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Self-reported side effects following COVID-19 vaccination in athletes: A retrospective study

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ABSTRACT

Billions of coronavirus disease 19 (COVID-19) vaccines have been administered worldwide. However, limited data on side effects have been reported in athletes. This study aimed to describe the incidence of side effects following COVID-19 vaccination in athletes and to identify the factors associated with the main side effects in this population. Information on COVID-19 vaccination, side effects, and overall symptom duration was retrospectively collected from recreational and competitive athletes. A total of 460 participants were included in this study. Fever and arm pain were more frequently reported after the first-dose vaccination, 9.6% vs 4.6%, $p = .007$ and 81.3% vs 24.9%, $p \leq .001$. Myalgia was more common after the second-dose vaccination, 0.65% vs. 7.1% $p \leq .001$. Males were more likely to present with arm pain after the first and second vaccinations. Those with SARS-CoV-2 infection before vaccination were less likely to present with arm pain after the first dose of vaccination (OR: 0.162, $p \leq .001$) and more likely to present with fever after the second dose of vaccination (OR: 3.442, $p = .046$). First-dose vaccination with the BNT162b2 vaccine compared to other brands was characterized by lower odds of fever (OR: 0.394, $p = .017$). Our results indicated mild adverse effects and a short duration of symptoms in athletes following COVID-19 vaccination.

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Introduction

The emergency use of COVID-19 vaccines was initially authorized between December 2020-January 2021.[1,2] Since then, billions of doses of the COVID-19 vaccine have been administered worldwide. Data from randomized clinical trials of COVID-19 vaccines and real-world data on adverse events following immunization (AEFI) report that 50% to 90% of individuals receiving COVID-19 vaccination have experienced almost all AEFI such as arm pain, fatigue, myalgia, fever, and headache. Adverse events that result in any of the following conditions are considered serious: inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, interventions to prevent permanent impairment or damage, congenital anomaly/birth defect, life-threatening conditions, and death.[3] It should be mentioned that deciding whether a side effect is caused by a vaccine is challenging, and many factors may influence the cause–effect relationship. Errors in the immunization process, anxiety related to immunization, comorbidities, and drugs may be possible explanations for events, and a causality approach provides important information regarding a cause–effect relationship.[4,5] Indeed, a previous study focused on AEFI against human papilloma virus concluded that only half of the severe AEFI could be associated with vaccination.[6] In addition, a secondary analysis of serious adverse events following mRNA COVID-19 vaccination from randomized controlled trials reported a risk difference of 12.5 serious events per 10.000 vaccinated individuals.[7] A meta-analysis focusing on the safety of COVID-19 vaccines based on real-world studies found an overall incidence rate of 1.5% for adverse events, 0.4 per 10 000 for severe adverse events, and 0.1 per 10 000 for death after vaccination.[8]

For sports medicine physicians, screening for vaccination status is of great importance, considering that athletes are frequently exposed to an increased risk of infectious diseases.[9] In addition, highly contagious infections, such as SARS-CoV-2, may result in absence from competition for prolonged periods and complications related to COVID-19 disease.[10] It has been reported that up to 17% of athletes may present persistent symptoms after SARS-CoV-2 infection,[11] and abnormal spirometry with low breathing reserve during incremental exercise has been described.[12] A recent study reported that aerobic performance was compromised approximately 50 days after infection, indicating that caution is necessary with prolonged and high-intensity exercise in long-COVID-19 athletes.[13]

Although COVID-19 vaccination in athletes is necessary to reduce the disease burden and return to sport activities,[14] vaccine hesitancy is mainly related to concerns about AEFI and the timing of training and competition.[15] Several reports have begun to emerge on AEFI for COVID-19 in athletes, but there are little data on the incidence of COVID-19 AEFI among athletes.[16,17] Therefore, in this study, we aimed to describe the incidence of COVID-19 AEFI in recreational

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and competitive athletes and identify the factors associated with the main side effects in this population.

Materials and methods

Study population

This was a retrospective data analysis in which competitive and recreational athletes referred to the Exercise and Sports Medicine Unit, "Antonio Cardarelli Hospital," Campobasso, University of Molise, Italy, for clinical evaluation between January 2021 and March 2022 were screened for enrollment. The inclusion criteria were as follows: a) administration of at least one dose of COVID-19 vaccine and b) administration of COVID-19 vaccines indicated by the National Governmental Recommendations. Data from athletes with intellectual disabilities and competitive wheelchair athletes were excluded. Competitive athletes exercise regularly for >10 h per week and participate in official sports competition.[18] Recreational athletes exercise >4 h per week but do not participate in official competitions.[18,19]

Information regarding COVID-19 vaccination, vaccine brand, and the number of vaccine administrations was collected and registered for each athlete. The anamnestic questionnaire included the presence of fever, fatigue, cough, shortness of breath, chest pain, myalgia, headache, arm pain at the injection site, venous thrombosis, allergic reaction, or anaphylaxis, and other or no symptoms. Overall symptom duration (days) was also recorded. These symptoms were chosen based on the adverse effects reported in vaccine clinical trials. For the purposes of this study, information regarding vaccination was applied to athletes who received the first or second dose of vaccination no longer than 1 month before enrollment.

Information on SARS-CoV-2 infection was also collected. The study protocol was approved by the Institutional Review Board of the Department of Medicine and Health Sciences, University of Molise, and the participants provided written informed consent for anonymous clinical data analysis.

Statistical analysis

Descriptive statistics, including median, interquartile range (IQR), mean, minimum and maximum range, number, and percentage, were used to describe the baseline characteristics of the study population. The Shapiro–Wilk test was used to test the normality of the data distribution. Chi-square, Fisher's exact, and Wilcoxon tests were performed to evaluate differences in side effects and symptom duration between the first, second, and third doses of vaccines. Binary logistic regression analysis was performed to identify the factors associated with the reporting of AEFI for COVID-19. For the logistic regression analysis, parsimonius criteria were used. Considering the frequency of reported side effects, the following dependent variables were selected: arm pain at the injection site, fever, and myalgia. Statistical significance was set at $p \leq .05$. Statistical analyses were performed using STATA SE 16.1 software StataCorp LLC, Texas, USA.

Results

Characteristics of the population

This study included 460 participants who received at least one dose of the COVID-19 vaccine. In total, 365 (79.3%) participants received second-dose vaccine. Median age was 20.5 years, IQR was 15.5–43, and there were 301 (65.4%) males. Furthermore, 418 (90.9%) participants were competitive athletes and 42 (9.1%) were recreational athletes. The baseline population characteristics are reported in Table 1.

Side effects of COVID-19 vaccines reported by participants

The most frequent side effects after first-dose vaccination were arm pain at the injection site in 374 (81.3%) and fever in 44 (9.6%) participants. After the second vaccination dose, 91 (24.9%) patients experienced arm pain at the injection site and 26 (7.1%) experienced myalgia. Other side effects such as nausea, dizziness, diarrhea, and heart palpitations were reported by few patietns and ranged from 1.1% to 1.52% among the first- and second-dose vaccinations. In our population, no anaphylaxis, allergic reactions, myocarditis, pericarditis, thrombosis, stroke, or hospitalization were reported. Fever and arm pain were more frequently reported after the first-dose vaccination than after the second dose: 44 (9.6%) vs 17 (4.6%) $p = .007$ and 374 (81.3%) vs 91 (24.9%) $p \leq .001$. Myalgia was more common after the second-dose vaccination, 3 (0.65%) vs 26 (7.1%) $p \leq .001$. Headache, fatigue, and other symptoms did not differ significantly between the groups. Overall symptoms duration was significantly shorter after the second-dose vaccination, compared to first-dose vaccination: 0.98 ± 0.61 days vs 0.41 ± 0.73 days $p \leq .001$. The data on the side effects reported after the first and second vaccinations are shown in Table 2.

Factors associated with side effects

Arm pain

Male gender was more likely to present arm pain after the first and the second vaccinations: OR: 5.387, 95% CI 3.004–9.523, $p \leq .001$ and OR: 1.888, 95% CI 1.089–3.275, $p = .024$. Athletes with previous SARS-CoV-2 infection were less likely to present arm pain after the first-dose vaccination OR: 0.162, 95% CI 0.079–0.331, $p < .001$ (Table 3).

Table 1. Population characteristics.

Baseline Population Characteristics $n = 460$	
Age, median, IQR	20.5 (15.5–43)
Male, n (%)	301 (65.4)
Female, n (%)	159 (34.6)
SARS-CoV-2 infection, n (%)	48 (10.8)
Recreational sports, n (%)	42 (9.13)
Competitive sports, n (8%)	418 (90.87)
First-dose mRNA-1273, n (%)	47 (10.22)
Second-dose mRNA-1273, n (%)	41 (8.91)
First-dose BNT162b2, n (%)	345 (75.0)
Second-dose BNT162b2, n (%)	290 (63.04)
First-dose ChAdOx1-S, n (%)	56 (12.17)
Second-dose ChAdOx1-S, n (%)	34 (7.39)
JNJ-78436735, n (%)	12 (2.61)

IQR: interquartile range.

Table 2. Side effects reported after the first- and second-dose vaccinations.

Population Characteristics	First Dose ($n = 460$)	Second Dose ($n = 365$)	p-value
Fever, n (%)	44 (9.6)	17 (4.6)	.007
Myalgia, n (%)	3 (0.65)	26 (7.1)	≤.001
Arm pain at the injection site, n (%)	374 (81.3)	91 (24.9)	≤.001
Headache, n (%)	12 (2.61)	7 (1.92)	.642
Fatigue, n (%)	22 (4.8)	23 (6.3)	.759
Other symptoms, n (%)	7 (1.52)	4 (1.1)	.789
Symptoms duration days, mean, SD (minimum-maximum)	0.98 ± 0.61 (0–7)	0.41 ± 0.73 (0–5)	≤.001

SD: Standard Deviation.

Table 3. Factors associated with arm pain.

	First-Dose Vaccination			Second-Dose Vaccination		
Variables	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.006	0.987–1.026	.488	0.989	0.972–1.006	.212
Gender (male)	5.387	3.004–9.523	≤.001	1.888	1.089–3.275	.024
SARS-CoV-2 infection	0.162	0.079–0.331	≤.001	1.055	0.469–2.368	.897
Recreational sport vs competitive	0.517	0.220–1.371	.200	1.783	0.763–4.319	.199
BNT162b2 vs others	1.690	0.574–4.975	.341	1.158	0.589–2.274	.670

OR: Odds Ratio; CI: Confidence Interval.

Fever

The incidence of fever after the first-dose vaccination decreased with each year of increasing age, but without reaching statistical significance OR: 0.975, 95% CI 0.950–1.000, $p = .055$. First-dose vaccination with the BNT162b2 vaccine, compared to other brands, was characterized by lower odds of fever: OR: 0.394, 95% CI 0.186–0.843, $p = .017$. Athletes with previous SARS-CoV-2 infection were more likely to present fever after the second-dose vaccination OR: 3.442, 95% CI 1.020–11.607, $p = .046$ (Table 4).

Fatigue and myalgia

Age, sex, SARS-CoV-2 infection, vaccine brands, and recreational vs. competitive sports did not show any influence on reporting fatigue and myalgia after the first, second, and third doses of vaccinations (Tables S1 and S2).

Discussion

In the present study, arm pain at the injection site, fever, myalgia, and fatigue were the most common side effects of the COVID-19 vaccination in a cohort of 460 competitive and recreational athletes. Our results regarding the most common side effects are in line with those of a previous study focused on BNT162b2 side effects in a group of 127 elite athletes.[16] Arm pain at the injection site is reported at a frequency of 83.1% in subjects aged 18–55 years[20] and is the most common side effect reported after both doses of COVID-19 vaccination. In elite athletes, the frequency of fever after the first-dose vaccination was 2%, compared to 18% after the second dose. In our study, fever was reported more frequently after the first vaccination dose than after the second. It should be mentioned that in our study different brands of vaccines were included and the median age was 20.5 years. It has been reported that among the young population receiving COVID-19 vaccination, fever occurred in up to 1.9% of participants.[21] Furthermore, the BNT162b2 vaccine, compared with other brands, was characterized by lower odds of fever after the first dose of vaccination. A previous study also reported that fever after BNT162b2 was less frequent than that after mRNA-1273 and JNJ-78436735 vaccines.[22]

A recent study observed that among elite athletes, myalgia was more frequent after the first dose of vaccination.[17] In our study, myalgia was more frequent after the second vaccination dose than after the first. In the above mentioned study, 52% of the participants were administered BNT162b2 vaccine, 41% Ad26.COV2.S, and only 3% mRNA-1273. In our population, 75% of the participants received BNT162b2 vaccine as first dose, while Ad26.COV2.S was administered only in 2.61%. Important differences in the vaccine brands may explain these results. In addition, in a population of athletes which received only the BNT162b2 vaccine, myalgia occurred more frequently after the second dose.[10,16]

Other side effects such as nausea, dizziness, diarrhea, and heart palpitations were reported in 1.1% to 1.52% of the population, which is in line with previous reports.[1,20]

Serious side effects, such as anaphylaxis, myocarditis, and thrombosis, were not reported in our study, and none of the patients required hospital admission after

Table 4. Factors associated with fever.

	First-Dose Vaccination			Second-Dose Vaccination		
Variables	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.975	0.950–1.000	.055	0.997	0.962–1.033	.887
Gender	0.677	0.347–1.321	.254	0.478	0.165–1.394	.177
SARS-CoV-2 infection	0.818	0.276–2.428	.719	3.442	1.020–11.607	.046
Recreational sport vs competitive	0.881	0.234–3.310	.852	1.089	0.180–6.563	.925
BNT162b2 vs ChAdOx1-S and mRNA-1273	0.394	0.186–0.843	.017	0.525	0.154–0.535	.303

OR: Odds Ratio; CI: Confidence Interval.

COVID-19 vaccination. The incidence of anaphylaxis is extremely rare: at 4.8 per million doses of BNT162b2 and 5.1 - per million doses of mRNA-1273.[23] Myocarditis and pericarditis have also been reported, with an incidence of 1 case in 100.000 and 27 in 100.000 vaccinations, respectively.[24]

Male sex was significantly associated with arm pain at the injection site after both the first and second doses of vaccinations. Gender variations regarding side effects have also been reported in previous studies.[22,25,26] Genetic and hormonal factors may influence the different immune responses in males and females. Indeed, a more pronounced immune response has been suggested in females following COVID-19 infection.[27] However, in the present study, male gender had higher odds of experiencing arm pain. It has been suggested that estrogens modify the pain threshold, and sex hormones have been reported to modulate the endogenous opioid system in experimental models.[28,29] Furthermore, COVID-19 and the immune response to SARS-CoV-2 infection may further influence the side effects following vaccination. In our study population, arm pain was inversely associated with SARS-CoV-2 infection before vaccination, whereas fever after vaccination was independently associated with SARS-CoV-2 infection. Although data regarding COVID-19 infection and side effects following vaccination are not initially conclusive, different studies have observed an increased risk of side effects in patients with COVID-19 before vaccination.[22,26]

Interestingly, symptoms duration after the second dose was shorter than that after the first dose. In a previous study, Hull et al. reported that despite the presence of side effects in elite athletes, SARS-CoV-2 vaccination was not associated with the need to interrupt the training program.[16] In addition, it has been reported that athletes receiving influenza immunization should anticipate modification of trainings for 2 days after vaccination.[30] Furthermore, two other studies reported that acute exercise reduced adverse effects following influenza and human papilloma virus vaccination,[31,32] and a recent study observed that exercise did not increase side effects related to COVID-19 vaccination.[33] Modification of the immune response and an increase in IL-6 production have been suggested as possible mechanisms that influence the production of anti-inflammatory cytokines, resulting in the amelioration of tolerance to adverse effects. Interestingly, vaccinated individuals with high physical activity levels are characterized by higher COVID-19 vaccine effectiveness than those with low physical activity.[34]

The spontaneous reporting of AEFI and active surveillance programs are important for monitoring the safety and effectiveness profile of vaccination.[35] Notably, a post-marketing active surveillance study focusing on AEFI after influenza vaccination among healthcare workers confirmed the safety of the vaccine and reported a high response rate in reporting adverse effects.[36] In our study, we adopted an active reporting system of side effects based on symptoms related to AEFI, and this method resulted in a higher frequency of AEFI than passive self-reporting. This is valuable because passive spontaneous reporting of adverse events is characterized by a lower sensitivity.[37] In particular, non-serious adverse events, which are not life-threatening, are under-reported; however, in specific subgroups such as athletes, it is important to schedule competitions and training.

Our findings are important for athletes when planning training seasons and competitions. Hesitance to COVID-19 vaccination has been reported in various studies, and the main reasons seem to be related to concerns about side effects and safety.[38] Our data highlight the side effects of COVID-19 vaccination among athletes and serve to limit potential barriers to vaccine hesitancy among physically active populations. In addition, by considering training programs and participation in competitions, our analysis may help athletes better plan their activities in a sports context.

Study limitations: The first limitation of our study is that the cohort is not large enough to detect rare side effects, which may be underpowered in our analysis. Second, the completion of the second dose by all participants may influence the results. Another limitation of our study was the lack of comparison between physically inactive and sedentary populations. Future studies should investigate the role of physical activity in patients with AEFI.

Conclusions

Arm pain at the injection site, fever, fatigue, and myalgia are the most common side effects of the COVID-19 vaccination among athletes. Arm pain at the injection site and fever were more common, and the overall symptom duration was significantly longer after the first vaccination dose. Male sex was significantly associated with arm pain at the injection site. SARS-CoV-2 infection before vaccination was significantly associated with arm pain and fever. The BNT162b2 vaccine was associated with lower odds of fever after the first dose than the other vaccines. Our results indicated mild side effects and a short duration of symptoms in athletes following COVID-19 vaccination.

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Author's contributors

KK: Conceptualization and study design. SV and the FDA acquired the data. KK and GG analyzed and interpreted the data. KK and GG drafted the first version of the manuscript. All the authors critically revised and edited the manuscript. KK and GG supervised the study.

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Data availability statement

The data are available upon request. All requests were addressed by the corresponding author.

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