Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

COVID-19 Vaccine Myocarditis*

Cautious Reassurance in an Era of Dynamic Uncertainty

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"Reports have appeared of changes in the ECG in connection with vaccination against small-pox."
Ahlborg et al[1]

Reports of COVID-19 mRNA vaccine–associated myocarditis ("vaccine myocarditis") first emerged in the spring of 2021. For myocarditis researchers, this was reminiscent of previous vaccines that have historically been associated with myocarditis, including the smallpox vaccine.[2,3] With large-scale vaccination efforts ongoing around the world, there is continually accumulating perspective on this rare adverse event of mRNA COVID-19 vaccination. Reassuringly, this has contributed to an increase in research on the topic of myocarditis in the literature (**Figure 1**).[4] Further information on the outcomes in patients with vaccine myocarditis is critically important to allow for ongoing risk-benefit analyses at both individual and population levels.

STRENGTHS OF FINDING

In this issue of the *Journal of the American College of Cardiology,* Lai et al[5] report retrospective data comparing the 6-month outcomes in 104 cases of COVID-19 mRNA vaccine-associated myocarditis after BNT162b2 (Pfizer-BioNTech) exposure in the Hong Kong Territory national health registry with the outcomes in a historical control group of 762 non-COVID-19 viral myocarditis cases between 2000 and 2019. They report 6-month outcomes measures showing a 92% lower mortality risk in the vaccine myocarditis group compared with the earlier viral myocarditis group. This included 1 death in the vaccine myocarditis group (1%) vs 84 deaths (11%) in the viral myocarditis group. Similarly, there was 1% dilated cardiomyopathy and 1.9% heart failure in the vaccine myocarditis group vs 3.7% and 12.2%, respectively, in the earlier viral myocarditis group. Overall, the results are reassuring for patients hospitalized with vaccine myocarditis due to BNT162b2.[5]

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The strengths of the study included the following: 1) the data were extracted from the entire single national health database of Hong Kong for hospitalized patients, thus minimizing selection or self-referral bias; 2) the analysis adopted a common inclusion criteria, using ICD-9 codes and hospital clinical records submitted by the same health care provider teams; and 3) the complication endpoints were captured by the system at a common time interval of 6 months, with validated criteria.

CHALLENGES IN CASE DEFINITION AND COMPARATOR GROUP

The study does have several limitations, some of which have already been identified by the investigators.[5] The first is the absence of standardized case definition criteria. Vaccine-associated myocarditis is currently defined worldwide by either the Brighton Collaboration or the Centers for Disease Control (CDC) criterion.[6] Both include objective findings of myocarditis and exclusion of alternative causes of symptoms. There are 5 levels of certainty in the Brighton criterion (definitive, probable, possible, insufficient evidence, and not myocarditis) and 3 levels of certainty in the CDC criteria (confirmed, probable, and suspected).[6] Neither criterion was

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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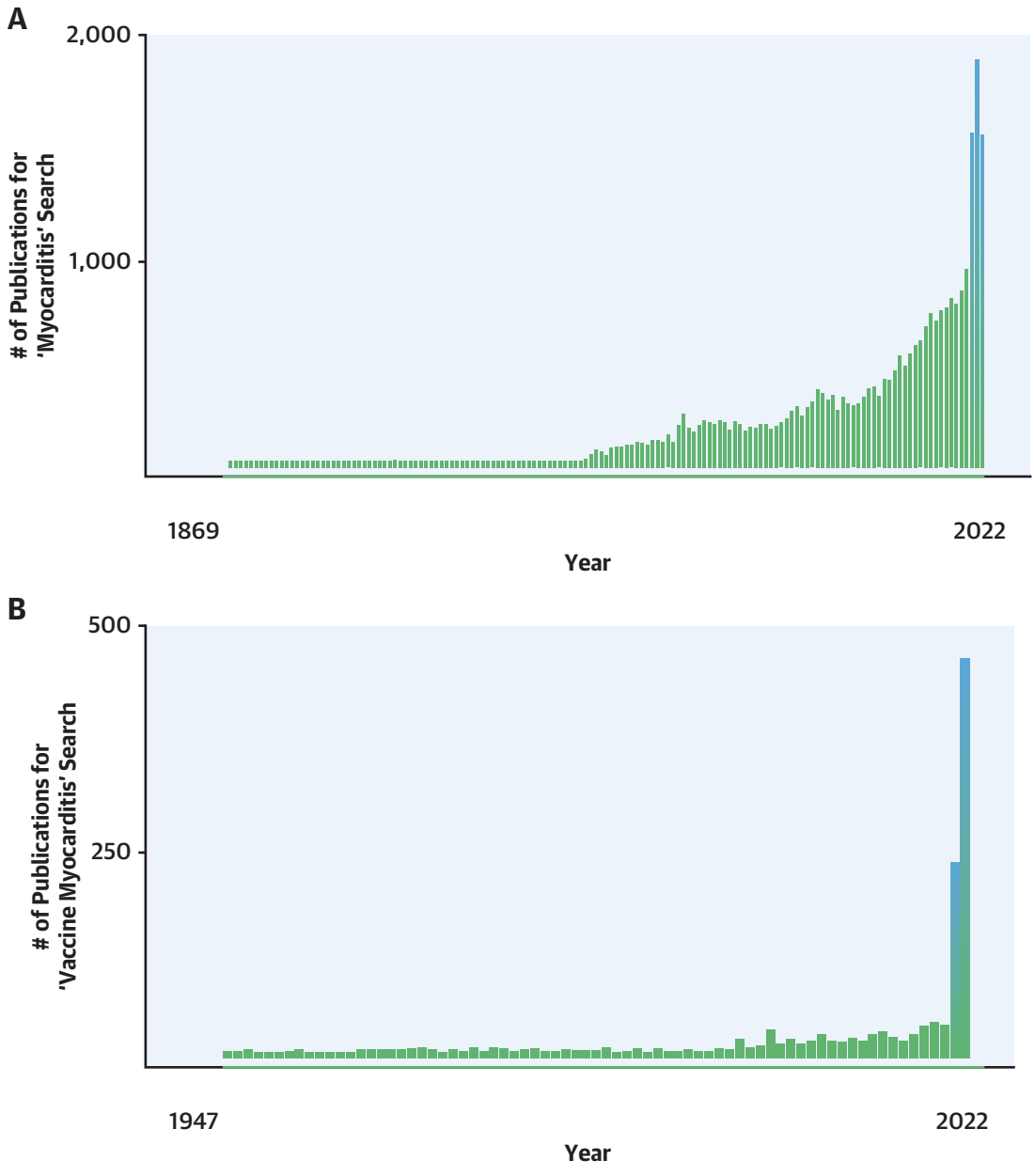
FIGURE 1 Trends in Myocarditis Research



A PubMed search for myocarditis-related publications as of September, 2022. **(A)** Search results for the term "myocarditis." The earliest publication was in 1869. **(B)** Search results for the terms "vaccine myocarditis." The earliest publication was in 1947.

reported in this study.[5] The advantage of the standardized Brighton Collaboration or the CDC criterion is the ability to compare data from cohorts globally. The CDC and Brighton criteria include cardiac magnetic resonance (CMR) imaging for their higher levels of certainty.[6] Both draw from the Lake Louise criteria for myocarditis, which were revised in 2018 to incorporate novel CMR mapping techniques.[7] In the study by Lai et al,[5] the authors report they were not able to confirm the myocarditis diagnoses with

clinical investigative data such as CMR because they were not available in their database. Further, the inability to confirm exclusion of other potential causes of myocarditis can lead to heterogeneity of disease inclusion and subsequent prognosis.

Although this study found significant assurance in terms of the relatively better outcomes of patients hospitalized with vaccine myocarditis compared with that of prepandemic viral myocarditis, the latter is not an ideal comparator group. Viral myocarditis is a very heterogeneous group of conditions that are influenced by local seasonal viral patterns, underlying population comorbidities, and the availability of gold standard diagnostic criteria such as analysis of endomyocardial biopsy specimens to definitively diagnose the cause of myocarditis. A potential better comparator that is also relevant for risk assessment is to use COVID-19-induced myocarditis. The PCORNet has examined records of 15,215,178 patients from 40 health care systems and found that the risk of adverse cardiac events such as myocarditis/pericarditis after COVID-19 infection, compared with that after the second vaccine dose in young males, is still 1.8 to 5.6 times higher after COVID-19 infection than from COVID-19 vaccination.[8]

CHALLENGES IN PATHOPHYSIOLOGY AND BIOLOGICAL MECHANISMS OF VACCINE MYOCARDITIS

The full pathophysiology of vaccine myocarditis is not yet understood. Multiple mechanisms by which COVID-19 mRNA vaccines contribute to myocarditis have been raised, each influenced by sex hormones, age, and genetic HLA factors.[4] First, mRNA itself might induce immune reactivity if it is detected as an antigen. Although this may help explain multisystem inflammatory syndrome, it does not explain isolated myocarditis specifically. Second, SARS-CoV-2 spike protein may have cross reactivity with cardiac contractile proteins and induce autoimmunity. Third, sex hormones such as testosterone may promote certain inflammatory responses, and estrogen may decrease certain responses.[4] Fourth, there is the possibility that the delivery mRNA lipid nanoparticle vector itself may be contributing to the immunogenicity. Further study is needed into all of these hypotheses.

THE FUTURE OF VACCINE MYOCARDITIS

Given the anticipated need for regular COVID-19 booster vaccinations and advancements in mRNA technologies for various other medical indications, vaccine myocarditis will continue to be an ongoing challenge into the foreseeable future. It is exciting to see the global enthusiasm and renaissance in myocarditis research (**Figure 1**). We will need to work collaboratively to capture the longer-term outcomes in these patients, to identify the specific individual risk factors leading to the development of myocarditis, and mitigation strategies for those who are affected. Joining global collaborations will be critical for our collective success. Whereas this present study provides a reassuring initial look at 6-month outcomes data after BNT162b2 vaccination, it is not yet time to roll down our sleeves.

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