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Short communication

Temporal relationship of myocarditis and pericarditis following COVID-19 vaccination: A pragmatic approach

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ABSTRACT

Background: Complications following COVID-19 vaccination, particularly with mRNA vaccines, rarely include myocarditis and pericarditis. This work principally aimed at defining a realistic temporal relationship between vaccination and myocarditis/pericarditis development.

Methods: All relevant cases reported from week 52/2020 through week 41/2021 in the VAERS database were retrieved and analyzed for licensed vaccines. These included BNT162b2, mRNA-1273, and AD26.COV2·S. Incidence rates were calculated using the corresponding administered vaccine doses as denominators. Additionally, analyzed parameters included demographics, dose series, hospitalization length and outcome.

Results: Overall, 2016 myocarditis and 1380 pericarditis cases, ($4.96/10^6$ and $3.40/10^6$ administered vaccine doses, respectively), were recorded. Most myocarditis cases occurred following BNT162b2 ($5.60/10^6$ doses) in males <30 years. Pericarditis affected predominantly males <40, both sexes >40 years, and was most common post AD26.COV2·S ($4.78/10^6$ doses). Hospitalization was required for 40.3% and 27.2% of myocarditis and pericarditis cases, respectively. A bimodal pattern was found for both myocarditis and pericarditis, with two peaks that coincided temporally, but were reversed in intensity. The first peak was recorded 1–3 days post-vaccination and was more pronounced in myocarditis, while the second was recorded 15–30 days post-vaccination and was more intense in pericarditis.

Conclusions: Myocarditis/pericarditis after COVID-19 vaccination is rare and depicts a bimodal pattern.

The beginning of the third pandemic year of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) finds humanity still largely depending on vaccines to control coronavirus disease 2019 (COVID-19). Myocarditis and pericarditis are rare, but concerning complications following vaccination against COVID-19, particularly with the novel mRNA-based vaccines [1–4]. A limitation in the estimation of the actual incidence of such complications is the time interval between vaccination and cardiac inflammation symptoms onset that has been reported to vary widely, ranging from 0 to 144 days [5].

To define a realistic temporal relationship between vaccination and myocarditis or pericarditis development, we analyzed all relevant cases recorded in the Vaccine Adverse Event Reporting System (VAERS) from week 52/2020 (December 21 to 27, 2020) through week 41/2021 (October 11 to 17, 2021). An early warning system co-managed by the United States (US) Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), VAERS documents and analyzes possible adverse events post-vaccination reported by healthcare professionals, vaccine manufacturers and patients [5]. As a passive reporting system, VAERS is subject to misreporting biases. However, the risk is minimized since reported adverse events undergo internal evaluation, including detection and merge of duplicated cases [5,6]. We used the public database of VAERS that is coded using the MedDRA system. The Brighton Collaboration definitions are used only for cases for which additional follow-up, including collection of medical records, is done by CDC and FDA investigators [5].

Reported data on cases of myocarditis and pericarditis post COVID-19 vaccination were collected for all licensed COVID-19 vaccines, which included Comirnaty (Pfizer-BioNTech BNT162b2 mRNA vaccine), Spikevax (Moderna mRNA-1273 vaccine), and Janssen (Johnson & Johnson, J&J recombinant viral vector adenovirus vaccine). The

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corresponding numbers of administered COVID-19 vaccine doses as of October 15, 2021, were retrieved from the public database "Our World in Data" and used as denominators to estimate incidence rates per 10^6 doses for each vaccine [7]. The mean myocarditis and pericarditis rates for these COVID-19 vaccines were calculated by summing all myocarditis and all pericarditis cases post COVID-19 vaccination reported to VAERS for all COVID-19 vaccines, and then dividing by the corresponding total number of administered doses. Analyzed parameters included vaccination (vaccine manufacturer, dose series), event (onset interval, hospitalization days, category), and demographic information of cases (age, sex).

A total of 406,570,875 doses of COVID-19 vaccines were administered in the US from week 52/2020 through week 41/2021 [7]. Overall, 406,150,000 COVID-19 vaccine doses were delivered during the study period, for which the vaccine name was known [7]. The numbers of administered vaccine doses by manufacturer were as follows: Pfizer-BioNTech 237.33 $\times$ 10^6, Moderna 153.55 $\times$ 10^6 and Janssen/J&J 15.28 $\times$ 10^6. Overall, 2016 myocarditis and 1380 pericarditis cases were notified to VAERS during the study period (Table 1). Thus, the mean rates of myocarditis and pericarditis of the three licensed COVID-19 vaccines overall were estimated at 4.96/10^6 and 3.40/10^6 administered vaccine doses, respectively. Myocarditis incidence was highest following vaccination with Pfizer-BioNTech's BNT162b2 (5.60/10^6 doses), lower with Moderna's mRNA-1273 (4.15/10^6 doses), and lowest following Janssen/J&J's AD26.COV2·S (3.27/10^6 doses). The incidence of pericarditis, on the other hand, was highest post AD26.COV2.S vaccination (4.78/10^6 doses) and comparable post vaccination with BNT162b2 or mRNA-1273 (3.52/10^6 and 3.07/10^6 doses, correspondingly).

Table 1
Summarized characteristics of reported myocarditis and pericarditis cases post COVID-19 vaccination for all vaccines combined.

	Myocarditis (n = 2016) n (%)	Pericarditis (1380 n (%)
Sex		
Males	1508 (74.8)	865 (62.7)
Females	474 (23.5)	497 (36.0)
Unknown sex	34 (1.7)	18 (1.3)
Age group (years)		
6–17	482 (23.9)	139 (10.1)
18–29	689 (34.2)	342 (24.8)
30–39	279 (13.8)	218 (15.8)
40–49	173 (8.6)	165 (12.0)
50–59	119 (5.9)	188 (13.6)
60–64	50 (2.5)	88 (6.4)
65–79	95 (4.7)	165 (11.9)
≥80	10 (0.5)	25 (1.8)
Unknown age	119 (5.9)	50 (3.6)
Vaccine dose		
Dose 1	539 (26.7)	459 (33.3)
Dose 2	1078 (53.5)	680 (49.3)
Dose 3	13 (0.7)	12 (0.9)
Unknown dose	386 (19.1)	229 (16.5)
Hospitalization (days)*		
0–4	2619 (73.0)	2040 (80.7)
5–9	298 (8.3)	201 (7.9)
≥10	114 (3.2)	87 (3.5)
Unknown	558 (15.5)	201 (7.9)
Event category post vaccination*		
Hospitalization	1447 (40.3)	689 (27.3)
Emergency room or office visit	1485 (41.5)	1435 (56.8)
Life threatening	319 (8.9)	183 (7.2)
Permanent disability	77 (2.2)	64 (2.5)
Death	37 (1.0)	5 (0.2)
Other	218 (6.1)	153 (6.0)

* For corresponding reported events (n = 3589 for myocarditis and n = 2529 for pericarditis).

Both disorders affected males predominantly (74.8% myocarditis/62.7% pericarditis). About half of myocarditis (49.8%) and a third of pericarditis (28.6%) cases incurred in males <30 years. Approximately 39.3% of vaccine-related pericarditis incurred in males <40, while 53.4% of cases incurred, equally in both sexes, in subjects >40 (15.8% in 30–39 and ~ 12.0% in the 40–49, 50–59, and 65–79 age groups).

Vaccine dose information was missing in 19.1% of myocarditis and 16.5% of pericarditis cases, while 0.7% and 0.9% of corresponding cases occurred after the third dose. The majority of heart inflammation cases post COVID-19 vaccination occurred after the second rather than the first vaccine dose (53.5%/26.7% for myocarditis and 49.3%/33.3% for pericarditis, Table 1). This effect was heightened among vaccine recipients younger than 30 years of age for both disorders.

Hospitalization was required for 40.3% of reported myocarditis cases; 24.7% of myocarditis events were treated in the emergency room, 16.7% in office visits, while 8.9% were life-threatening. Most myocarditis cases required two hospitalization days (20.3%), 19.7% required zero, while 15.5%, 9.8%, and 7.7% required 3, 1, and 4 hospitalization days, respectively. Among pericarditis events, 31.6% were treated in the emergency room and 25.2% in office visits, while 27.2% were hospitalized, with 7.2% of events being life-threatening. Most pericarditis cases required zero hospitalization days (37.8%), followed by 17.5%, 10.9%, and 9.3% that required 2, 1, and 3 days, respectively. Events leading to permanent disability were rare (2.1% for myocarditis and 2.5% for pericarditis) and deaths even rarer, but higher for myocarditis than pericarditis (1.0% vs. 0.2%, respectively). In six myocarditis and three pericarditis cases, existing hospitalization was prolonged. The relatively low hospitalization rates that were found may not be surprising given that most vaccine-related myocarditis and pericarditis cases are reported to be mild and self-limited [8,9].

Data analysis revealed a bimodal pattern for both myocarditis and pericarditis with two peaks that coincided temporally, but which were reversed in intensity as depicted by the relative percentages of recorded events (Fig. 1). The first peak (1–3 days post vaccination) was more pronounced in myocarditis (~18–19% of cases each day vs. 10–12.5% for pericarditis cases), whereas the second peak (15–30 days post vaccination) was more intense in pericarditis (accounting for 14% compared to 9% for myocarditis cases). Intriguingly, this bimodal pattern for both myocarditis and pericarditis was common for all COVID-19 vaccines, irrespectively of platform (mRNA- or vector-based). Does this imply that this bimodal pattern stems from the pathophysiology of the induced heart inflammation?

We hypothesize that the first peak could represent a rapid immune reaction to extra RNA species inoculated with mRNA vaccines, or due to acute toxicity to the high inoculates of recombinant replication-incompetent adenovirus vector encoding the SARS-CoV-2 spike protein of vectored vaccines, as we have previously described [3,4]. The second peak could be attributed to delayed immune responses to mRNA produced by the vaccinees' cells.

Our findings agree with those of Diaz et al. [8] who reported median onset of 3.5 days (IQR, 3.0–10.8) for myocarditis in younger subjects after the second vaccination and 20 days (IQR, 6.0–41.0) for pericarditis that affected older patients later. Similar results have been reported in the literature [10–12]. A population-based study that quantified the risk of several rare cardiac adverse events associated with COVID-19 vaccination reported an increase in the risk of myocarditis within a week of receiving the first dose of both (simian) adenovirus and mRNA vaccines, and a higher risk after the second dose of both mRNA vaccines; an increase in the risk of pericarditis was only found in the 1–28 days following a second dose of the mRNA-1273 vaccine in this study [9]. Real-world data indeed show increased rates for myocarditis and pericarditis after COVID-19 vaccines: In the pre-vaccine period, the mean monthly number of myocarditis or myopericarditis cases was reported to

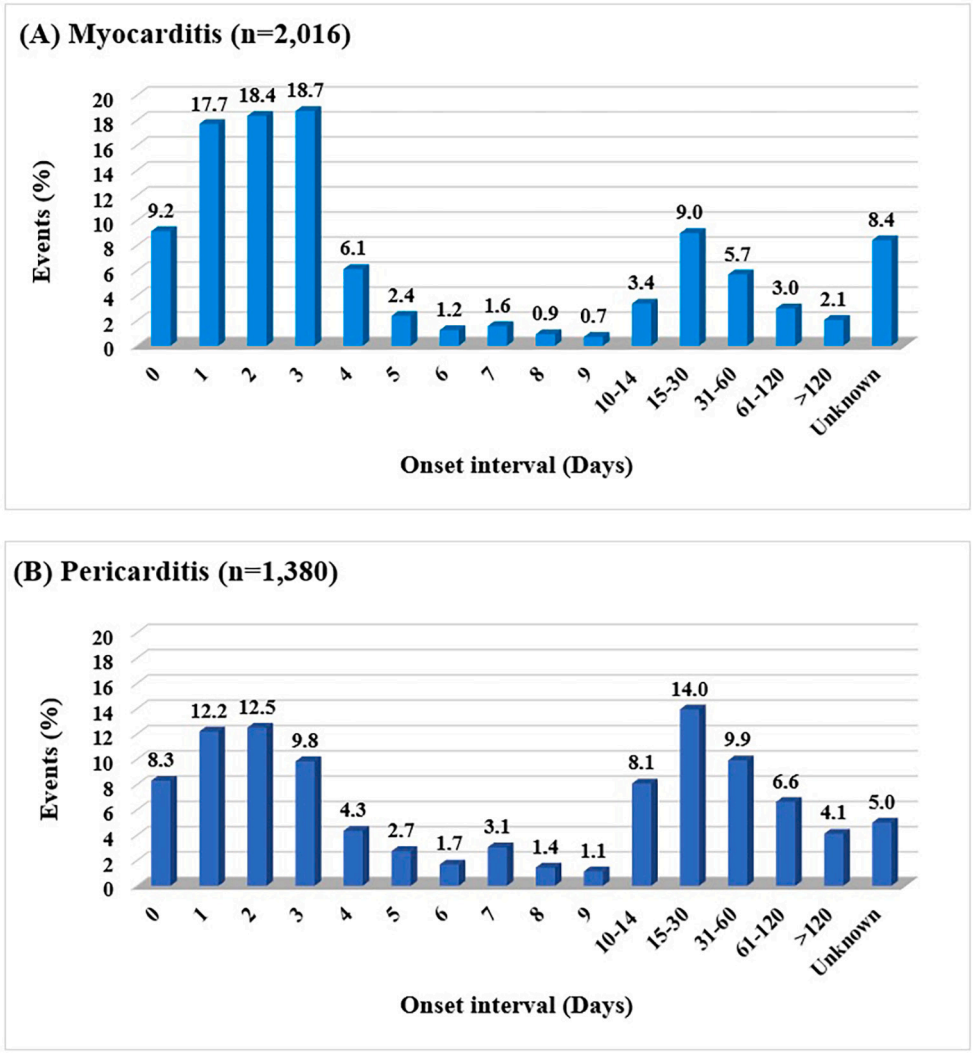

Fig. 1. Time delay between COVID-19 vaccination and myocarditis (A) and pericarditis (B) onset.

be 16.9 compared to 27.3 in the vaccine period ($P < .001$), while the mean numbers of pericarditis cases were 49.1 and 78.8, respectively, during the same periods ($P < .001$) [8].

The use of real-life data retrieved from VAERS, one of the largest reporting systems on vaccine-associated adverse events globally, is a strength of the current study. VAERS complements other vaccine safety monitoring systems in the US, including v-safe and the Vaccine Safety Datalink [13]. The lack of an accurate denominator of vaccine doses administered in this system which cannot generally determine cause and effect, is a potential limitation. In addition, the onset interval was unknown for 8.4% and 5.0% of myocarditis and pericarditis cases, respectively. Other limitations, pertaining principally to the usage of such a passive reporting system that can rapidly detect a potential safety problem, possibly include reporting bias which could under- or overestimate true heart inflammation rates. However, in our view, this was likely not the case given the enhanced COVID-19 vaccine safety scrutiny as mass vaccination strategies were implemented around the world under the attention of mass media. The agreement of our results to the findings of other studies offers further validity [8–12].

Our pragmatic analysis, that is based on real-world data of one of the world's most reliable vaccine adverse event reporting systems, offers unique insights into the temporal relationship between myocarditis and pericarditis onset after COVID-19 vaccination. Further research is warranted to fully characterize this temporal relationship and its significance without diminishing the confidence in vaccination [14].

Author statement

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