Science, Public Health Policy, and the Law
Volume: v5.2019-2024
November 2024
Peer Reviewed

An Institute for Pure and Applied Knowledge (IPAK)

Public Health Policy Initiative (PHPI)

Letter to the Editor: Long-Term Prognosis of Patients with Myocarditis Attributed to COVID-19 mRNA Vaccination, SARS-CoV-2 Infection, or Conventional Etiologies

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Letter to the Editor

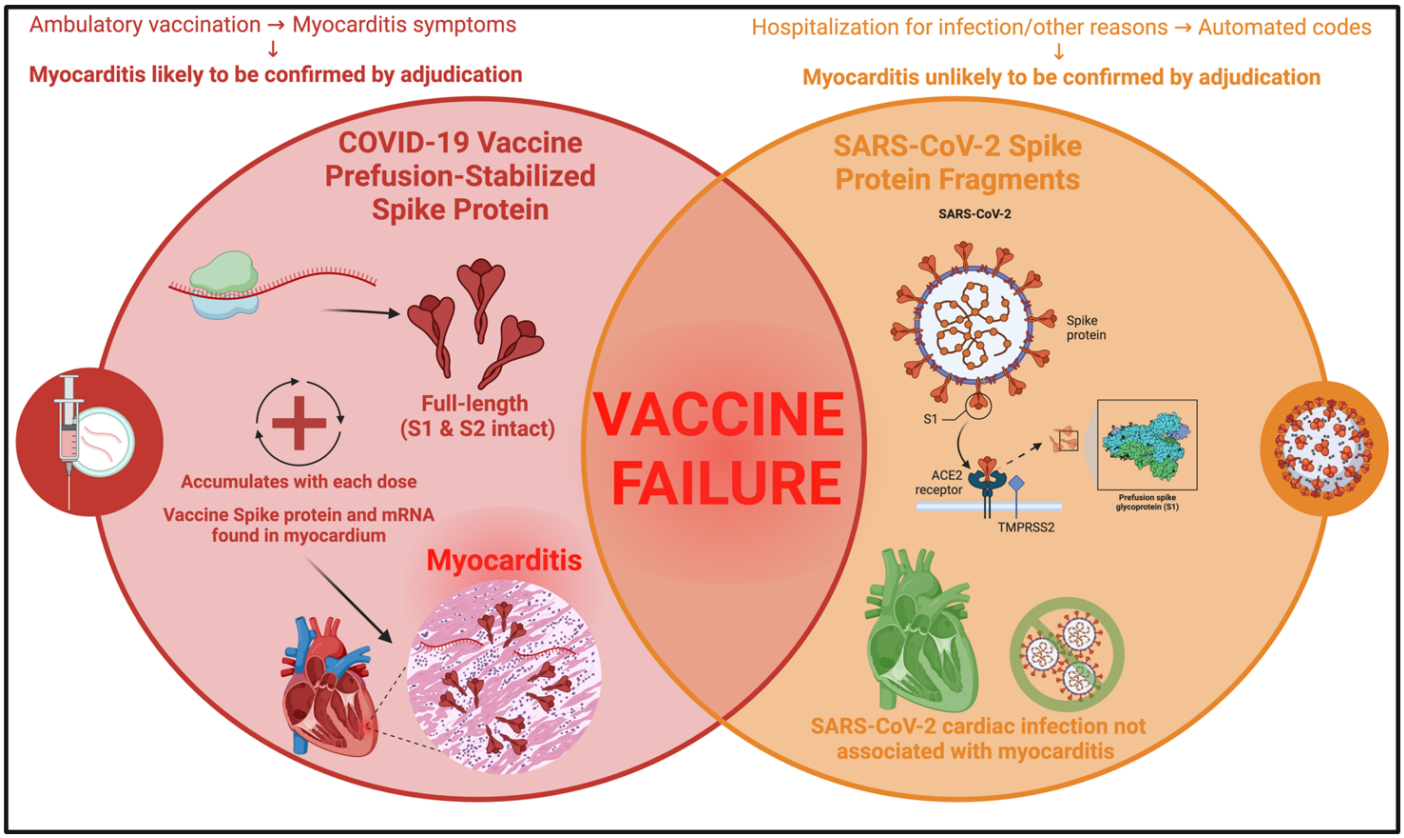
Semenzato *et al.* incorrectly concluded that patients who develop myocarditis following an mRNA COVID-19 vaccination experience fewer cardiovascular complications at 18 months compared to those with alleged myocarditis following a COVID-19 infection or an unusually large series of those with "conventional" myocarditis allegedly not related to the infection or the vaccine [1]. The study methodology raises numerous concerns. According to Table 2, among the post-COVID-19 myocarditis and 'conventional' myocarditis groups, 46.3% and 52.3% received at least one COVID-19 vaccine, respectively. Since Semenzato *et al.* did not incorporate a proper clinical adjudication protocol for myocarditis, it is likely that a substantial number of patients in the post-COVID-19 and 'conventional' groups actually had cardiovascular conditions and laboratory results that triggered automated codes mapping to myocarditis. For example, elevated troponin values commonly found with hospitalized illness do not alone indicate myocarditis. Moreover, vaccine-induced myocarditis was defined as patients diagnosed with myocarditis within 7 days of inoculation, while post-COVID-19 myocarditis was given a 30-day window since the initial infection. The authors cite Le Vu et al. as justification for this methodological choice [2], where 331 hospitalized cases experienced myocarditis or pericarditis from 8 to 21 days following vaccination and were not classified as "post-vaccination cases" because they didn't occur within 7 days. The 7-day vaccine myocarditis window is obviously biased and may be approximately four times more likely to ascribe myocarditis to the infection as opposed to the vaccine. After COVID-19 vaccination, the mRNA has been found in blood 28 days after injection [3] and the vaccine-derived prefusion stabilized Spike protein is circulatory in blood for at least six months [4], suggesting there is a very large window after vaccination where myocarditis is a plausible vaccine injury syndrome.

To investigate the percentage of vaccine-induced myocarditis that occurs after the 7-day window, the Vaccine Adverse Event Reporting System (VAERS) data was queried using the SYMPTOM and NUMDAYS variables [5]. For this study, we used both the VAERS Domestic and Foreign data sets. A

single SYMPTOM variable was constructed by concatenating individual SYMPTOM [1-n] variables. NUMDAYS is the number of days between the onset date and the vaccination date. A query for 'myocarditis' and 'myopericarditis' was conducted using the SYMPTOM variable yielding $N_{\_myo\_tot} = 18{,}494$ reports, whereby $N_{\_myo\_tot\_ND\_valid} = 14{,}224$ had valid data with respect to the NUMDAYS variable. Only records with valid NUMDAYS data were included in subsequent calculations; entries with "NA" were excluded. The number of reports that occurred more than 7 days post injection was $N_{\_myo\_tot\_ND\_valid\_7\ days} = 4{,}602$. The percentage of reports occurring 7 days post injection was calculated as follows: $N_{\_myo\_tot\_ND\_valid\_7\ days}/N_{\_myo\_tot\_ND\_valid} \times 100$. 32.4% of myocarditis/myopericarditis cases were reported more than 7 days after the last vaccination, meaning that 67.6% of reports qualify as “vaccine-induced myocarditis” according to the definition provided by Semenzato *et al.* [1]. Notably, among these reported post-injection myocarditis cases more than 7 days after injection, 67.5% were listed as "not recovered" at the time of the report, of which the mean age was 35. These data indicate that Semenzato *et al*’s choice of post-vaccine myocarditis limited to 7 days after injection was biased and worked to falsely reduce cases of myocarditis attributed to vaccination. The authors do partially acknowledge this limitation in eTable4, where they redefine cases of post-vaccine myocarditis as having received an mRNA vaccine within the previous 30 days instead of 7 days. This more balanced analysis resulted in a higher weighted hazard ratio (wHR) for the composite outcome in post-vaccine myocarditis cases (wHR = 0.84) compared to the original analysis (wHR = 0.55), which would significantly alter Semenzato *et al.*’s conclusions.

The conclusions made by Semenzato *et al*. are not consistent with the literature. Watanabe and Hama found that the myocarditis mortality rate ratio (MMRR) was significantly higher in the COVID-19 vaccinated population compared to the general population during the three years preceding the COVID-19 pandemic, with a pronounced increase among young adults (MMRR: 7.80 for individuals in their 30s) [6]. The OpenSAFELY study found that myocarditis occurred only among COVID-19 vaccinated children and not SARS-CoV-2 infected children, with a sample size of over 1 million participants [7]. Both mRNA and vaccine-derived Spike protein with inflammation have been found in the human heart in those who died after COVID-19 vaccination and in those with vaccine-induced myocarditis, respectively (**Figure 1**) [8, 9]. Whereas autopsies of individuals who died from SARS-CoV-2 infection indicate that cardiac infection with the virus is not associated with myocarditis [10].

In conclusion, the study by Semenzato *et al*. is misleading. SARS-CoV-2 infection does not cause serious myocarditis [7, 10], whereas COVID-19 vaccination is well recognized to cause symptomatic and fatal myocarditis [6, 11]. Future prospective cohort studies should classify patients correctly, have extended and equal windows of observation, and clinical adjudication with exam, ECG, blood biomarkers, and cardiac imaging. The use of automated data sources alone should not be relied upon for comparative studies because it is subject to investigator bias and is greatly misleading.



Accumulation ofCOVID-19 vaccine-derived Spike protein and mRNA in the heart resulting in myocarditis. SARS-CoV-2 cardiac infection is not associated with myocarditis. _{*Created with Biorender.com}

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