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A global push to create vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ultimately culminated in the issuance of Emergency Use Authorizations in the United States for the Pfizer-BioNTech and Moderna coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines in December 2020, followed thereafter by a similar issuance for the single-dose Janssen/Johnson & Johnson vaccine in February 2021. As of July 2021, more than 187 million people received at least 1 dose of a COVID-19 vaccine and 162 million people were fully vaccinated in the United States. Potential side effects associated with the vaccine have been closely monitored by the Vaccine Adverse Event Reporting System. As of June 11, 2021, there were over 1,226 cases of myocarditis reported after an mRNA COVID-19 vaccine. A number of case reports and series have recently been published describing patients who experienced myocarditis after receiving the COVID-19 vaccination. However, it is uncertain if these cases may have been secondary to other etiologies of myocarditis. To help determine whether a correlation exists between COVID-19 vaccination and myocarditis, the present study compared the gender-specific cumulative incidence of myocarditis and myocardial injury in a cohort of COVID-19 vaccinated patients at a tertiary care center in 2021 with the cumulative incidence of these conditions in the same subjects exactly 2 years earlier. We found that the age-adjusted incidence rate of myocarditis in men was higher in the vaccinated than the control population, rate ratio 9.7 (p = 0.04). However, the age-adjusted incidence rate of myocarditis in women was no different between the vaccinated and control populations, rate ratio 1.28 (p = 0.71). We further found that the rate of myocardial injury was higher in both men and women in 2021 than in 2019 both before and after vaccination, suggesting that some of the apparent increase in the diagnosis of myocarditis after vaccination may be attributable to factors unrelated to the COVID-19 vaccinations. In conclusion, our study reaffirms the apparent increase in the diagnosis of myocarditis after COVID-19 vaccination in men but not in women, although this finding may be confounded by increased rates of myocardial injury in 2021. The benefits of COVID-19 vaccination to individual and public health clearly outweigh the small potential increased risk of myocarditis after vaccination.
Cases meeting the European Society of Cardiology’s diagnostic criteria for clinically suspected myocarditis or pericarditis of any possible etiology were classified as myopericarditis cases.11,12 Patients with active COVID-19 infections and a history of myocarditis or pericarditis were excluded. The cases meeting the criteria for myocarditis/myopericarditis cases. The cases are detailed in the Supplementary Appendix 1. No cases of myocarditis were seen in the 3.4% of the sample that was aged 18 to 24.

As depicted in Figures 1 and 2, the age-adjusted incidence rate of myopericarditis in men was higher in the vaccinated group than in the control group (0.1170 per 100,000 person-days in the vaccinated and 0.0121 per 100,000 person-days in the control population, rate ratio 9.7 [p = 0.04]). In women, the age-adjusted incidence rate of myopericarditis was no different between vaccinated patients and controls (0.0420 per 100,000 person-days in the vaccinated and 0.0329 per 100,000 person-days in the control population, rate ratio 1.28 [p = 0.71]). Survival analyses showed a suggestion of a difference in the cumulative incidence of myopericarditis between vaccinated patients and controls in men (p = 0.08) but not in women (p = 0.66).

Possible changes in patient willingness to seek medical evaluation and in the delivery of health care during the COVID-19 pandemic may have led to a differential diagnosis of myopericarditis in 2021 versus 2019. Thus, we examined the cumulative incidence in each year of acute myocardial injury (Figure 3, Table 2). There were no significant differences in the age-adjusted cumulative incidence of inpatient admissions. As listed in Table 2, the age-adjusted cumulative incidence of these diagnoses and inpatient admissions were not different between the 2 cohorts of either gender.

Myocarditis may be difficult to distinguish from MI and other forms of myocardial injury. To address this, we also examined the incidence of ICD-10 diagnostic coding for MI and of elevations of troponin-T as a marker of myocardial injury (Figure 3, Table 2). There were no significant differences in the age-adjusted cumulative incidence of coded MIs in men or women. There were, however, increases in the age-adjusted cumulative incidence of troponin elevation in both men and women in 2021 compared with 2019. We considered possible explanations for this relatively increased rate of myocardial injury in 2021, including the COVID-19 vaccinations and/or active COVID-19 infections. As listed in Table 3, there were few active COVID-19 infections diagnosed in the vaccinated cohort. Additionally, in the vaccinated cohort, the rates of myocardial injury immediately before vaccination per 100,000 were comparable with those seen after vaccination.

### Table 1
Baseline characteristics

| Variable                  | Vaccinated cohort (2020-2021) | Control cohort (2018-2019) |
|---------------------------|------------------------------|-----------------------------|
| Total patients            | 268,320                      | 235,343                     |
| Male                      | 107,750 (40%)                | 94,546 (40%)                |
| White                     | 156,906 (58%)                | 142,635 (61%)               |
| Asian                     | 31,154 (12%)                 | 27,924 (12%)                |
| Black                     | 17,351 (6%)                  | 16,060 (7%)                 |
| Hispanic                  | 10,863 (4%)                  | 9,555 (4%)                  |
| Other                     | 13,404 (5%)                  | 11,263 (5%)                 |
| Unknown                   | 38,642 (14%)                 | 27,906 (12%)                |
| Age (years)               |                              |                             |
| 18-24                     | 8,742 (3%)                   | 8,601 (4%)                  |
| 25-34                     | 75,863 (28%)                 | 64,508 (27%)                |
| 45-64                     | 99,670 (37%)                 | 94,882 (40%)                |
| ≥65                       | 84,045 (31%)                 | 67,352 (29%)                |
| Vaccine type              |                              |                             |
| Pfizer-BioNTech           | 145,698 (54%)                | –                           |
| Moderna                   | 111,006 (41%)                | –                           |
| Janssen/Johnson & Johnson | 11,499 (4.3%)                | –                           |
| Average follow-up (days)  |                              |                             |
| Mean ± sd                 | 73.5 ± 33.8                  | 74.2 ± 33.4                 |
| Median [IQR]              | 71 [46-99]                   | 72 [47-100]                 |
| Maximum                   | 292                          | 290                         |
| Prior episode of care     |                              |                             |
| at BIDMC                  | 250,418 (93%)                | 205,530 (87%)               |

SD = standard deviation; IQR = interquartile range; BIDMC = Beth Israel Deaconess Medical Center.
Figure 1. Incidence rate of myopericarditis with 95% confidence intervals, stratified by gender, age at time of 1st COVID-19 vaccination, and type of vaccine. Panel A represents men, panel B represents women. CI = confidence interval; J&J = Johnson & Johnson.
Discussion

This study found a statistically significant increase in the age-adjusted incidence of myopericarditis in vaccinated men. Viruses are considered the leading etiology of myopericarditis. However, research has demonstrated that there were fewer cases of non–COVID-19 viral illnesses in 2021 compared with previous years (e.g., due to masking, physical distancing, and improved hand
This study excluded patients with active COVID-19 illness at the time of diagnosis of myopericarditis and only 1 man had a known COVID-19 diagnosis before developing myopericarditis. Taken together, this suggests that viral illnesses did not drive the increased incidence of myopericarditis in vaccinated men. Because it is not designed to detect causality, this study suggests a possible association between COVID-19 vaccination and the development of myopericarditis.

There was no difference in the age-adjusted incidence of myopericarditis in vaccinated women. Previous research has demonstrated that there are slightly higher rates of myopericarditis of any cause in men than in women. One proposed potential mechanism for this difference in incidence is that the higher levels of estradiol in women may confer a cardioprotective effect. If COVID-19 vaccination is a causative factor in the development of myopericarditis in some people, the same mechanisms may be making men more susceptible than women after COVID-19 vaccination. Indeed, we saw the highest rates of myopericarditis after COVID-19 vaccination in men ages 25 to 44, which is consistent with recent cases series on adult patients who developed myocarditis after COVID-19 vaccination. As demonstrated in Supplementary Appendix 1, 7 of 10 cases of myopericarditis in mRNA vaccinated subjects occurred after the second dose. Interestingly, 2 of 3 patients who developed myocarditis after the first dose of mRNA vaccination had mild COVID-19 infections about 1 month previous. In these patients, it is possible that the recent infection primed the patients’ immune systems for a hyperactive response to the vaccination. Alternatively, their presentations may simply have been a result of smoldering COVID-19 myocarditis.

The higher rates of myocardial injury seen in 2021 compared with 2019 may confound interpretation of population-based data regarding myopericarditis associated with COVID-19 vaccination. There is no obvious explanation for this phenomenon, but it suggests that there may be factors at play driving myocardial injury in 2021 that were not present in 2019. One possibility is an increased propensity to seek medical care in the COVID-19 era. If this were the case, we might also expect to see increased rates of acute appendicitis, acute pancreatitis, and overall inpatient admissions, which we did not. Another possibility is an increase in MIs; however, the rates of billed MIs by ICD-10 codes were not different between the 2 cohorts. We also considered heightened scrutiny for potential cardiovascular adverse reactions after COVID-19 vaccination. However, the cumulative incidence of troponin-T elevation during the median 74 days immediately preceding COVID-19 vaccination was similar to that observed in the median 74 days immediately after vaccination, arguing against an ascertainment bias and suggesting temporal factors independent of COVID-19 vaccination itself. Smoldering after COVID-19 myocarditis might explain some cases of troponin elevation. However, the absolute difference seen in patients with myocardial injury in 2021 versus 2019 was much larger than the prevalence of documented SARS-CoV-2 antigen or nucleic acid test positivity at a time when all patients evaluated in the emergency department or as inpatients underwent routine COVID-19 nucleic acid testing. Alternatively, increased emotional stress and more unhealthy lifestyles during the pandemic may have resulted in heightened inflammatory states and worsening cardiovascular health.

This study has several important limitations. This is not a randomized controlled trial. Whereas it would be ideal to have a randomized sample of comparable vaccinated and unvaccinated subjects, patients who choose to undergo COVID-19 vaccination may have different baseline characteristics from those who choose not to undergo vaccination. Using subjects as their own control minimizes selection biases but precludes separating the exposure of interest (COVID-19 vaccination) from other temporal factors and means that the vaccinated cohort was 2 years older, which we attempted to control for using age adjustment. We likely missed some myopericarditis patients for the following reasons. The Massachusetts Immunization Information System database lags variably in time to database update after vaccination and use of it limits this study to patients vaccinated in the state of Massachusetts. Additionally, ICD-10 diagnostic codes are relatively subjective and not applied uniformly in clinicians. Finally, whereas 93% of the vaccinated group received care at BIDMC previously, some may have sought care for their myopericarditis elsewhere.

Our study reaffirms the apparent increase in the diagnosis of myopericarditis in men (particularly aged 25 to 44 years) after COVID-19 vaccination. The absolute incidence rate of myopericarditis in both men and women is less than the morbidity seen in patients who developed inflammation in the setting of COVID-19 infection and less than the risk of breakthrough infection after COVID-19.
Furthermore, the fact that troponin-T elevations occurred at comparable rates immediately after COVID-19 vaccination as immediately preceding vaccination suggest that some of the apparent increase in the diagnosis of myopericarditis after vaccination may be attributable to other changes in cardiovascular health in the United States population unrelated to the vaccine itself. The benefits of COVID-19 vaccination to individual and public
Table 3
Myocardial injury by year and vaccine status

| Variable                                | 2018-2019 2020-2021 | 2020-2021 2020-2021 | 2018-2019 vs. 2020-2021 | 2018-2019 vs. 2020-2021 | 2020-2021 vs. 2020-2021 |
|-----------------------------------------|---------------------|---------------------|-------------------------|-------------------------|-------------------------|
| Subjects at risk                        | 235,343             | 268,320             | 268,320                 |                         |                         |
| Troponin-T specimens obtained           | 2,721               | 4,037               | 4,162                   | p<0.0001                | p<0.0001                |
| Number of specimens per capita          | 1.2%                | 1.5%                | 1.6%                    | p<0.0001                | p=0.44                  |
| Unique patients sampled for troponin-T  | 1,441               | 2,025               | 2,164                   |                         |                         |
| Percent of subjects at risk sampled     | 0.6%                | 0.8%                | 0.8%                    | p<0.0001                | p<0.0001                |
| Specimens with troponin-T ≥0.02 ng/mL   | 782                 | 1,512               | 1,508                   |                         |                         |
| Percent of specimens that were elevated | 28.7%               | 37.4%               | 36.2%                   | p<0.0001                | p<0.0001                |
| Specimens with troponin-T ≥0.10 ng/mL   | 377                 | 744                 | 741                     |                         |                         |
| Percent of specimens that were elevated | 13.9%               | 18.4%               | 17.8%                   | p<0.0001                | p<0.0001                |

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