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ORIGINAL ARTICLE

A single-center COVID-19 vaccine experience with CoronaVac and BNT162b2 in familial Mediterranean fever patients

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Abstract

Aim: To determine frequency of adverse events and attacks related to vaccination in recipients of CoronaVac and BNT162b2 in familial Mediterranean fever (FMF) patients, and to search whether history of prior COVID-19 or a booster dose increases occurrence of adverse events/attacks.

Methods: FMF patients were surveyed for administration of any COVID-19 vaccine and vaccine-related adverse events or FMF attacks. Demographic, clinical, vaccine-related data, history of COVID-19 infection before or after vaccination, adherence to FMF treatment during vaccination were collected.

Results: A total of 161 vaccinated FMF patients were included. Ninety-three patients out of 161 had reported suffering from an adverse event/attack after a vaccine dose. There were 54.7% of BNT162b2 recipients who reported any adverse event after any vaccine dose in comparison to 29.9% of CoronaVac recipients ($P < .001$). There were 22.2% of BNT162b2 recipients who reported suffering from a FMF attack within 1 month after vaccination in comparison to 19.4% of CoronaVac recipients ($P = .653$). When patients with or without adverse event/attack were compared, no significant differences were observed in means of demographics, comorbid diseases, disease duration, total vaccine doses, or treatments adhered to for FMF. Rates of adverse events/attacks were similar between patients with and without prior COVID-19. In booster recipients, adverse events/attacks were most frequent after the booster dose.

Conclusions: A considerable number of FMF patients suffered from vaccine-related adverse events/attacks, particularly with BNT162b2. No serious events or mortalities due to vaccination were detected. Demographics, clinical characteristics and prior history of vaccination did not significantly affect these results. We observed an increased rate of adverse events/attacks with booster dose administration.

KEYWORDS
adverse events, COVID-19, familial Mediterranean fever, safety, vaccine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic has become the major global health problem since first human cases were reported in December, 2019 and despite the efforts, a curative treatment regimen is yet to exist except some promising results reporting decreased mortality and hospitalization rates with some antiviral and anti-inflammatory agents.[1] Hence, preventive measures have emerged, among which, vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) has been the foremost measure since vaccination is accepted to be the most effective strategy against infectious diseases.[2]

Several vaccines against SARS-CoV 2 have been developed by various countries and companies using different platforms such as inactivated vaccines, adenovirus vector vaccines and messenger ribonucleic acid (mRNA) vaccines.[3,4] In order to head off the rapidly spreading pandemic, these vaccines were put into use worldwide with emergency use authorizations, prior to completion of full procedures for approval, which raised some safety concerns alongside facilitation of vaccination, particularly for mRNA vaccines due to lack of any previous experience with any other disease. Likewise, the inactive vaccine CoronaVac (Sinovac) has been used since December, 2020 and BNT162b2 (Pfizer-BioNTech) since April, 2021 in our country.

Patients with autoimmune and auto-inflammatory rheumatic diseases compose a special population regarding the effects of COVID-19 vaccines due to presence of an already dysregulated immune system and long-term use of various immunosuppressant and anti-inflammatory agents. There have already been concerns for development of severe immune-mediated side effects such as myocarditis, multisystem inflammatory syndrome and Guillain-Barré syndrome related to COVID-19 vaccination, which means we should consider whether COVID-19 vaccination leads to disease flares or further adverse events in patients with rheumatic diseases.[5–9] Several studies have investigated vaccine safety in various rheumatic diseases with no significant safety signals; however, knowledge regarding familial Mediterranean fever (FMF) patients is still scarce.[10–14]

FMF is an auto-inflammatory disease characterized by mutations in *MEFV* gene encoding pyrin, which plays an important role as a part of the innate immune system in first defense against pathogens, as a recognizer of pathogen-associated proteins or "patterns".[15]Since pyrin-mediated inflammasome response is dysregulated and hyperreactive due to mutations in FMF patients, exposure to SARS-CoV 2 proteins via vaccination may potentially trigger inflammation, leading to attacks and/or increased rate of adverse events in FMF patients. Peet et al[16] reported no safety concerns for COVID-19 vaccines in 175 patients with auto-inflammatory diseases, only 13 of them being FMF patients. Haslak et al[17] reported an acceptable safety profile in children and young adults with auto-inflammatory diseases, the majority of whom were FMF patients. In a recent study, Shechtman et al[18] reported no increased safety signal after BNT162b2 in adult FMF patients with an increase in systemic adverse events after the second dose. However, comprehensive data regarding safety of different COVID-19 vaccine types, effects of a booster dose or history of COVID-19 infection prior to vaccination are still missing.

Effectiveness and safety of a booster dose following primary vaccination is another matter of debate. Primary vaccination is defined as completing the required series of doses for a single kind of vaccine, which differs according to type of vaccine. A booster dose, on the other hand, may also be required due to waning protective effects of primary vaccination and can be administered by another type of vaccine.[19] Although a booster dose is advocated for prolonged immunity, it further evokes safety issues regardless of being the same type with the primary vaccination or heterogeneous vaccination.[19]

In this single-center study, we investigated frequency of adverse events and attacks related to vaccination in recipients of CoronaVac and BNT162b2 comparatively in our FMF patients. Additionally, we also searched whether history of COVID-19 prior to vaccination or application of a booster dose increased occurrence of adverse events and/or FMF attacks.

2 | METHODS

This study was conducted as a single-center, cross-sectional study. Ethics approval was obtained by Ankara City Hospital ethics committee and the study was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. An official permission was also obtained from the Ministry of Health.

FMF patients meeting Tel-Hashomer criteria[20] who had been followed in our clinic were reached via telephone numbers recorded in hospital records between October 1 and December 1, 2021 and surveyed for administration of any COVID-19 vaccine and vaccine-related adverse events or FMF attacks, upon verbal consent. Written consent could not be obtained due to study design. Patients younger than 18 years of age at the time of any vaccination and patients who did not want to participate were excluded.

Data regarding demographics, comorbidities, *MEFV* mutations and medical treatment administered for FMF were collected from hospital databases and confirmed during surveys. Presence of adverse events and/or FMF attacks after any vaccine dose was set as primary outcome and collected via telephone survey. Additionally, number of vaccine doses, types of vaccines (CoronaVac or BNT162b2), interval between adverse event/FMF attack and vaccine dose, history of COVID-19 infection before or after vaccination, adherence to FMF treatment during vaccination were also collected via telephone surveys. Primary vaccination was accepted as completed in presence of 2 consecutive vaccinations of the same kind. Booster vaccination is defined as any dose of any vaccine after completion of primary vaccination. Any adverse event or attack within 1 month after vaccine administration which was suspected to be related with vaccination by the patient was recorded in accordance

with the Vaccine Adverse Event Reporting System (VAERS).[21] Severity of adverse events was also accordingly assessed. A FMF attack was defined by patient feedback according to resemblance to a previously experienced attack.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) v22.0. Normality of continuous variables was evaluated with Kolmogorov–Smirnov test in addition to visual analyses with plots and histograms. Continuous variables are presented either with median (interquartile range [IQR] or min-max) or mean ± standard deviation (SD) and compared by Mann–Whitney-*U* or Student's *t* tests according to normality. Categorical variables are presented with numbers and percentages and compared by χ^2 test. *P* values <.05 were considered statistically significant for all analyses.

3 | RESULTS

Out of 464 FMF patients, 194 could be reached via telephone in which 30 were unvaccinated and 3 did not consent to enrolment. A total of 161 vaccinated FMF patients were included in the study. Among the remaining 270 patients, 2 were detected to be dead due to reasons unrelated to COVID-19 vaccination. Distribution of COVID-19 vaccines is presented in Figure 1. Demographics, clinical properties, FMF treatment agents are presented in Table 1. There were 96.3% of patients who adhered to FMF treatment during vaccination.

Two-hundred and thirteen doses of BNT162b2 and 140 doses of CoronaVac were administered to 161 patients (Table 2). There were 72.7% of patients who were ever vaccinated by BNT162b2 while 41.6% were by CoronaVac. Median (min-max) vaccine doses were 2 (1–4) in both groups. One hundred and forty-five patients completed primary vaccination, 54.0% with BNT162b2 while 36.0% were with CoronaVac. Thirty-seven patients had booster doses (14.9% BNT162b2, 8.7% of CoronaVac).

Among 117 patients who ever received BNT162b2, 64 (54.7%) reported any adverse event after any vaccine dose in comparison to 20 out of 67 (29.9%) who ever received CoronaVac (*P* < .001). Most common side effects were fever, malaise, local pain/arm pain and arthralgia in both groups. None of the patients reported headache after CoronaVac while 9.4% reported it after BNT162b2. None of the patients suffered from a severe adverse event, while a single patient developed palmoplantar pustular psoriasis with arthritis after a BNT162b2 dose, requiring hospitalization for optimal treatment. There were 22.2% of BNT162b2 recipients who reported suffering from a FMF attack within 1 month of vaccination in comparison to 19.4% of CoronaVac recipients (*P* = .653). When attacks within a week of vaccination were taken into consideration, these frequencies reduced to 20.5% vs 16.4% (*P* = .496), respectively. The interval between vaccination and FMF attack was median (IQR) 7.0 (12.5) days in BNT162b2 recipients and 10.0 (13.5) days in CoronaVac recipients. Data regarding vaccine safety are presented in Table 2.

A total of 93 patients out of 161 reported suffering from an adverse event or FMF attack after a vaccine dose. When patients with or without adverse event/attack were compared, no significant differences were observed in means of demographics, comorbid diseases, disease duration, total vaccine doses and treatments adhered for FMF, except for an increased rate of canakinumab use in patients with adverse events/attacks nearly reaching statistical significance (7.5% vs 1.5%, *P* = .081) (Table 3).

Out of 145 patients who completed primary vaccination, 6 (4.1%) of them reported having COVID-19 at least 14 days after the last dose. COVID-19 infection was more frequent in patients with CoronaVac primary vaccination, without reaching statistical significance (7.0% vs 2.3%, *P* = .215). A total of 37 patients had a booster dose after primary vaccination (23 BNT162b2, 14 CoronaVac). A single patient in each group had COVID-19 after the booster dose (7.1% vs 4.3%, *P* = .715) (Table S1).

When 37 patients who received any booster dose after completion of primary vaccination with either vaccine types were investigated, 27% suffered from an adverse event or FMF attack after the first dose of vaccination, while this was 21.6% after the second dose and 32.4% after the booster dose (first dose vs second dose, *P* = .011; first dose vs booster dose, *P* = .029; second dose vs booster dose, *P* = .004).

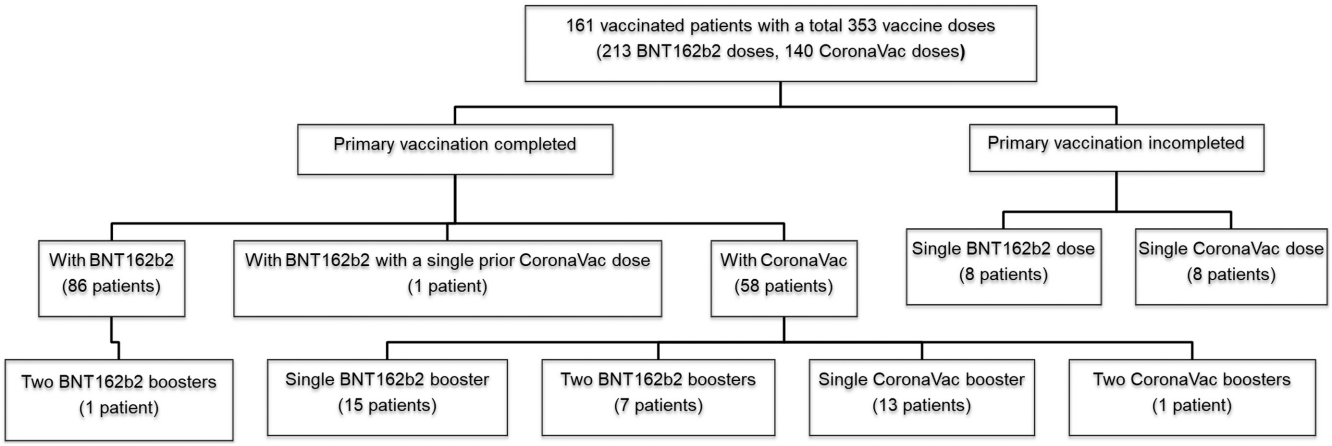

FIGURE 1 Distribution of vaccines among patients

TABLE 1 Demographics and clinical characteristics of FMF patients who were vaccinated for COVID-19

	N = 161
Age, y, mean ± SD	40.5 ± 11.7
Gender, female, n (%)	92 (57.1)
BMI, mean ± SD	25.9 ± 4.6
Active smokers, n (%)	54 (33.5)
Patients with ≥1 comorbidities, n (%)	83 (51.6)
Comorbidities, n (%)	
Hypertension	27 (16.8)
Diabetes mellitus	16 (9.9)
Chronic kidney disease	17 (10.6)
Coronary artery disease	6 (3.7)
Renal transplantation	3 (1.9)
Amyloidosis	15 (9.3)
Other	53 (32.7)
Time from diagnosis, y, median (min – max)	12.0 (1.0–50.0)
FMF attack characteristics, n (%)	
Abdominal pain	141 (87.6)
Fever	116 (72.0)
Pleuritic pain	83 (51.6)
Arthritis/arthralgia	47 (29.2)
Erysipelas-like erythema	9 (20.9)
Attack duration, d, mean ± SD	3.8 ± 1.8
MEFV mutations, n (%)[a]	
M694V heterozygous	20 (27.0)
M694V homozygous	16 (21.6)
E148Q heterozygous	7 (9.5)
M694V/M680I compound heterozygous	7 (9.5)
M694V/V726A compound heterozygous	6 (8.1)
M694V/E148Q compound heterozygous	5 (6.8)
M680I homozygous	3 (4.1)
V726A heterozygous	2 (2.7)
P369S/R408Q compound heterozygous	2 (2.7)
Others[b]	4 (5.6)
No mutations detected	2 (2.7)
Treatment agents, n (%)	
Colchicine	150 (93.2)
Anakinra	27 (16.8)
Canakinumab	8 (5.0)
TNFα inhibitors	4 (2.5)
Adherence to FMF drugs during vaccination, n (%)	155 (96.3)

Abbreviations: BMI, body mass index; FMF, familial Mediterranean fever; SD, standard deviation; TNFα, tumor necrosis factor alpha.

[a]Evaluated over 74 in whom results of *MEFV* gene analysis could be obtained.

[b]M680I heterozygous, G304R heterozygous, M680I/R761H compound heterozygous, M694V/V726Q/R202Q triple mutation each in single patient.

Thirty-nine patients had COVID-19 infection prior to completion of the primary vaccination. Of these, 61.5% suffered from an adverse reaction or FMF attack after any COVID-19 vaccine dose when compared to 56.6% of the patients without COVID-19 infection prior to vaccination ($P = .584$).

4 | DISCUSSION

Our results demonstrated that 93 out of 161 FMF patients (57.1%) had vaccine-related adverse events or FMF attacks after any dose of BNT162b2 or CoronaVac. The number of patients who reported adverse events after BNT162b2 was significantly higher. None of the patients had life-threatening, severe adverse events. There were 22.2% of BNT162b2 recipients who reported suffering from a FMF attack within 1 month after vaccine in comparison to 19.4% of CoronaVac recipients. Demographics, clinical features regarding FMF and history of COVID-19 prior to vaccination were not observed to be significantly related with the occurrence of adverse events/attacks. Significantly more patients reported adverse events/attacks after the booster dose when compared to primary vaccination doses. Rates of COVID-19 infection after primary vaccination and booster with BNT162b2 were observed to be lower despite not reaching statistical significance.

Several studies had investigated vaccine safety among patients with rheumatic diseases. Global Rheumatology Alliance reported that among 2860 subjects, 47.2% had any adverse event and 13.4% had any rheumatic disease flare.[13] Fan et al[14] reported 29.9% of patients had adverse events and 10.5% had disease flare. When studies regarding auto-inflammatory patients were investigated, Peet et al[16] reported adverse events in 51.4% of 138 vaccine administrations and disease flares in 18.8%, without any serious adverse event. In children and adults under the age of 21, Haslak et al[17] reported among 223 patients (comprising 123 FMF patients) 46.9% of non-biologic users and 39.5% of biologic users suffered from an adverse event. Severe events were reported in 2 patients. Disease flare within 1 month was reported 11.7% and 14.0% in these groups, respectively. Despite a relatively higher adverse event/attack rate in our study, we did not observe any life-threatening adverse events. Fatigue, headache, myalgia, arthralgia, fever and nausea-vomiting were the most common adverse events reported by Haslak et al.[17] Similarly, Peet et al[16] most commonly reported fatigue, myalgia, fever, headache and localized symptoms. Shechtman et al[18] evaluated BNT162b2 safety among 273 adult FMF patients, reporting 65.5% local and 26% systemic adverse events after the first dose and 60% local and 50.4% systemic adverse events after the second dose. The most common adverse events were local reaction/pain, fatigue, myalgia and fever. In our study, the total number of patients with any adverse event after any vaccine dose was 57.1%. Relatively lower incidence in our results may be due to the fact that 27.3% of our patients were only vaccinated by CoronaVac and our results demonstrated significantly fewer patients reported any side effect

TABLE 2 Adverse events and FMF attacks in vaccine recipients

	Total number of vaccinated patients = 161		
	BNT162b2	CoronaVac	*P*
Total vaccine doses, n	213	140	
Patients ever vaccinated with BNT162b2 and CoronaVac, n (%)	117 (72.7)	67 (41.6)	
Dose per patient, median (min-max)	2 (1–4)	2 (1–4)	
Patients with primary vaccination completed with BNT162b2 or CoronaVac, n (%)[a]	87 (54.0)	58 (36.0)	
Patients with a booster with BNT162b2 or CoronaVac, n (%)	23 (14.2)	14 (8.6)	
Patients vaccinated with BNT162b2 or CoronaVac alone, n (%)	94 (58.4)	44 (27.3)	
Patients with an adverse event after any dose of BNT162b2 or CoronaVac, n (%)[b]	64/117 (54.7)	20/67 (29.9)	**<.001**
Adverse events, n (%)[b]			
Fever	13 (11.1)	6 (9.0)	.644
Malaise	21 (17.9)	4 (6.0)	**.023**
Local pain/arm pain	17 (14.5)	4 (6.0)	.079
Arthralgia	19 (16.2)	4 (6.0)	**.043**
Myalgia	6 (5.1)	0 (0.0)	.059
Headache	11 (9.4)	0 (0.0)	**.010**
Nausea	6 (5.1)	1 (1.5)	.215
Vomiting	4 (3.4)	1 (1.5)	.439
Numbness	3 (2.6)	0 (0.0)	.186
Teeth pain	1 (0.9)	0 (0.0)	.448
Abdominal pain	5 (4.3)	1 (1.5)	.307
Hypotension	1 (0.9)	0 (0.0)	.448
Chest pain	1 (0.9)	0 (0.0)	.448
Flashes	1 (0.9)	0 (0.0)	.448
Backpain	2 (1.7)	0 (0.0)	.282
Weight loss	1 (0.9)	0 (0.0)	.448
Sore throat	1 (0.9)	0 (0.0)	.448
Dizziness	4 (3.4)	3 (4.5)	.718
Dyspnea	1 (0.9)	0 (0.0)	.448
Psoriasis	1 (0.9)	0 (0.0)	.448
Zona zoster	0 (0.0)	1 (1.5)	.185
Cough	0 (0.0)	1 (1.5)	.185
Diarrhea	0 (0.0)	1 (1.5)	.185
Patients with FMF attack within 1 mo after any dose of BNT162b2 or CoronaVac, n (%)[b]	26 (22.2)	13 (19.4)	.653
Attack within 1 wk, n (%)	15 (12.8)	6 (9.0)	.428
Attack within 2 wk, n (%)	20 (17.1)	9 (13.4)	.512
Attack within 3 wk, n (%)	24 (20.5)	11 (16.4)	.496
Time from vaccine dose to FMF attack, d, median (IQR)	7.0 (12.5)	10.0 (13.5)	.758

Abbreviations: FMF, familial Mediterranean fever; IQR, interquartile range.

[a] 9.9% of patients had only single dose of either vaccine.

[b] Over 117 ever vaccinated with BNT162b2 and 67 ever vaccinated with CoronaVac.

after any CoronaVac dose when compared to BNT162b2. Likewise, most common adverse events in our study were fever, malaise, local pain/arm pain and arthralgia. When FMF attacks were considered, we observed that 22.2% of BNT162b2 recipients and 19.4% of CoronaVac recipients reported suffering from a FMF attack within 1 month after any vaccine dose, which was similar to the results of the study of Shechtman et al,[18] who reported that approximately 19% of their patients had suffered from a FMF attack with 1 month after a BNT162b2 dose.

Polack et al[22] reported up to 83% local adverse events and up to 59% systemic events in 43 548 BNT162b2 recipients. As for CoronaVac, 0-28 day incidence of all adverse events were reported

TABLE 3 Clinical characteristics of patients with and without vaccine-related adverse events/attacks

	Total number of vaccinated patients = 161		
	With adverse events/attacks n = 93	Without adverse events/attacks n = 68	*P*
Age, y, mean ± SD	38.9 ± 12.4	41.9 ± 10.7	.113
Gender, female, n (%)	58 (62.4)	34 (50.0)	.117
BMI, mean ± SD	25.7 ± 4.9	26.1 ± 4.2	.681
Active smokers, n (%)	31 (33.3)	23 (33.8)	.948
Patients with ≥1 comorbidities, n (%)	46 (49.5)	37 (54.4)	.535
Comorbidities, n (%)			
Hypertension	12 (12.9)	15 (22.1)	.125
Diabetes mellitus	11 (11.8)	5 (7.4)	.349
Chronic kidney disease	11 (11.8)	6 (8.8)	.540
Coronary artery disease	2 (2.2)	4 (5.9)	.217
Renal transplantation	1 (1.1)	2 (2.9)	.387
Amyloidosis	9 (9.7)	8 (8.8)	.854
Time from diagnosis, y, median (min – max)	11.0 (1.0–41.0)	13.0 (2.0–50.0)	.121
Treatment agents, n (%)			
Colchicine	86 (92.5)	64 (94.1)	.683
Anakinra	16 (17.2)	11 (16.2)	.863
Canakinumab	7 (7.5)	1 (1.5)	.081
TNFα inhibitors	2 (2.2)	2 (2.9)	.750
Dose per patient, median (min-max)	2 (1–4)	2 (1–4)	.907

Abbreviations: BMI, body mass index; SD, standard deviation; TNFα, tumor necrosis factor alpha.

to be between 13%-22% varying on the vaccine dose.[23,24] Likewise, we observed that significantly more patients reported an adverse event after a dose of BNT162b2. Furthermore, Polack et al[22] also reported incidence of side effects was more frequent in younger patients. Fragoulis et al[10] demonstrated increased rates of adverse events in females and patients with chronic obstructive pulmonary disease among vaccine recipients with rheumatic diseases. Additionally, Li et al[25] indicated an increased rate of vaccine-related hospitalizations due to side effects in subjects with a history of COVID-19 infection prior to vaccination. Shechtman et al[18] reported adverse events and FMF attacks following vaccination were more common in FMF patients with higher disease activity and increased colchicine and canakinumab use. Similarly, in our study, patients with adverse events/FMF attacks had increased frequency of canakinumab use, nearly reaching statistical significance. When taken into consideration with results of Shechtman et al,[18] this finding may imply disease activity may actually be related to increased rates of vaccine-related adverse events/FMF attacks, since canakinumab is an agent selected in patients with high disease activity despite colchicine treatment. Our results did not imply any significant other relation between demographics, remaining clinical characteristics, history of prior COVID-19 infection and occurrence of adverse events/FMF attacks.

Thirty-seven patients in our study completed primary vaccination with at least 1 additional booster dose of either CoronaVac or BNT162b2. Among these, the number of patients with an adverse event/FMF attack after the second dose was significantly lower than the number of patients after the first dose, while the number of patients with an adverse event/FMF attack after the booster dose was significantly higher when compared to both first and second vaccine doses. Polack et al[22] revealed a decreased rate of local adverse events but increased rate of systemic events with the second dose of BNT162b2 when compared to the first dose. Haslak et al[17] reported a decrease in rate of overall adverse event occurrence with the second dose of BNT162b2 in patients with auto-inflammatory diseases. Shechtman et al[18] reported fewer local and more systemic side effects with the second BNT162b2 dose in FMF patients. In the study conducted by Aikawa et al,[26] in patients with rheumatic conditions who were administered 2 doses of CoronaVac, incidence of adverse events were lower after the second dose. As for booster dose administrations, several high-quality studies reported acceptable safety profiles both with homologous and heterologous boosters.[27–30] Regardless of the increased number of patients with adverse events/FMF attacks after the booster administration in our study, we did not observe any serious adverse event.

There are several limitations to our study to be mentioned. First, the small sample size, cross-sectional and single-center nature of the study hampers the power of our results and avoids general assumptions. Second, data regarding vaccine experience of our subjects collected via telephone survey and mainly based on subjects' self-reports and FMF attacks could not be confirmed by clinicians, which may have led to over-assumption of adverse events and FMF attacks. Another limitation is that the interval between vaccine doses was not evaluated, which may affect occurrence of vaccine-related adverse events/FMF attacks. Lastly, since this is a real-life study, vaccine types and doses administered to our patients were highly heterogeneous.

We observed a considerable number of FMF patients in our study suffering from vaccine-related adverse events and/or FMF attacks, particularly with BNT162b2. However, no serious events or mortalities due to vaccination were detected. Demographics, clinical characteristics and prior history of vaccination did not significantly affect these results. We observed an increased rate of adverse event/FMF attacks with booster dose administration. Larger, multi-center and longitudinal studies would further elucidate vaccine safety in FMF patients.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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