on day 1 to day 2 after the second dose ($p < 0.05$) (Fig. 4).

3.5. NRS correlation after first and second vaccination

Focusing on the paired data of the 374 survey respondents after receiving both vaccine doses, NRS values after the first and second doses were plotted on an XY diagram with a KDE plot with linear regression (Fig. 5 and Supplementary S3). For all adverse reactions, the correlations expressed by the coefficient of determination R^2 between the first-time and the second-time NRS were low, and the 95% confidence intervals for linear regression were widespread along the lines, except for NRS of day 0–2 in fever, fatigue and muscle pain. Among frequently occurring adverse reactions, such as fever and muscle pain, the KDE plot color-graded contour lines were distributed evenly along the XY axes; the same NRS score for severity tended to occur after both the first and second doses. However, for general fatigue, chills, headache, and joint pain, the KDE contour lines tended to extend in the positive direction of NRS values after the second dose, owing to higher NRS scores at earlier time points after receiving the second dose in comparison with those after the first dose (Fig. 5). The KDE plot contour lines of local adverse reactions such as skin pain, erythema, and itching, which occurred less frequently, also showed axially biased distributions of NRS values after the second dose (Supplementary Fig. S3).

4. Discussion

The characteristics and severity of adverse reactions of Comirnaty® may differ considerably between the first and second doses, even in the

Table 3
Incidence comparison and linear trend test of adverse effects among age groups after the first and second doses of Pfizer/BioNTech Comirnaty® one day after injection.

adverse reaction	dose	Incidence among generations (%)					Cochran-Armitage trend test	
		18–29	30–39	40–49	50–59	60–74	χ^2-value	*p*-value
fever	1st	13.2	8.7	5.9	1.0	0.0	13.326	0.000262
	2nd	75.0†	58.0†	55.4†	50.0†	45.5†	11.605	0.000658
general fatigue	1st	39.5	34.8	31.7	13.5	25.0	11.758	0.000606
	2nd	86.8†	82.6†	77.2†	70.8†	71.9†	7.457	0.00632
chills	1st	2.6	10.1	7.9	0.0	0.0	2.657	0.103
	2nd	42.1†	44.9†	39.6†	30.2†	31.3†	3.773	0.0521
headache	1st	11.8	11.6	15.8	9.4	9.4	0.216	0.642
	2nd	65.8†	42.0†	48.5†	52.1†	31.3	5.471	0.0193
muscle pain	1st	97.4	95.7	94.1	90.6	81.3	8.76	0.00308
	2nd	92.1	94.2	92.1	91.7	81.3	1.85	0.174
joint pain	1st	13.2	7.2	9.9	2.1	6.3	4.850	0.0277
	2nd	47.4†	37.7†	40.6†	39.6†	21.9	3.404	0.0650
skin pain	1st	15.8	20.3	16.8	21.9	21.9	0.815	0.367
	2nd	18.4	23.2	17.8	19.8	15.6	0.116	0.733
erythema	1st	3.9	7.2	5.9	7.3	3.1	0.0776	0.781
	2nd	15.8†	10.1	11.9	14.6	6.3	0.441	0.507
itching	1st	9.2	4.3	3.0	5.2	3.1	1.682	0.195
	2nd	10.5	10.1	7.9	10.4	12.5	0.0205	0.886
diarrhea	1st	0.0	2.9	5.0	2.1	3.1	0.863	0.353
	2nd	3.9	5.8	5.9	5.2	9.4	0.629	0.428

same vaccinee. In this study, we compared data from the same vaccinee to evaluate the incidence and severity of adverse reactions between the first and second doses to more accurately evaluate various adverse reactions after each inoculation. As a whole, the incidence of adverse reactions was reported to be higher after the second dose than after the first dose for nearly all items. Specifically, muscle pain (93.0%), general fatigue (28.6%), and skin pain (19.0%) were the most frequently reported reactions after the initial inoculation. After the second inoculation, the incidence of systemic adverse reactions such as fever (57.8%), chills (38.0%), headache (50.3%), and joint pain (39.6%) were significantly increased and diminished 7 days after injection. The NRS score for severity tended to be higher after the second dose than after the first dose.

The incidence of systemic reactions was increased after the second dose, consistent with previous studies [1–9]. However, compared with studies in the US [1], this survey had more participants who complained of fatigue (78.1% vs. 47.8%), muscle pain (91.4% vs. 36.8%), and fever (57.8% vs. 21.5%). Muscle pain, which had the highest incidence in our study, occurred in over 90% of participants after the first and second doses. However, because there was no significant difference between the first and second doses by sex or age, it appears that a direct local reaction is associated with intramuscular injection of the vaccine.

Regarding sex differences, the incidence and NRS values tended to be higher in women than in men in our study. Although a study in the US [1] did not provide detailed information on sex difference, studies in the UK [2], South Korea [4], and the Czech Republic [7] have reported that women have a higher incidence of adverse reactions. Immune and vaccine reactions after immunization with other vaccines reportedly differ between men and women [11]. Women in all age groups show a higher antibody response and have more adverse reactions to vaccination than do men [12]. Because sex differences in the responses to vaccines have been reported across diverse age groups, biological and behavioral differences between the sexes likely contribute to sex-specific differences in the adverse reactions to vaccination. Specifically, hormonal differences between men and women may significantly affect the outcome of vaccination and the incidence and intensity of adverse reactions: both estradiol and testosterone are associated with enhanced functional responses by dendritic cells, whereas progesterone exerts immunosuppressive effects on dendritic cells [13,14]. Several researchers have reviewed the contribution of differences in numerous immunological, genetic, hormonal, and environmental factors between males and females to the mechanism of sex- and gender-specific vaccine responses and outcomes [11,13,14].

The comparison by age group showed an increased incidence and NRS of adverse reactions in younger age groups, especially for systemic adverse reactions such as fever and general fatigue. A large population-based study in the US found that participants over the age of 65 years had a lower incidence of adverse reactions than participants under the age of 65 years [1], consistent with our study. Several relevant reports have shown a high incidence and severity of adverse reactions with COVID-19 vaccines in younger age groups. Along with the production of neutralizing antibodies, release of inflammatory cytokines from activated specific T cells occurs with vaccination [15]; thus, the increase in interferon-γ concentration among young adults is greater after COVID-19 vaccination than after COVID-19 infection [16]. The fact that COVID-19 infection is less severe in young people and less severe in women than men may have an association with strong adverse effects after vaccination. In other words, the effective immune response in vaccination may cause strong adverse effects but produce effective protective immunity against the pathogens. It has become clear that the immunity to SARS-CoV2 acquired by the COVID-19 vaccination significantly prevents the aggravation of COVID-19 [17]. However, there are no reports on whether neutralizing antibodies are more likely to be produced in young people and women, although it has been reported that, in various vaccines, vaccine efficacy and the intensity of adverse reactions are correlated among age and sex [11–14]. Because strong adverse reactions may not always match the degree of neutralizing antibody production, further investigation is required to examine the association between adverse responses and protective immunity. A unique feature in our study is that we analyzed changes in NRS levels after the first and second doses in the same vaccinee. We also visually assessed the relationship between severity after the first and second doses. In general, systemic adverse reactions such as fever and general fatigue were more frequent in younger age groups and women and significantly more severe after the second dose than after the first dose. Muscle pain at the injection site was the most frequent complaint and occurred with the same severity after the first and second doses. Local reactions such as skin pain, erythema, and itching were less frequent but had a longer duration in older age groups. However, as a whole, it is important to understand that all adverse reactions were relieved within a week.

This survey has several limitations in interpreting the incidence and averaged intensity of adverse reactions. The vaccinees themselves voluntarily reported the occurrence and intensity of adverse reactions, and only 13.2% of vaccinees in the first dose and 8.9% of vaccinees in the second dose participated in this survey. The observed high incidence

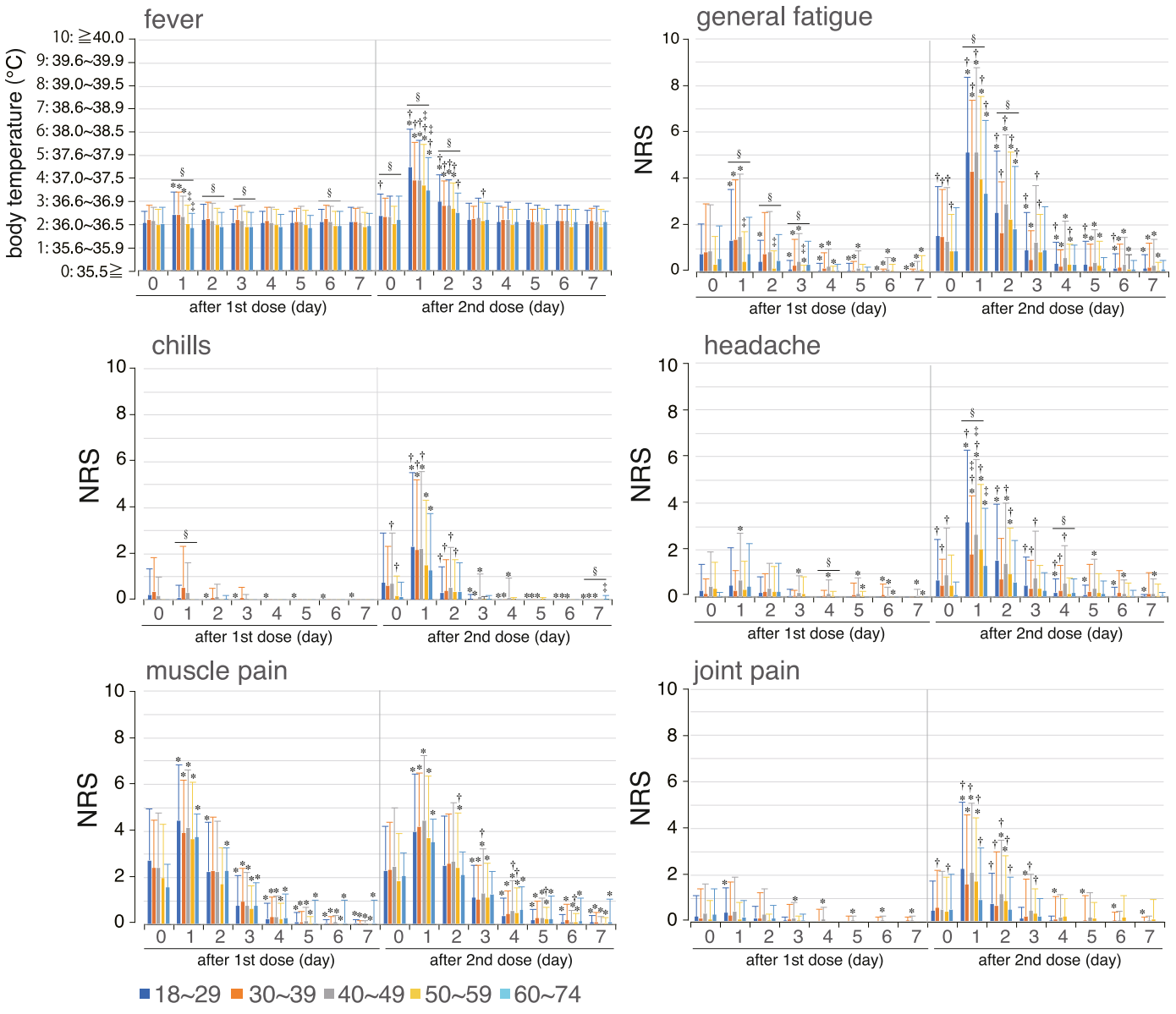

Fig. 4. Comparison of numeric rating scale (NRS) scores by age group. Six major adverse reactions (fever, general fatigue, chills, headache, muscle pain, and joint pain) after the first and second doses of Pfizer-BioNTech Comirnaty® COVID-19 vaccine. †$p < 0.05$ vs. 1st dose using paired *t*-test. *$p < 0.05$ vs. NRS scores on day 0 with repeated measures ANOVA, Student–Newman–Keuls multiple comparisons test. §$p < 0.05$ among age groups with repeated measures ANOVA. ‡: $p < 0.05$ vs. age group 18–29 years using Student–Newman–Keuls multiple comparisons test.

of adverse reactions may be because vaccinees without strong adverse reactions may not have actively participated in this study. Therefore, comparing the incidence rates of each country must be undertaken with care. Also, because this survey included medical students and healthcare professionals, the complaints of non-healthcare workers may differ from those of professionals. We hope that enlightening the public about vaccines may fill these gaps.

5. Conclusions

Some of the adverse reactions of the Pfizer-BioNTech Comirnaty® COVID-19 vaccine have gender and age differences. However, nearly all adverse reactions disappear within a week. Therefore, these side effects are not a significant concern in recommending vaccination. Regarding vaccination with Comirnaty®, providing appropriate information concerning the incidence and extent of adverse reactions by age and sex are important for correct understanding among the public to increase the uptake of COVID-19 vaccination and help to control the COVID-19 pandemic.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki. The survey (data collection and management) was performed with the approval (ERB-C-1968) of the research ethics committee of Kyoto Prefectural University of Medicine. Informed consent was obtained online from all participants via the study website before the survey start.

Declaration of competing interest

The authors declare that they have no conflicts of interests.

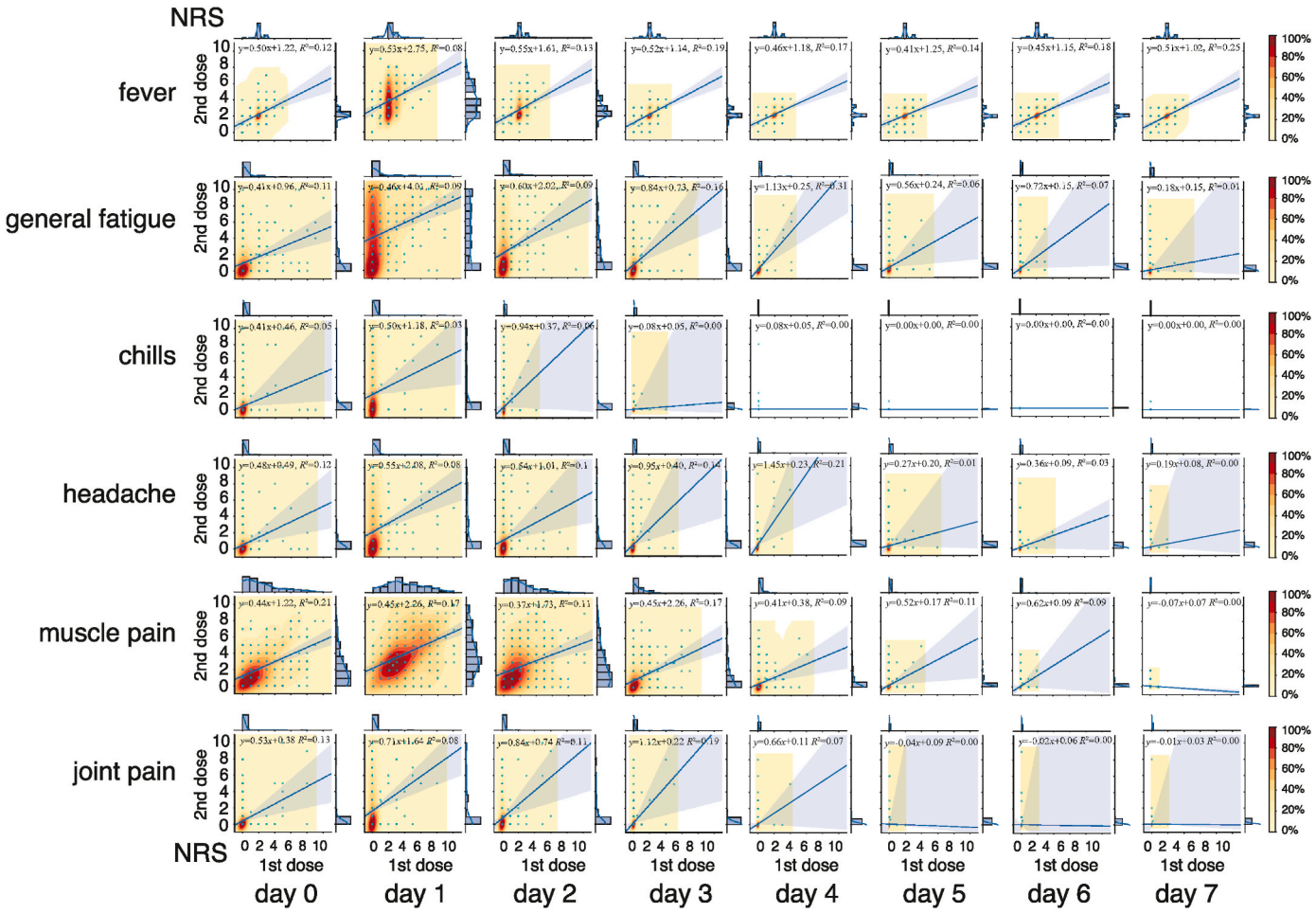

Fig. 5. Correlation of numeric rating scale (NRS) scores after the first and second doses of Pfizer-BioNTech Comirnaty® COVID-19 vaccine. Six major adverse reactions (fever, general fatigue, chills, headache, muscle pain, and joint pain). Paired NRS data of the 374 survey respondents after receiving both vaccine doses were plotted on an XY diagram with a kernel density estimation (KDE) plot, linear regression, and marginal histograms with density curves on the marginal axes. The KDE contour lines were color-graded at 11 levels between 0% and 100%. Dark blue line shows a linear regression of NRS values between doses, and light blue area represents the 95% confidence interval of linear regression. R^2: the coefficient of determination.

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Data availability statement

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

Author contributions

Ayano Maruyama, Teiji Sawa and Norito Katoh contributed to the design of the study, carried out the experiment and drafted the manuscript. Satoshi Teramukai participated in the statistical verification. All authors met JCMJE authorship criteria and have read and agreed to the published version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.03.015.

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