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Relation of fever intensity and antipyretic use with specific antibody response after two doses of the BNT162b2 mRNA vaccine

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ABSTRACT

Background: The reactogenicity of BNT162b2 COVID-19 vaccine has been commonly reported and antipyretic medications are often used for mitigating adverse reactions. Possible associations between the reactogenicity events and specific antibody responses have not been fully investigated, nor has the influence of using antipyretics.

Methods: Serum samples were collected from hospital healthcare workers with no COVID-19 history and the SARS-CoV-2 spike-specific IgG titer after two doses was measured. Degree of solicited adverse reactions in a day, including the highest body temperature, were reported using a self-reporting diary for five days after each dose. The highest body temperature during the five days was divided into three grades (<37.0 °C, 37.0–37.9 °C, or ≥ 38.0 °C). Self-medicated antipyretics were reported using a questionnaire.

Results: The data of 335 participants were available for analysis. Multivariate analysis extracted the fever grade after the second dose (standardized coefficient beta = 0.301, $p < 0.0001$), female sex (beta = 0.196, $p = 0.0014$), and age (beta = -0.119, $p = 0.0495$) as being significantly correlated with the IgG titers. The positive correlation of the fever grade after the second dose with the IgG titers was also observed when analyzed by sex and age. The use of antipyretics did not interfere with the IgG titers irrespective of the fever grade.

Conclusions: The fever intensity after the second dose was associated with the IgG titer and antipyretic medications may be beneficial to mitigate the suffering from adverse reactions, without interfering with the acquisition of sufficient antibody responses.

1. Introduction

Vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are considered the most effective approach for curbing the pandemic, and several effective vaccines are being produced. Of these, BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine (Pfizer, Inc., and BioNTech) has been reported to be 95% effective in preventing symptomatic COVID-19 [1]. Local and systemic adverse reactions after mRNA COVID-19 vaccination are relatively more common than those observed for other vaccines, such as seasonal influenza and pneumococcal vaccines [1–4]. Of note, specific adverse events after the second dose are more common than after the first for most of the systemic events reported, especially for fever [1,2]. The possible correlations between the reactogenicity and antibody response after SARS-CoV-2 vaccination have not been fully characterized. In a phase III trial of BNT162b2, around 40% of the vaccinees used antipyretic or pain medications (antipyretics) to mitigate the severity of their reactions [1]. The possible association between the use of antipyretics and antibody response to the SARS-CoV-2 vaccination is also unclear, even though the possibility of interference from the use

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of antipyretics with the immunogenicity of the vaccination is of great concern.

We have routinely conducted serological tests for antibodies to the receptor binding domain of the S1 subunit of the viral spike protein (IgG(S-RBD)) and antibodies targeting the viral nucleocapsid protein (IgG(N)) for hospital healthcare workers in Japan as an infection control measure against COVID-19 [5]. In this study, we measured the IgG(S-RBD) titers of healthcare workers after two doses of BNT162b2. Possible factors related to the IgG(S-RBD) titers, including the vaccinees background, the specific adverse reactions, and the use of antipyretics were investigated.

2. Participants and methods

2.1. Participants

Our SARS-CoV-2 vaccination program began in March 2021 and followed the manufactures recommendation of two 30 μg doses of BNT162b2 administered three weeks apart. Serum samples were collected after the start of the vaccination program, in May 2021. We included in the analysis those who had serum sampling done 14 days or more after the second dose. The exclusion criteria were: 1) diagnosed with COVID-19 by laboratory tests (either polymerase chain reaction or antigen test), 2) positive results for IgG(N), 3) the use of non-steroidal anti-inflammatory drugs (NSAIDs) in a day before vaccination, and 4) receiving immunosuppressive therapy. Serum samples collected in February 2021 were used for the measurement of the pre-vaccination IgG(S-RBD) titers.

All participants provided written informed consent before undergoing any of the study procedures. The study was approved by the ethical review board of Fukuoka City Hospital (approval number 222).

2.2. Participant demographic and clinical characteristics, reactogenicity, and use of antipyretics

The following data were gathered by a questionnaire: sex, age, job, past history of COVID-19, exposure to COVID-19 patients while working, and history of allergies and underlying diseases (hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, cerebrovascular disease, heart disease, thrombosis, bronchial asthma, chronic obstructive pulmonary disease, cancer, and immune disorders). The height and weight from our previous study were used in the present analysis

Information on the solicited local and systemic adverse reactions were collected through a web-based self-reporting diary from day 1 (vaccination day) to day 5 after each dose. The solicited data were as follows: 1) local reactions (pain at the infection site, redness, swelling, and itching), and 2) systemic reactions (fever, fatigue, headache, chills, nausea, diarrhea, muscle pain, joint pain, and rash). Other than fever, these variables were subjectively assessed using a six-point scale ranging from 0 (none) to 5 (maximum). If any symptoms were present, the scale was self-judged with the instruction that 3 would be moderate. The scale of 3 and over was treated as present for the analysis. Axillary body temperature was measured daily, and the maximum temperature during the five days was divided into three grades (<37.0 °C, 37.0–37.9 °C, and ≥ 38.0 °C).

The questionnaires on the self-medicated antipyretics included the name of the antipyretic used, the duration from vaccination to the subsequent use of antipyretics, and the timing of using antipyretics. The type, dose, and timing of the antipyretics used were chosen by the participants. We did not provide criteria for the use of antipyretics, such as the threshold of body temperature or specific post-vaccination symptoms.

2.3. Serological testing

IgG(S-RBD) and IgG(N) titers were measured using the SARS-CoV-2 IgG II assay and SARS-CoV-2 IgG assay, respectively (Abbott Laboratories Co., Ltd., Park, IL, USA). Signal-to-cutoff values of ≥ 50.0 arbitrary units (AU)/mL and ≥ 1.4 AU/mL were applied for IgG(S-RBD) and IgG(N) positivity, respectively [6]. Seroconversion was defined as positive conversion from a titer below the cut-off value to a titer above it after vaccination.

2.4. Statistical analysis

The IgG(S-RBD) titer was log-transformed and a value of 0.0 AU/mL was treated as 0.1 AU/mL. The median, interquartile range (IQR), geometric mean titer (GMT), and 95% confidence intervals (CI) were calculated. Student's *t* test was used for two categorical variables, and ANOVA for three or more. Correlation coefficients were calculated using Spearman's rank correlation test. A multivariate linear regression model was done using a stepwise selection procedure with the constraint of age and sex. The level of significance was set at < 5%, two-sided. All analyses were performed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Demographic characteristics

Demographic data are summarized in Table 1. The requirements for two doses and more than 14 days from vaccination to sample collection were satisfied by 343 staff members. Of these, seven were excluded due to IgG(N) ≥ 1.4 AU/mL and one due to the use of an NSAID before vaccination, leaving the data of 335 participants available for analysis. The median age was 40 years (IQR, 31–48), 74.9% were female, all were immunocompetent, and 88.1% had no underlying diseases. The interval between vaccine doses was 21 days for most participants: 18 had them within a range of 15–24 days. The median duration from the second vaccination to sample collection was 34 days (IQR, 33–36, range, 29–50).

3.2. IgG(S-RBD) titers according to demographic characteristics

GMTs of IgG(S-RBD) after vaccination are shown according to the demographic characteristics in Table 1. Serum samples before vaccination were available from 262 of the 335 participants, all of whom were under the cut-off value of 50.0 AU/mL, with a GMT of 0.28 AU/mL (95 %CI, 0.22–0.35) (Table 1). The GMT of IgG(S-RBD) for all 335 serum samples collected after vaccination was 8,814 AU/mL (95 %CI, 8,188–9,487), and the median was 9,466 AU/mL (IQR, 5,949–13,782 AU/mL). Seroconversion was observed in all participants whose IgG(S-RBD) titers before vaccination were available.

Univariate analyses of factors associated with the IgG(S-RBD) titers extracted female sex ($p < 0.001$), age ($r = -0.163$, $p = 0.003$), and non-doctor ($p = 0.017$) as significant.

3.3. IgG(S-RBD) titers by adverse reactions

The GMTs of IgG(S-RBD) after vaccination according to the solicited local and systemic reactions are shown in Table 2. A complete questionnaire was available from 235 of the 335 participants. The only significant variable associated with the IgG(S-RBD) titers after the first dose was no-rash ($p = 0.011$). After the second dose, the fever grade ($p < 0.001$), fatigue ($p = 0.006$), headache ($p = 0.017$),

Table 1
Geometric mean titer after the second dose, by demographic characteristics.

		No. (%)	GMT (95 %CI)	p-value
No. tested	Before vaccination	262	0.28 (0.22–0.35)	
	After vaccination	335	8,814 (8,188–9,487)	
Sex	Male	84 (25.1)	6,690 (5,681–7,878)	<0.001[a]
	Female	251 (74.9)	9,665 (8,930–10,462)	
Age, median (IQR)		40 (31–48)	r = -0.163‡	0.003[b]
	<40	162 (48.4)	9,749 (8,844–10,747)	
	40–54	135 (40.3)	8,222 (7,364–9,180)	
	≥55	38 (11.3)	7,338 (5,365–10,038)	
Body Mass Index†	<18.5	24 (9.8)	10,631 (8,093–13,963)	0.143[c]
	18.5–25.0	192 (78.4)	8,948 (8,169–9,802)	
	≥25.0	29 (11.8)	7,427 (5,492–10,043)	
Job Category	Doctor	34 (10.2)	6,451 (4,966–8,380)	0.017[a]
	non-Doctor	301 (89.9)	9,126 (8,461–9,845)	
	Nurse	186 (55.5)	9,177 (8,376–10,055)	
	Pharmacist	12 (3.6)	9,578 (6,632–13,832)	
	Others	103 (30.8)	8,985 (7,774–10,385)	
Exposure to COVID-19 patients	No	206 (38.5)	9,249 (8,400–10,184)	0.099[a]
	Yes	129 (61.5)	8,160 (7,279–9,147)	

a: *t*-test.
b: Spearman's rank correlation test.
c: ANOVA.
† Comparison within the data available.

Table 2
Geometric mean titers by adverse reaction variables for each dose.

		Dose 1			Dose 2		
		No. (%)	GMT (95 %CI)	p-value	No. (%)	GMT (95 %CI)	p-value
Use of antipyretic Medications							
Use of Antipyretic Medications after Vaccination	No	293 (87.5)	8,922 (8,243–9,658)	0.373[a]	191 (57.0)	8,163 (7,384–9,026)	0.017[a]
	Yes	42 (12.5)	8,084 (6,574–9,940)		144 (43.0)	9,757 (8,766–10,857)	
Local Reactions							
Pain at inInjection site	No	116 (49.4)	8,728 (7,674–9,924)	0.400[a]	131 (55.7)	8,993 (7,998–10,113)	0.840[a]
	Yes	119 (50.6)	9,406 (8,343–10,605)		104 (44.3)	9,154 (8,015–10,457)	
Redness	No	233 (99.2)	9,014 (8,257–9,840)	0.318[a]	222 (94.5)	9,034 (8,243–9,901)	0.763[a]
	Yes	2 (0.9)	17,742 (161–811,757)		13 (5.5)	9,581 (7,470–12,286)	
Swelling	No	225 (95.7)	9,135 (8,362–9,979)	0.517[a]	218 (92.8)	9,009 (8,226–9,867)	0.630[a]
	Yes	10 (4.3)	7,612 (4,154–13,944)		17 (7.2)	9,797 (6,914–13,880)	
Itching	No	228 (97.0)	9,061 (8,291–9904)	0.966[a]	224 (95.3)	9,122 (8,333–9,984)	0.437[a]
	Yes	7 (3.0)	9,166 (4,192–17,108)		11 (4.7)	7,974 (5,573–11,408)	
Systemic Reactions							
Fever	<37.0 °C	218 (92.8)	9,137 (8,356–9,990)	0.290[b]	93 (39.6)	7,186 (6,314–8,180)	<0.001[b]
	37.0–37.9 °C	15 (6.4)	8,927 (5,617–14,188)		91 (38.7)	9,374 (8,152–10,781)	
	≥38 °C	2 (0.9)	4,276 (597–30,620)		51 (21.7)	13,035 (10,943–15,528)	
Fatigue	No	205 (87.2)	8,972 (8,190–9,829)	0.603[a]	108 (46.0)	7,947 (6,992–9,030)	0.006[a]
	Yes	30 (12.8)	9,723 (7,211–13,111)		127 (54.0)	10,139 (9,014–11,402)	
Headache	No	215 (91.5)	8,920 (8,145–9,772)	0.260[a]	153 (65.1)	8,404 (7,523–9,386)	0.017[a]
	Yes	20 (8.5)	10,750 (7,781–14,853)		82 (34.9)	10,440 (9,082–12,001)	
Chills	No	229 (97.5)	9,126 (8,366–9,959)	0.557[a]	159 (67.7)	8,045 (7,229–8,952)	<0.001[a]
	Yes	6 (2.6)	6,964 (2,313–20,970)		76 (32.3)	11,633 (10,127–13,366)	
Nausea	No	230 (97.9)	9,061 (8,295–9,899)	0.963[a]	217 (92.3)	8,925 (8,147–9,777)	0.218[a]
	Yes	5 (2.1)	9,204 (3,796–22,325)		18 (7.7)	10,922 (7,930–15,038)	
Diarrhea	No	229 (97.5)	9,020 (8,255–9,854)	0.536[a]	220 (93.6)	9,059(8,274–9,922)	0.964[a]
	Yes	6 (2.6)	10,967 (5,178–23,233)		15 (6.4)	9,131 (6,396–13,038)	
Muscle Pain	No	188 (80.0)	8,847 (8,000–9,784)	0.229[a]	168 (71.5)	8,668 (7,805–9,625)	0.103[a]
	Yes	47 (20.0)	9,988 (8,398–11,877)		67 (28.5)	10,141 (8,654–11,865)	
Joint Pain	No	223 (94.9)	9,166 (8,397–10,007)	0.430[a]	176 (74.9)	8,720 (7,872–9,661)	0.122[a]
	Yes	12 (5.1)	7,364 (4,117–13,170)		59 (25.1)	10,174 (8,596–12,041)	
Rash	No	231 (98.3)	9,152 (8,379–9,995)	0.011[a]	231 (98.3)	9,074 (8,306–9,911)	0.875[a]
	Yes	4 (1.7)	5,207 (3,582–7,570)		4 (1.7)	8,549 (2,842–25,704)	

a: *t*-test.
b: ANOVA.

chills (p < 0.001), and the use of antipyretics (p = 0.017) were positively associated with the IgG(S-RBD) titers (Table 2).

3.4. Factors independently associated with IgG(S-RBD) titers

Multivariate linear regression analysis using the factors significant in the univariate analyses extracted the fever grade after the second dose (p < 0.0001, standardized regression coefficient beta 0.301 [95 %CI, 0.182–0.421]), female sex (p = 0.0014, beta 0.196 [95 %CI, 0.076–0.315]), and age (p = 0.0495, beta −0.119 [95 %CI, −0.238–0.000]) as significant (adjusted R^2 0.162). We also analyzed the data using an adverse reaction scale of 1 (minimum) or higher as having had a reaction (Table s1). The final model of the multivariate analysis did not change; the fever grade after the second dose, female sex, and age were retained.

The correlation between the fever grade after the second dose and the IgG(S-RBD) titers was analyzed by sex and age. Distribution of the IgG(S-RBD) titers is depicted as box plots, as shown in Fig. 1. A significant, positive association of the fever grade after the second dose with the IgG(S-RBD) titers was also observed with significance in all of the analyses by sex (A) and age (B) except for participants aged 55 years or older.

3.5. Influence of use of antipyretic medications on IgG(S-RBD) titers

The analyses for the correlation between the use of antipyretics and the IgG(S-RBD) titers are shown in Table 3. The data on duration from vaccination to subsequent use of antipyretics was not available for one participant after the first dose and five after the second. The respective GMTs of IgG(S-RBD) were 9,458 AU/mL and 8,304 AU/mL for the groups with and without antipyretics, without significance (p = 0.083). The types of antipyretics mainly used were acetaminophen only and loxoprofen only, in 70 and 43 participants, respectively. Both acetaminophen and loxoprofen were used in 13 participants. Other NSAIDs including ibuprofen, acetylsalicylic acid, and meloxicam were used by 14, 8, and one participant. Drugs combining acetaminophen and ibuprofen or isopropylantipyrine were used for one patient each. There was no significant difference in the GMTs among the types of the antipyretic (acetaminophen, loxoprofen, both of them, and others) (p = 0.785). The duration from each vaccination to subsequent use of antipyretics was not significant (p = 0.598 and p = 0.480 for the first and second doses, respectively). Only the timing of using antipyretics was significant (p = 0.046). The GMT of the IgG(S-RBD) in the group with antipyretics only after the first dose was 5,769 AU/mL (95 % CI, 3,089–10,770). For the group with antipyretics only after the second dose, it was 10,038 AU/mL (95 %CI, 8,861–11,373). The proportions of participants with a fever of 38.0 °C or higher in these two groups were 11.1% (1/9) and 27.9% (31/111). When the timing of using antipyretics was added to the final model of the multivariate analysis, it was not retained as an independent factor associated with the IgG(S-RBD) titers.

The influence of the use of antipyretics on the IgG(S-RBD) titers by the fever grade after the second dose is shown in Table 4. The groups with higher fever showed higher GMTs of IgG(S-RBD), both in the groups with and without antipyretics. The GMT was lower in the group with antipyretics than in the group without for a fever of 38.0 °C or higher (12,586 AU/mL vs 15,045 AU/mL), but without significance (p = 0.402). No significant differences were observed in the other grades of fever.

4. Discussion

In the serological assay we used, an IgG(S-RBD) titer of 4,160 AU/mL or higher has been reported to be a surrogate measure of effective antibody neutralization [7,8]. In this study, the IgG(S-RBD) titers of all participants were positive (≥50.0 AU/mL) and the GMT was 8,814 AU/mL, which shows adequate antibody production, comparable to the findings of previous studies done under similar conditions [7,9]. These results indicate that two doses of BNT162b2 provided sufficient antibody responses against SARS-CoV-2 in naive hospital healthcare workers.

In this study, age and sex showed significant correlations with the IgG(S-RBD) titers, consistent with the previous results [10,11]. The relationship between the reactogenicity and the antibody response after SARS-CoV-2 vaccination has not been well

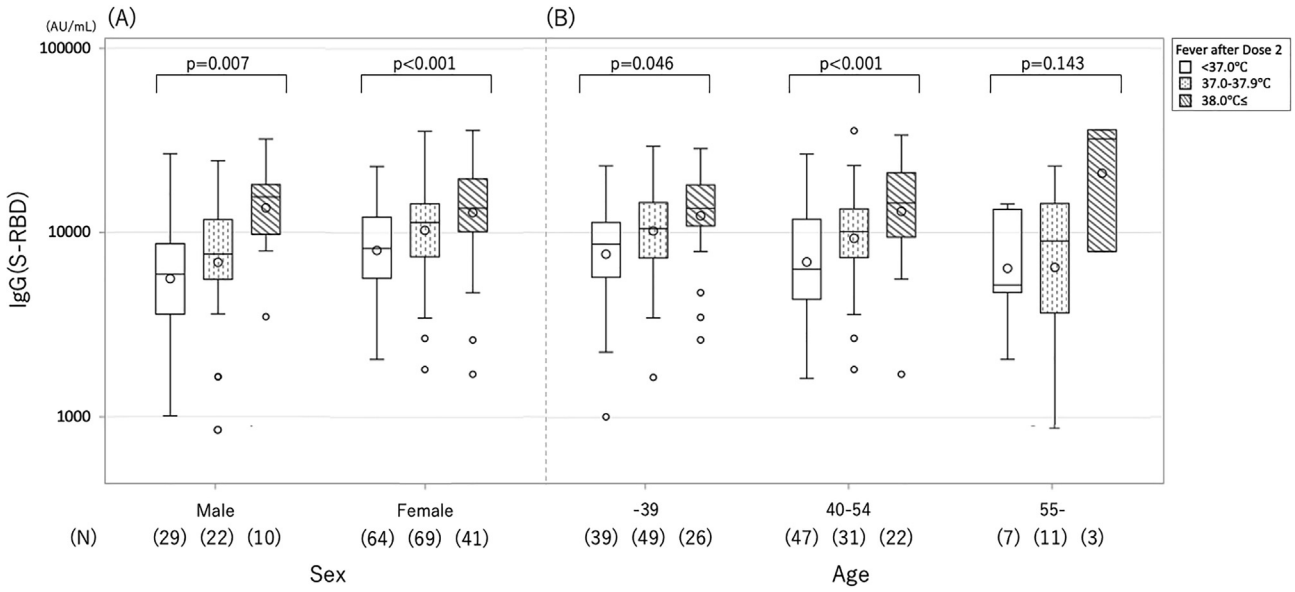

Fig. 1. Distribution of IgG(S-RBD) titers by the fever grade after the second vaccination, according to sex and age. Box-and-whisker plots for distribution of IgG(S-RBD) titers. A box represents interquartile range and a horizontal line and circle in a box represents median and mean, respectively. A vertical line represents the range, excluding outliers. A circle out of a box represents an outlier. Differences in the GMTs of IgG(S-RBD) among the grades of fever were analyzed using ANOVA.

Table 3
Effect of antipyretic use on IgG(S-RBD) titer.

			No. (%)	GMT (95 %CI)	p-value
Use of Antipyretics	No		182 (54.3)	8,304 (7,502–9,193)	0.083[a]
	Yes		153 (45.7)	9,458 (8,501–10,524)	
Antipyretic Type	Only Acetaminophen		70 (45.8)	8,955 (7,634–10,506)	0.785[b]
	Only Loxoprofen		43 (28.1)	9,585 (7,745–11,861)	
	Both		13 (8.5)	10,216 (7,093–14,714)	
	Others†		27 (17.7)	10,584 (8,122–13,794)	
Duration between Vaccination and Subsequent Use of Antipyretics ‡	After Dose 1	≤6 hrs	18 (43.9)	9,005 (7,003–11,578)	0.598[b]
		7–24 hrs	21 (51.2)	7,294 (5,250–10,135)	
		≥25 hrs	2 (4.9)	6,905 (N/A)	
	After Dose 2	≤6 hrs	33 (23.7)	8,822 (7,140–10,900)	0.480[b]
		7–24 hrs	91 (65.5)	10,286 (8,977–11,786)	
		≥25 hrs	15 (10.8)	9,254 (6,094–14,051)	
Timing of Using Antipyretics	Only After Dose 1		9 (5.9)	5,769 (3,089–10,770)	0.046[b]
	Only After Dose 2		111 (72.6)	10,038 (8,861–11,373)	
	After Both Doses		33 (21.6)	8,862 (7,168–10,958)	

N/A, not available.
a: *t*-test
b: ANOVA.
† Antipyretics, including over-the-counter drugs, such as ibuprofen, acetylsalicylic acid, meloxicam, and drugs combining acetaminophen and an Non-Steroidal Anti-Inflammatory Drug (with or without acetaminophen and/or loxoprofen).
‡ The interval between each vaccination and the subsequent use of antipyretics was not available for one participant after the first dose and for five after the second dose.
GMT, geometric mean titer.

Table 4
Influence of antipyretic use on IgG(S-RBD) titer by fever grade after the second dose.

Fever	Use of Antipyretics after Dose 2	No. (%)	GMT (95 %CI)	p-value
<37.0 °C	No	70 (75.3)	7,405 (6,368–8,608)	0.427[a]
	Yes	23 (24.7)	6,561 (5,012–8,592)	
37.0–37.9 °C	No	50 (55.0)	9,253 (7,621–11,236)	0.839[a]
	Yes	41 (45.1)	9,524 (7,723–11,746)	
≥38.0 °C	No	10 (19.6)	15,045 (9,986–22,662)	0.402[a]
	Yes	41 (80.4)	12,586 (10,299–15,382)	

a: *t*-test.
GMT, geometric mean titer.

characterized. Debes et al. showed a significant correlation between the presence of either fever, chills, or fatigue and the IgG(S-RBD) titers [11]. To date, the individual influence of each local or systemic adverse reaction on the antibody response has not been separately investigated. Among the solicited local and systemic reactions in this study, the fever grade after the second dose, but not the first, was significantly, independently associated with the IgG(S-RBD) titers, with the correlation consistently observed when analyzed by sex and age (Fig. 1). It has been reported that fever after the second dose is more common than after the first dose of SARS-CoV-2 mRNA vaccines [1,2]. Our findings showed a relationship between fever after the second dose and the post-vaccination antibody responses, but the possible causal relation remains to be clarified. Elucidating the mechanism may lead to a better understanding of the immunogenicity of SARS-CoV-2 mRNA vaccines.

If fever is associated with the post-vaccination antibody response, then the use of antipyretic medications might affect the immunogenicity of vaccination. In a review of the antipyretic effects on the immune response to vaccinations other than SARS-CoV-2, no negative influence of the use of antipyretics was observed, except when used prophylactically [12]. Several in vitro laboratory studies have reported that antipyretics, especially NSAIDs, inhibited several pathways leading to antibody responses [12–14]. Our findings indicate that the type of antipyretic and the duration from vaccination to administration were not relevant to post-vaccination antibody response. Among the participants with a fever of 38.0 °C or higher after the second dose, the GMT of IgG(S-RBD) was lower in the group with than without antipyretics (12,586 AU/mL vs 15,045 AU/mL), but the difference was not significant. It is also notable that the GMT of 12,586 AU/mL in the group with antipyretics was much higher than the 4,160 AU/mL that is the suggested benchmark for effective antibody neutralization [7,8]. We consider that the use of antipyretics may be beneficial to mitigate the suffering caused by the specific adverse reactions, including fever, without interfering with the antibody response to SARS-CoV-2 vaccination.

This study has some limitations. First, the sample size was limited to 335 cases, of which only 262 were available for the pre-vaccination antibody testing. Second, the results were obtained only from analyses based on the IgG(S-RBD) titers measured within two months after the second dose. The antibody titer declines over time [15], thus the factors associated with the long-term persistence of the post-vaccination antibody response need to be investigated in further studies. Third, the type, dose, and timing of antipyretic usage were chosen by the participants and are thus arbitrary. In addition, criteria for the use of antipyretics, such as the threshold of body temperature or specific post-vaccination symptoms, were not provided. Prospective studies are needed to clarify the influence of antipyretics on the antibody response after SARS-CoV-2 vaccination.

5. Conclusion

In addition to sex and age, the intensity of fever after the second dose of BNT162b2 was significantly correlated with the IgG(S-RBD) titers of vaccinees with no COVID-19 history. The antipyretic or pain medications may be beneficial to mitigate the suffering from

adverse reactions to SARS-CoV-2 vaccination, without interfering with the acquisition of sufficient antibody responses.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.02.025.

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