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PRODUCT REVIEW

The impact of previous SARS-CoV-2 infection on post-vaccine adverse events in individuals vaccinated with TURKOVAC or CoronaVac –inactivated COVID-19 vaccines

Mine Durusu Tanriover[a,b], Ozlem Altuntas Aydin[c], Rahmet Guner[d], Orhan Yildiz[e], Ilhami Celik[f], Sukran Kose[g], Sila Akhan[h], Emin Halis Akalin[i], Aykut Ozdarendeli[j,k], Serhat Unal[b,l], Ihsan Ates[m,n], Ates Kara[o,p] and the TURKOVAC Study Group*

[a]Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [b]Vaccine Institute, Hacettepe University, Ankara, Türkiye; [c]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye; [d]Infectious Diseases and Clinical Microbiology Clinic, Ankara Yildirim Beyazit University, Ankara City Hospital, Ankara, Türkiye; [e]Department of Infectious Diseases and Clinical Microbiology, Erciyes University Faculty of Medicine, Kayseri, Türkiye; [f]Department of Infectious Diseases and Clinical Microbiology, Kayseri City Training and Research Hospital, Kayseri, Türkiye; [g]Infectious Diseases Clinic, University of Health Sciences, Izmir Tepecik Training and Research Hospital, Izmir, Türkiye; [h]Department of Infectious Diseases and Clinical Microbiology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye; [i]Department of Infectious Diseases and Clinical Microbiology, Bursa Uludag University Faculty of Medicine, Bursa, Türkiye; [j]Department of Microbiology, Erciyes University Faculty of Medicine, Kayseri, Türkiye; [k]Vaccine Research, Development and Application Centre (ERAGEM), Erciyes University, Kayseri, Türkiye; [l]Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [m]Department of Internal Medicine, University of Health Sciences Ankara City Hospital, Ankara, Türkiye; [n]General Directorate of Health Services, Republic of Türkiye Ministry of Health, Ankara, Türkiye; [o]Department of Pediatrics, Pediatric Infectious Disease, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [p]Turkiye Vaccine Institute, TUSEB Aziz Sancar Arastirma Merkezi, Ankara, Türkiye

ABSTRACT

This study- a secondary analysis of data from a randomized, observer-blinded, non-inferiority study among volunteers between 18–55 y old in Türkiye- evaluated the impact of previous SARS-CoV-2 infection before the first dose of inactive TURKOVAC on post-vaccine local and systemic adverse events (AEs) comparing with CoronaVac. Of 1266 participants analyzed, 27.7% had a previous COVID-19 history. Local and systemic AEs were observed in 37.3% and 39% of the participants. The frequency of AEs was slightly higher in the first 30 minutes and 24 hours among participants with a COVID-19 history; none were severe. 1203 participants had a second dose vaccination, and 27.3% had a history of COVID-19. The frequencies of local and systemic AEs after the second dose were similar between those with and without a COVID-19 history. The TURKOVAC and CoronaVac showed similar frequencies of local and systemic AEs in the first 30 minutes after vaccination.

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Introduction

As of May 2023, the coronavirus disease 2019 (COVID-19) pandemic has resulted in more than 765 million confirmed cases and almost 7 million deaths, as the World Health Organization (WHO) reported.[1] Today, the most effective strategies to prevent individuals from the disease and its spread in the population include vaccination and applying personal preventive measures. According to the WHO COVID-19 vaccine tracker, there are 50 approved vaccines worldwide, and 11 of them were granted emergency use listing by the WHO by the end of 2022.[2] During the pandemic period, four vaccines have received conditional approval for clinical use in Türkiye: the mRNA vaccine Comirnaty, adenovirus vector-based vaccine Sputnik V (Gamaleya), CoronaVac, and the TURKOVAC, a whole virion inactivated vaccine developed with the SARS-CoV-2 strain isolated from a patient in Türkiye with confirmed COVID-19.[3]

Following the successful results from preclinical studies, the safety and immunogenicity of TURKOVAC were evaluated in phase I and II trials. The results of the phase I trial showed that neutralizing antibodies were determined in 84%, and anti-SARS-CoV-2 specific antibodies were present at Day 43 in the sera of all vaccinated individuals.[4] The subsequent phase II study showed

CONTACT Ates Kara ateskara@hacettepe.edu.tr Department of Pediatrics, Pediatric Infectious Disease, Hacettepe University Faculty of Medicine, Ankara 06100, Türkiye.

*__the TURKOVAC Study Group:__ Alper Gunduz, Onur Ozalp, and Soner Sabirli (from Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Basaksehir Cam and Sakura City Hospital 34480 Istanbul, Türkiye); Bircan Kayaaslan, Imran Hasanoglu, and Ayse Kaya Kalem (from Infectious Diseases and Clinical Microbiology Clinic, Ankara Yildirim Beyazit University, Ankara City Hospital 06800 Ankara, Türkiye); Muge Ayhan, Belgin Coskun, Omer Aydos, and Gamze Kaya (from Infectious Diseases and Clinical Microbiology Clinic, Ankara City Hospital 06800 Ankara, Türkiye); Ahmet Cagkan Inkaya and Ahmet Gorkem Er (from Department Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine 06230 Ankara, Türkiye); Zeynep Ture Yuce and Gamze Kalin Unuvar (from Department of Infectious Diseases and Clinical Microbiology, Erciyes University Faculty of Medicine 38030 Kayseri, Türkiye); Aysin Kilinc Toker (from Department of Infectious Diseases and Clinical Microbiology, Kayseri City Training and Research Hospital 38080 Kayseri, Türkiye); Omer Demir (from Medical Pharmacology, Laboratory and Imaging Units, University of Health Sciences, Izmir Tepecik Training and Research Hospital 35020 Izmir, Türkiye); Sonay Arslan and Zeynep Bayraktar (from Department of Infectious Diseases and Clinical Microbiology, Kocaeli University Faculty of Medicine 41001 Kocaeli, Türkiye); Ugur Onal (from Department of Infectious Diseases and Clinical Microbiology, Uludag University Health Application and Research Center 16059 Bursa, Türkiye).

that total immunoglobulin G responses against SARS-CoV-2 were significantly higher in the 6 μg dose group than in the 3 μg dose group, without no significant difference between neutralizing antibody titers and T cell response[4] Most recently, the phase III trial evaluating the efficacy, immunogenicity, and safety of the two-dose schedules of TURKOVAC versus CoronaVac (Sinovac Life Sciences Co., Ltd., Beijing, China) reported that TURKOVAC was non-inferior to CoronaVac in terms of efficacy and demonstrated a good safety and tolerability profile.[5]

In addition to these favorable outcomes from the safety and efficacy trials, addressing the outcomes in vulnerable populations is important since these groups are excluded from clinical trials.[6] Individuals with prior COVID-19 are one of the special subpopulations, and assessment of the vaccine outcomes in this group is crucial, given the prevalence of the disease. Nevertheless, the rapid accumulation of data from these individuals revealed insights into the risk-benefit profiles of vaccines and drove the implementation policies during the pandemic.[7] Current evidence suggests that the immune response to vaccination improves as the time between a prior infection and the vaccination increases,[8] and health authorities, including the Centers for Disease Control and the WHO, recommend vaccination after COVID-19 but consider delaying for a 3-month period.[9,10] Previous studies reported increased systemic adverse events in individuals with prior COVID-19 after mRNA or vector-based vaccines, which was considered to occur due to immune priming.[11,12] The first vaccine dose after COVID-19 induced antibody responses similar to the levels after the second dose in individuals without prior COVID-19 history.[13]

Given the importance of evaluating the effects of COVID-19 on subsequent vaccination and the lack of data regarding TURKOVAC on this subject, this study was conducted as a secondary analysis of the phase III trial of TURKOVAC, in which the local and systemic adverse events were evaluated in demographic subgroups, after administration of the first and second vaccinations, comparatively between patients with and without a COVID-19 diagnosis before initial vaccine application.

Materials and methods

The original phase III study is a randomized, observer-blinded, non-inferiority phase III clinical trial to assess the efficacy, immunogenicity, and safety of the two-dose TURKOVAC versus the two-dose CoronaVac among volunteers between 18–55 y old in Türkiye (Registered at ClinicalTrials.gov, NCT04942405). Participants were randomly assigned in a ratio of 1:1 to one of the two arms to receive either 0.5 mL of the inactivated study vaccine TURKOVAC or 0.5 mL of CoronaVac in two doses 28 d apart. The dosage of TURKOVAC and CoronaVac vaccines for this study was 3 μg/0.5 mL for each. The study protocol was published elsewhere[5] and approved by the Clinical Research Ethics Board of Hacettepe University (No: KA-21070 and Date: 21 June 2021). Informed consent was obtained from all volunteers involved in the study.

The history of past COVID-19 infection was evaluated and confirmed from the medical histories, patient records, and anti-spike antibody positivity results.

The SARS-CoV-2 IgG spike assessments were done using Abbott SARS-CoV-2 IgG II Quant analysis, a chemiluminescence microparticle immunological assay (CMIA) that detects IgG antibodies against SARS-CoV-2 in human serum and plasma qualitatively and quantitatively on an ARCHITECT i System. This assay is also used to evaluate the immunity of individuals by determining the IgG antibodies against the spike receptor-binding domain (RBD) of SARS-CoV-2 quantitatively. The cutoff for this test is 50.0 AU/mL, and values lower than this threshold are considered negative, whereas values equal to or higher than this limit are considered positive results.

The primary outcome of this study was evaluating the impact of previous COVID-19 disease before the first dose of inactive COVID-19 vaccines on post-vaccine local and systemic adverse effects. Secondary outcomes evaluated the progression and the type of adverse events in demographic subgroups after the second vaccination dose. Since this is a secondary analysis of the original phase III study, all data were included in the current analyses. The adverse event assessment was a secondary objective, and the related endpoint was the incidence of adverse reactions within 7 d after each vaccination dose in that study.[5] Thus, our study evaluated the adverse events that progressed in the first 7 d after vaccine doses. An Interactive Voice Response System (IVRS) was used to monitor the adverse events at every visit, and both predefined symptoms (solicited events) and other patient-reported unspecified symptoms (unsolicited events) were recorded and analyzed.[5]

Statistical analyses

Descriptive data for adverse events in subcategories were presented using frequency and percentages. Categorical data were compared between independent groups (adverse event positive vs. negative, and local vs. systemic adverse events) using the Chi-square test, or the Fisher's exact test if assumptions for a Chi-square test were not met. A two-sided p-value <.05 (type-I error level of 5%) was considered statistically significant. All analyses were performed using the PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1266 participants, 341 (27%) females and 925 (73%) males, were included in this study. Age distribution showed that 238 (18.8%) participants were between 18–29 y, 487 (38.5%) were between 30–39 y, and 541 (42.7%) were between 40–55 y. About 351 (27.7%) participants had a history of COVID-19 disease before the vaccine application. Local and systemic adverse events were observed in 37.3% and 39% of the study group, respectively. The rate of adverse events between the participants with and without a history of COVID-19 disease before vaccine application was similar (76.4%, both groups). When the adverse events were evaluated in sex groups, 48.4% and 49.5% of females and 33.5% and 35.4% of

males with a positive COVID-19 history had local and systemic adverse events. Adverse event progression was significantly higher among females with previous COVID-19 ($p = .043$), but not in males ($p = .58$). When the adverse event progression was compared separately in patients with and without COVID-19 history, females had a significantly higher proportion of adverse events in both groups ($p < .001$) than males.

The proportions of local and systemic adverse events in age groups were 50.5% and 45.1% in 18–29 y, 38% and 48.8% in 30–39 y, and 27.5% and 25.2% in 40–55 y groups, respectively. In the 30–39-year-old age group, adverse events were significantly higher among individuals with a COVID-19 history ($p = .013$), but individuals without a COVID-19 history in the 40–55-year-old age group had significantly more adverse events ($p < .001$). When adverse event progression was evaluated in COVID-19 history subgroups, the 18–29-year-old age group had the highest adverse event proportions ($p < .01$, both groups). The distribution of adverse events in the study groups according to demographic characteristics is presented in Table 1.

The timing of adverse events in the study groups is summarized in Table 2. Although the proportion of local and systemic events was slightly higher in the first 30 minutes and 24 hours among the patients with a COVID-19 history, none were classified as severe adverse events. After the first 24 hours, local adverse events were slightly higher, and systemic adverse events were slightly lower in the patients with positive COVID-19 history in the first 3- and 7-d following vaccination; also, none were classified as severe adverse events.

1203 participants had a second dose of TURKOVAC or CoronaVac application, and 329 (27.3%) of them had a history of COVID-19. Among them, local and systemic

Table 1. Adverse events in demographic subgroups of participants with and without COVID-19 disease history before the vaccine application.

		Adverse event				
	No adverse event n (%)	Local n (%)	Systemic n (%)	Total N	p^1	p^2
All participants						
COVID-19 disease before vaccination					0.99	0.18
Positive history	83 (23.6)	131 (37.3)	137 (39)	351		
Negative history	216 (23.6)	308 (33.7)	391 (42.7)	915		
Sex						
Females					0.043	0.47
Positive history	2 (2.2)	44 (48.4)	45 (49.5)	91		
Negative history	21 (8.4)	103 (41.2)	126 (50.4)	250		
Males						
Positive history	81 (31.2)	87 (33.5)	92 (35.4)	260	0.58	0.25
Negative history	195 (29.3)	205 (30.8)	265 (39.8)	665		
p^3		<0.001				
p^4		<0.001				
Age groups						
18–29 years						
Positive history	4 (4.4)	46 (50.5)	41 (45.1)	91	0.08	0.36
Negative history	16 (10.9)	61 (41.5)	70 (47.6)	147		
30–39 years					0.013	0.99
Positive history	17 (13.2)	49 (38)	63 (48.8)	129		
Negative history	84 (23.5)	120 (33.5)	154 (43)	358		
40–55 years					<0.001	0.18
Positive history	62 (47.3)	36 (27.5)	33 (25.2)	131		
Negative history	116 (28.3)	127 (31)	167 (40.7)	410		
p^5		<0.001				
p^6		<0.001				

p1:no adverse event vs. adverse event; p2: local vs. systemic adverse event; p3: no adverse event vs. adverse event in females with COVID-19 history; p4: no adverse event vs. adverse event in females without COVID-19 history; p5: no adverse event vs. adverse event in males with COVID-19 history; p6: no adverse event vs. adverse event in males without COVID-19 history.

Table 2. Timing of adverse events after first dose of TURKOVAC in participants with and without COVID-19 disease history.

		Adverse event				
	No adverse event n (%)	Local n (%)	Systemic n (%)	Total N	p^1	p^2
In first 30 minutes						
Positive history	346 (98.6)	4 (1.1)	1 (0.3)	351	0.37	1
Negative history	907 (99.1)	7 (0.8)	1 (0.1)	915		
In first 24 hours						
Positive history	258 (73.5)	68 (19.4)	25 (7.1)	351	0.2	0.54
Negative history	704 (76.9)	147 (16.1)	64 (7)	915		
In first 3 days					0.4	0.27
Positive history	200 (57)	94 (26.8)	57 (16.2)	351		
Negative history	545 (59.6)	211 (23.1)	159 (17.4)	915		
In first 7 days					0.85	0.2
Positive history	189 (53.8)	95 (27.1)	67 (19.1)	351		
Negative history	498 (54.4)	220 (24)	197 (21.5)	915		

$p^{1:}$ no adverse event vs. adverse event; $p^{2:}$ local vs. systemic adverse event.

Table 3. Adverse events after the second dose of COVID-19 vaccination in participants with and without COVID-19 disease history.

		Adverse event				
	No adverse event n (%)	Local n (%)	Systemic n (%)	Total N	p^1	p^2
All participants						
COVID-19 disease before vaccination					0.89	0.68
Positive history	271 (82.4)	1 (0.3)	57 (17.3)	329		
Negative history	717 (82)	6 (0.7)	151 (17.3)	874		

$p^{1:}$ no adverse event vs. adverse event; $p^{2:}$ local vs. systemic adverse event.

adverse events were observed in 0.3% and 17.3%, respectively, which was also similar among participants without a COVID-19 history (Table 3).

Local and systemic adverse events were similar in TURKOVAC and CoronaVac in the first 30 minutes after vaccine application ($p = 1.0$). After 30 minutes, the participants in the TURKOVAC group with a COVID-19 history had higher proportions of local and systemic adverse events ($p < .001$). However, participants without a COVID-19 history had more local adverse events after TURKOVAC ($p < .001$), whereas systemic adverse events were more observed after CoronaVac injection ($p < .001$). These differences were observed in the first 24 hours, 3 d, and 7 d after the applications of both vaccines. After the second dose of vaccine applications, local and systemic adverse events were similar between the TURKOVAC and CoronaVac groups regardless of the history (Table 4).

Discussion

This study showed that confirmed COVID-19 infection before COVID-19 vaccination had no significant impact on the incidence and severity of the post-vaccine local and systemic adverse events associated with the TURKOVAC vaccine. The comparisons between

Table 4. Timing of adverse events in the TURKOVAC and CoronaVac groups with and without COVID-19 disease history.

		Adverse event				
	No adverse event n (%)	Local n (%)	Systemic n (%)	Total N	p^1	p^2
In the first 30 minutes						
Positive history						
TURKOVAC	174 (98.3)	2 (1.1)	1 (0.6)	177	1	1
CoronaVac	172 (98.9)	2 (1.1)	-	174		
Negative history						
TURKOVAC	452 (99.1)	4 (0.9)	-	456	1	1
CoronaVac	455 (99.1)	3 (0.7)	1 (0.2)	459		
In the first 24 hours						
Positive history						
TURKOVAC	111 (62.7)	51 (28.8)	15 (8.5)	177	<0.001	<0.001
CoronaVac	147 (84.5)	17 (9.8)	10 (5.7)	174		
Negative history						
TURKOVAC	323 (70.8)	106 (23.2)	27 (5.9)	456	<0.001	<0.001
CoronaVac	381 (83)	41 (8.9)	37 (8.1)	459		
In the first 3 days						
Positive history						
TURKOVAC	79 (44.6)	65 (36.7)	33 (18.6)	177	<0.001	0.16
CoronaVac	121 (69.5)	29 (16.7)	24 (13.8)	174		
Negative history						
TURKOVAC	223 (48.9)	156 (34.2)	77 (16.9)	456	<0.001	<0.001
CoronaVac	322 (70.2)	55 (12)	82 (17.9)	459		
In the first 7 days						
Positive history						
TURKOVAC	72 (40.7)	66 (37.3)	39 (22)	177	<0.001	0.14
CoronaVac	117 (67.2)	29 (16.7)	28 (16.1)	174		
Negative history						
TURKOVAC	203 (44.5)	159 (34.9)	94 (20.6)	456	<0.001	<0.001
CoronaVac	295 (64.3)	61 (13.3)	103 (22.4)	459		
First 7 days-2nd dose						
Positive history						
TURKOVAC	149 (84.2)	4 (2.3)	24 (13.6)	177	0.94	0.67
CoronaVac	146 (83.9)	2 (1.1)	26 (14.9)	174		
Negative history						
TURKOVAC	388 (85.1)	4 (0.9)	64 (14)	456	0.61	1
CoronaVac	396 (86.3)	3 (0.7)	60 (13.1)	459		
In 7 days after the 2nd dose						
Positive history						
TURKOVAC	136 (80)	1 (0.6)	33 (19.4)	170	0.24	1
CoronaVac	135 (84.9)	-	24 (15.1)	159		
Negative history						
TURKOVAC	359 (83.1)	1 (0.2)	72 (16.7)	432	0.42	0.22
CoronaVac	358 (81)	5 (1.1)	79 (17.9)	442		

$p^{1:}$ no adverse event vs. adverse event; $p^{2:}$ local vs. systemic adverse event.

participants with and without COVID-19 history revealed that 76.4% of both groups had any adverse events after vaccination. Additionally, local adverse events occurred 3.6% more, and systemic adverse events were 3.7% less in the positive COVID-19 history group, but the differences were not significant, and none were severe adverse events. The analyses in demographic subgroups also revealed similar outcomes in sex and age groups and between the comparative vaccine CoronaVac.

The recently published study by Tanriover et al.[5] reporting the interim results of the randomized, observer-blinded, non-inferiority phase III study for efficacy, immunogenicity, and safety of the two-dose schedules of TURKOVAC versus CoronaVac showed the safety and non-inferiority of the TURKOVAC and a relative risk reduction of 41.03% (95% CI 12.95–60.06) after 14 d of the second dose administration among healthy volunteers between 18–55 y old. The interim safety analyses were conducted in the modified intention-to-treat group including 915 participants who received at least one dose of the study vaccine, and total adverse events were higher in the TURKOVAC arm (58.8% vs. 49.7%, $p = .004$), which none of them were grade IV adverse events or deaths, 1 patient in the TURKOVAC arm had grade III and the remaining were either grade I or II adverse events.[5] The current study included the entire study population of 1266 participants and showed an equal proportion of adverse events in both study arms without a difference. On the other hand, the COVID-19 positivity before the second dose of COVID-19 vaccination was 27.3% in the present study. The previous phase III study by Tanriover et al.[5] reported that 375 cases had antibody positivity at baseline and were excluded from the study, and 59 patients out of 915 (modified intent-to-treat group) were diagnosed with COVID-19 before the second dose of vaccination. Although these patients were excluded from the modified per-protocol group, they were comparatively lower than that in the present study (6.5% vs. 27.3%) regarding the COVID-19 positivity before the second dose of COVID-19 vaccination.

Another recently published study by Omma et al.[14] evaluated the safety and immunogenicity of CoronaVac and TURKOVAC vaccines used as homologous booster dose after the second dose of CoronaVac primary vaccination. Authors reported that two vaccines were similar regarding the frequency of adverse events, which were 34.3% in the TURKOVAC arm and 24.6% in the CoronaVac arm ($p = .11$), and local and systemic adverse events were also similar in both booster vaccine groups. When our results regarding the similarity of adverse events after the second dose of vaccine administrations are considered, those results suggest that the safety profile of TURKOVAC is consistent over time after the post-booster administration of the vaccine.

The question about the impact of past COVID-19 history on the post-vaccine adverse events was raised during the development and administration of various vaccines. A literature search revealed that the majority of the studies that evaluated this concern was conducted for mRNA and viral vector vaccines. A previous cross-sectional study by Parés-Badell et al.[15] evaluated the local and systemic adverse events after administration of two mRNA vaccine types in 2879 healthcare workers and reported that adverse events were significantly higher for individuals with a history of COVID-19. Authors reported that 96% of participants with a history of COVID-19 related hospitalization, and 86% of participants with mild or moderate symptomatic COVID-19 had adverse events, whereas only 67% of individuals without a COVID-19 history had adverse events after two doses of mRNA vaccines. Another recent study by Bettinger et al.[16] evaluated the short-term safety of COVID-19 viral vector (Vaxzevria) and mRNA (Comirnaty, Spikevax) vaccines on 684,988 adults with a prior history of SARS-CoV-2 infection in the Canadian National Vaccine Safety Network, and reported that adverse events that impact daily activities or require medical assessment within 7 d after each vaccine dose were more likely in the presence of a previous COVID-19 history. Another nation-wide retrospective cohort study by Li et al.[17] evaluated the impact of previous microbiologically confirmed SAR-CoV-2 infection on hospitalization after mRNA vaccination and found an absolute risk increase about 1:1000 in individuals with a prior infection, but the risk was transient, hospitalizations were for a median of 2 d and patients returned to baseline health rapidly. A real-world safety and reactogenicity study by Mathioudakis et al.[11] also reported that prior COVID-19 infection was associated with increased risk of local or systemic adverse events after the first dose of mRNA or viral vector-based vaccine administrations and increased severity of any adverse events. This increased risk after the first-dose administration was also reported by Raw et al.[13] The difference between the first and second vaccine doses were evaluated in different studies and reported to be likely associated with the antibody response differences between seropositive and seronegative patients, in which IgG responses were significantly higher among seropositive patients at baseline.[18]

Despite the mRNA or vector-based vaccines, there is a paucity of studies that evaluated the impact of the previous history of a SARS-CoV-2 infection on the adverse events after inactivated COVID-19 vaccines. The only study identified through a comprehensive literature search was by Lai et al.[19] Authors evaluated the post-vaccination adverse events of special interest that were adapted from the WHO's Global Advisory Committee on Vaccine Safety among individuals with or without previous SARS-CoV-2 infection and compared the outcomes between CoronaVac and Comirnaty recipients. Their results showed no significant difference in adverse events, emergency visits or hospitalization rates between patients with and without a previous COVID-19 infection in both CoronaVac and Comirnaty groups. The result of that study was similar to our results showing no significant impact of previous SARS-CoV-2 infection on the post-vaccination adverse events associated with inactivated COVID-19 vaccines.

In conclusion, this is the first study that evaluated the impact of previous COVID-19 infection on adverse events after vaccination with inactivated virus vaccine – TURKOVAC comparing with CoronaVac, which showed no significant impact of previous infection on the incidence and severity of the post-vaccine local and systemic adverse events associated with the TURKOVAC vaccine.

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Author contributions

MDT, IA, and AK contributed to the conceptualization and methodology of the study. MDT, OAA, RG, OY, IC, SK, SA, EHA, SU, IA, AK, and the TURKOVAC Study Group contributed to the investigation of the study. MDT and SU contributed to the data curation. All in-line authors and the TURKOVAC Study Group contributed to the writing – review & editing of the Manuscript. MDT and SU conducted the project administration. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Mine Durusu Tanriover http://orcid.org/0000-0001-9565-4389
Ozlem Altuntas Aydin http://orcid.org/0000-0001-8035-1385
Rahmet Guner http://orcid.org/0000-0002-1029-1185
Orhan Yildiz http://orcid.org/0000-0001-6019-0430
Ilhami Celik http://orcid.org/0000-0002-2604-3776
Sukran Kose http://orcid.org/0000-0002-4228-1213
Sila Akhan http://orcid.org/0000-0002-2540-2060
Emin Halis Akalin http://orcid.org/0000-0001-7530-1279
Aykut Ozdarendeli http://orcid.org/0000-0002-6950-8545
Serhat Unal http://orcid.org/0000-0003-1184-4711
Ihsan Ates http://orcid.org/0000-0003-2858-6229
Ates Kara http://orcid.org/0000-0002-1654-3232

Data availability statement

Proposals should be submitted to the sponsor, Health Institutes of Türkiye, who holds all the financial and intellectual rights of the study and the study vaccine TURKOVAC.

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