

# Sex-specific differences in myocardial injury incidence after COVID-19 mRNA-1273 booster vaccination

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## Aims

To explore the incidence and potential mechanisms of oligosymptomatic myocardial injury following COVID-19 mRNA booster vaccination.

## Methods and results

Hospital employees scheduled to undergo mRNA-1273 booster vaccination were assessed for mRNA-1273 vaccination-associated myocardial injury, defined as acute dynamic increase in high-sensitivity cardiac troponin T (hs-cTnT) concentration above the sex-specific upper limit of normal on day 3 (48–96 h) after vaccination without evidence of an alternative cause. To explore possible mechanisms, antibodies against interleukin-1 receptor antagonist (IL-1RA), the SARS-CoV-2-nucleoprotein (NP) and -spike (S1) proteins and an array of 14 inflammatory cytokines were quantified. Among 777 participants (median age 37 years, 69.5% women), 40 participants (5.1%; 95% confidence interval [CI] 3.7–7.0%) had elevated hs-cTnT concentration on day 3 and mRNA-1273 vaccine-associated myocardial injury was adjudicated in 22 participants (2.8% [95% CI 1.7–4.3%]). Twenty cases occurred in women (3.7% [95% CI 2.3–5.7%]), two in men (0.8% [95% CI 0.1–3.0%]). Hs-cTnT elevations were mild and only temporary. No patient had electrocardiographic changes, and none developed major adverse cardiac events within 30 days (0% [95% CI 0–0.4%]). In the overall booster cohort, hs-cTnT concentrations (day 3; median 5, interquartile range [IQR] 4–6 ng/L) were significantly higher compared to matched controls ( $n = 777$ , median 3 [IQR 3–5] ng/L,  $p < 0.001$ ). Cases had comparable systemic reactivity, concentrations of anti-IL-1RA, anti-NP, anti-S1, and markers quantifying systemic inflammation, but lower concentrations of interferon (IFN)- $\lambda 1$  (IL-29) and granulocyte-macrophage colony-stimulating factor (GM-CSF) versus persons without vaccine-associated myocardial injury.

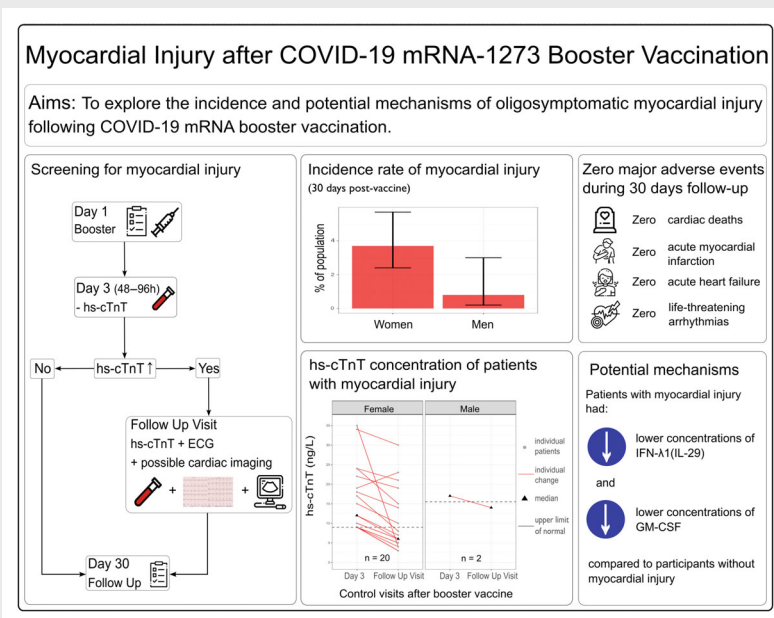
## Conclusion

mRNA-1273 vaccine-associated myocardial injury was more common than previously thought, being mild and transient, and more frequent in women versus men. The possible protective role of IFN- $\lambda 1$  (IL-29) and GM-CSF warrant further studies.

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## Graphical Abstract



Among 777 participants who received a COVID-19 mRNA-1273 booster vaccination, 40 (5.1%; 95% confidence interval [CI] 3.7–7.0%) had an elevated high-sensitivity cardiac troponin T (hs-cTnT) concentration on day 3, of whom 22 (2.8% [95% CI 1.7–4.3%]) were adjudicated as mRNA-1273 vaccine-associated myocardial injury. Females ( $n = 20$ , 3.7% [95% CI 2.3–5.7%]) had a higher incidence than males ( $n = 2$ , 0.8% [95% CI 0.1–3.0%]). Hs-cTnT elevations were mild and decreased from day 3 to the follow-up visit in all but one case. No participants developed major adverse cardiac events within 30 days. Participants with mRNA-1273 vaccine-associated myocardial injury had comparable systemic reactivity, but lower concentrations of interferon (IFN)- $\lambda$ 1 (IL-29) and granulocyte-macrophage colony-stimulating factor (GM-CSF) versus participants without vaccine-associated myocardial injury.

## Keywords

COVID-19 • mRNA vaccine • Myocardial injury • Myocarditis • COVID-19 booster vaccination • Cardiac troponin

## Introduction

Myocardial injury, manifesting clinically as myocarditis, has recently emerged as a possible severe adverse event following the administration of COVID-19 mRNA vaccines occurring mainly in young men a few days after vaccination. Using passive surveillance following vaccination with BNT162b2-mRNA (Pfizer-BioNTech) or mRNA-1273 (Moderna), COVID-19 mRNA vaccination-associated myocarditis is currently considered rare.<sup>1</sup> However, passive surveillance detects mostly severe cases requiring hospitalization.<sup>2,3</sup>

We hypothesized that COVID-19 mRNA-vaccine-associated myocardial injury following booster vaccination may be much more common, as symptoms may be unspecific, mild or even absent, escaping passive surveillance. Due to waning immunity months after mRNA COVID-19 vaccinations there is an apparent need for (repeated) booster vaccinations for billions of people worldwide.<sup>4,5</sup> Thus knowing the true incidence of mRNA-vaccine-associated myocardial injury is of major importance for informed decision-making by patients, physicians and public health authorities.

We therefore conducted a prospective active surveillance study to address this major unmet need. Secondary aims were to provide a ‘safety net’ for persons identified with COVID-19 mRNA-vaccine-associated myocardial injury to allow early detection and preventive measures to avoid possible aggravation, and to evaluate potential mechanisms underlying COVID-19 mRNA-vaccine-associated myocardial injury.

## Methods

## Study design and study population

This prospective investigator-initiated industry-independent active surveillance study was approved by the local ethics committee. Employees of the University Hospital Basel, Switzerland, scheduled to receive mRNA-1273 first booster vaccination, and who provided written informed consent, were offered active surveillance. Exclusion criteria were cardiac events or cardiac surgery within 30 days prior to vaccination or patients missing the study visit, therefore missing high-sensitivity cardiac troponin T (hs-cTnT) measurement on day 3.

## Active surveillance and laboratory methods

Medical history was assessed on the day of the booster vaccination (day 1). On day 3 (48–96 h) after vaccination, participants were assessed for possible myocarditis-related symptoms and a venous blood sample for the measurement of hs-cTnT (Elecsys, sex-specific 99th-percentile of healthy individuals and upper limit of normal [ULN] 8.9 ng/L in women and 15.5 ng/L in men, limit of detection 3 ng/L) was obtained.<sup>6,7</sup> If the hs-cTnT concentration was elevated on day 3, participants were informed, asked to avoid strenuous exercise in order to minimize additional strain of the myocardium and associated cardiomyocyte injury, and offered follow-up including clinical evaluation, a second hs-cTnT measurement, and a 12-lead electrocardiogram (ECG). The follow-up visit was scheduled, if feasible, the next working day. After extensive discussion with the local ethics committee and the COVID-19 task force of the University Hospital Basel, it was prioritized that this study should interfere as little as possible with the motivation of the hospital staff to obtain the mRNA-1273 first booster vaccination and the logistics of booster vaccination itself. Accordingly, blood draws were performed only after the vaccination.

## Potential mechanisms underlying vaccine-associated myocardial injury

We evaluated three potential mechanisms of COVID-19 mRNA-vaccination-associated myocardial injury: anti-interleukin-1 receptor antagonist (IL-1RA) autoantibodies,<sup>8</sup> pre-existing vaccine/infection-induced immunity against SARS-CoV-2 (i.e. anti-SARS-CoV-2-nucleoprotein [NP] and -spike [S1]-IgG), and systemic reactivity/inflammation. Anti-IL-1RA-, -NP-, and S1-IgG were quantified using the Luminex platform (Luminex Corporation, Austin, TX, USA)<sup>9</sup> (online supplementary methods). Systemic inflammation was assessed by measuring 14 biomarkers using the LEGENDplex™ Human Anti-Virus Response Panel (interleukin [IL]-1 $\beta$ , IL-6, IL-8, IL-10, IL-12p70, interferon [IFN]- $\alpha$ , IFN- $\beta$ , IFN- $\lambda$ 1[IL-29], IFN- $\lambda$ 2/3[IL-28], IFN- $\gamma$ , tumour necrosis factor [TNF]- $\alpha$ , interferon gamma-induced protein (IP)-10, granulocyte-macrophage colony-stimulating factor [GM-CSF]), the IL-1RA assay (both Biologend, San Diego, CA, USA), and C-reactive protein (CRP; Elecsys; ULN 5.0 mg/L).

## Adjudication of COVID-19 mRNA-vaccine-associated myocardial injury

Given the general superior sensitivity of hs-cTnT elevations versus the ECG or cardiac imaging for acute myocardial injury,<sup>10,11</sup> COVID-19 mRNA-vaccine-associated myocardial injury was defined as acute dynamic hs-cTnT elevation above the sex-specific 99th percentile ULN (8.9 ng/L in women and 15.5 ng/L in men) on day 3, without evidence of an alternative cause, irrespective of symptoms, ECG, or cardiac imaging abnormalities. In the absence of a baseline hs-cTnT concentration immediately prior to the vaccination, strict criteria were applied in the adjudication of COVID-19 mRNA-vaccine-associated myocardial injury. For the differentiation of acute COVID-19 mRNA-vaccine-associated myocardial injury versus possible chronic preexisting myocardial injury, four criteria were used: first, the extent of the hs-cTnT elevation (the higher the elevation, the

more likely acute); second, the extent in the change of hs-cTnT from day 3 to day 4 (the larger the change the more likely acute); third, previous hs-cTnT measurements if available in the medical history of the participants; and fourth, the likelihood for hs-cTnT elevation according to known causes of chronic myocardial injury, including age and preexisting cardiovascular diseases. To emphasize how physicians could miss COVID-19 mRNA-vaccine-associated myocardial injury in women, a sensitivity analysis, using a uniform ULN cut-off (14 ng/L) was used for adjudication. To further verify that COVID-19 mRNA booster vaccination may increase hs-cTnT concentration, hs-cTnT concentration on day 3 in the overall cohort receiving COVID-19 mRNA booster vaccination was compared to matched controls.

## Follow-up

Major adverse cardiac events (MACE) including acute heart failure, cardiac death, life-threatening arrhythmia and acute myocardial infarction (AMI) were assessed at 30-day follow-up.

## Matching

To assess cardiomyocyte injury also as a continuous variable, hs-cTnT concentrations on day 3 after vaccination were compared to age-, sex-, history of coronary artery disease/AMI-matched patients (controls) that had presented with acute chest discomfort to the emergency department in a multicentre study (NCT00470587) and were centrally adjudicated as having a non-cardiac cause. A total of 777 booster-vaccinated subjects and 3716 eligible controls (fulfilling inclusion criteria) were identified. Matching was conducted using a nearest neighbour propensity score matching method, without replacement of controls and with a case-to-control ratio of 1:1.<sup>12</sup> For details see online supplementary methods.

## Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), categorical variables as counts and percentages. Differences in characteristics between subjects with and without SARS-CoV-2 mRNA-vaccine-associated myocardial injury were assessed using the Mann-Whitney U test for continuous variables, and the Pearson  $\chi^2$  test or Fisher exact test for categorical variables, when appropriate. All hypothesis testing was 2-tailed with a significance level of  $p < 0.05$ . Statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Reporting is in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (online supplementary Table S7). We did not adjust for multiple testing for the evaluation of different potential mechanisms underlying COVID-19 mRNA-vaccine-associated myocardial injury due to the exploratory nature of the analysis.

## Results

From 10 December 2021 to 10 February 2022, 1871 employees of the University Hospital Basel were screened (1294 females [69.2%] and 577 males [30.8%]), of which 835 provided written informed consent to participate in the study, and of these, 777 (93%, 540 females [69.5%] and 237 males [30.5%]) were eligible for analysis (Table 1, Figures 1 and 2A). The median age was 37 years

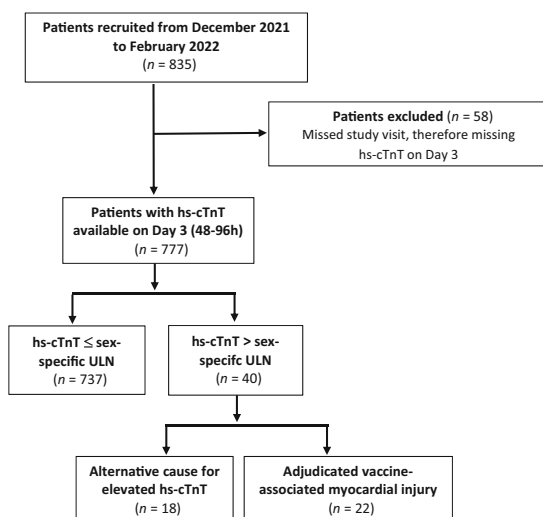
**Table 1** Baseline characteristics and vaccine-associated symptoms stratified by adjudicated vaccine-associated myocardial injury

Variable	Overall	No vaccine-associated myocardial injury	Vaccine-associated myocardial injury	p-value
<i>n</i>	777	755	22	
Age, years, median [IQR]	37 [30–50]	37 [29–50]	46 [33–54]	0.12
Sex, <i>n</i> (%)				
Male	237 (30.5)	235 (31.1)	2 (9.1)	0.03
Female	540 (69.5)	520 (68.9)	20 (90.9)	
History of COVID-19 infection, <i>n</i> (%)	82 (10.6)	80 (10.6)	2 (9.5)	1
No. of previous COVID-19 vaccinations, <i>n</i> (%)				
One vaccination <sup>a</sup>	1 (0.1)	1 (0.1)	0 (0.0)	0.20
One vaccination after COVID-19	37 (4.8)	37 (4.9)	0 (0.0)	
Two vaccinations	714 (92.0)	694 (92.0)	20 (90.9)	
Two vaccinations after COVID-19	24 (3.1)	22 (2.9)	2 (9.1)	
Days since last vaccination, median [IQR]	206.0 [188.0–230.0]	205.0 [188.0–229.0]	222.0 [187.2–253.2]	0.14
History of CAD, <i>n</i> (%)	3 (0.4)	3 (0.4)	0 (0.0)	1
History of AMI, <i>n</i> (%)	1 (0.1)	1 (0.1)	0 (0.0)	1
History of heart surgery <sup>b</sup> , <i>n</i> (%)	3 (0.4)	3 (0.4)	0 (0.0)	1
History of myocarditis, <i>n</i> (%)	3 (0.4)	3 (0.4)	0 (0.0)	1
History of heart failure, <i>n</i> (%)	2 (0.3)	2 (0.3)	0 (0.0)	1
Symptoms following vaccination, <i>n</i> (%)				
Chest pain	63 (8.1)	61 (8.1)	2 (9.1)	0.70
Palpitations	70 (9.0)	69 (9.1)	1 (4.5)	0.71
Dyspnoea	23 (3.0)	23 (3.0)	0 (0.0)	1
Fever and/or chills	270 (34.7)	263 (34.8)	7 (31.8)	0.95
Body aches	356 (45.8)	347 (46.0)	9 (40.9)	0.80
Biomarkers				
hs-cTnT (day 3), ng/L, median [IQR]	5 [4–6]	5 [4–6]	13.5 [9–18.8]	<0.001

AMI, acute myocardial infarction; CAD, coronary artery disease; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range.

<sup>a</sup>The patient with only one previous vaccination had received Johnson & Johnson's Janssen COVID-19 vaccine which is a full primary immunization. According to Swiss authorities, past COVID-19 infection and one vaccination were regarded equivalent to having had two vaccinations (without previous COVID-19 infection) for primary immunization in Switzerland.

<sup>b</sup>History of heart surgery: one bypass surgery, one atrial septal aneurysm and one atrial septal defect.

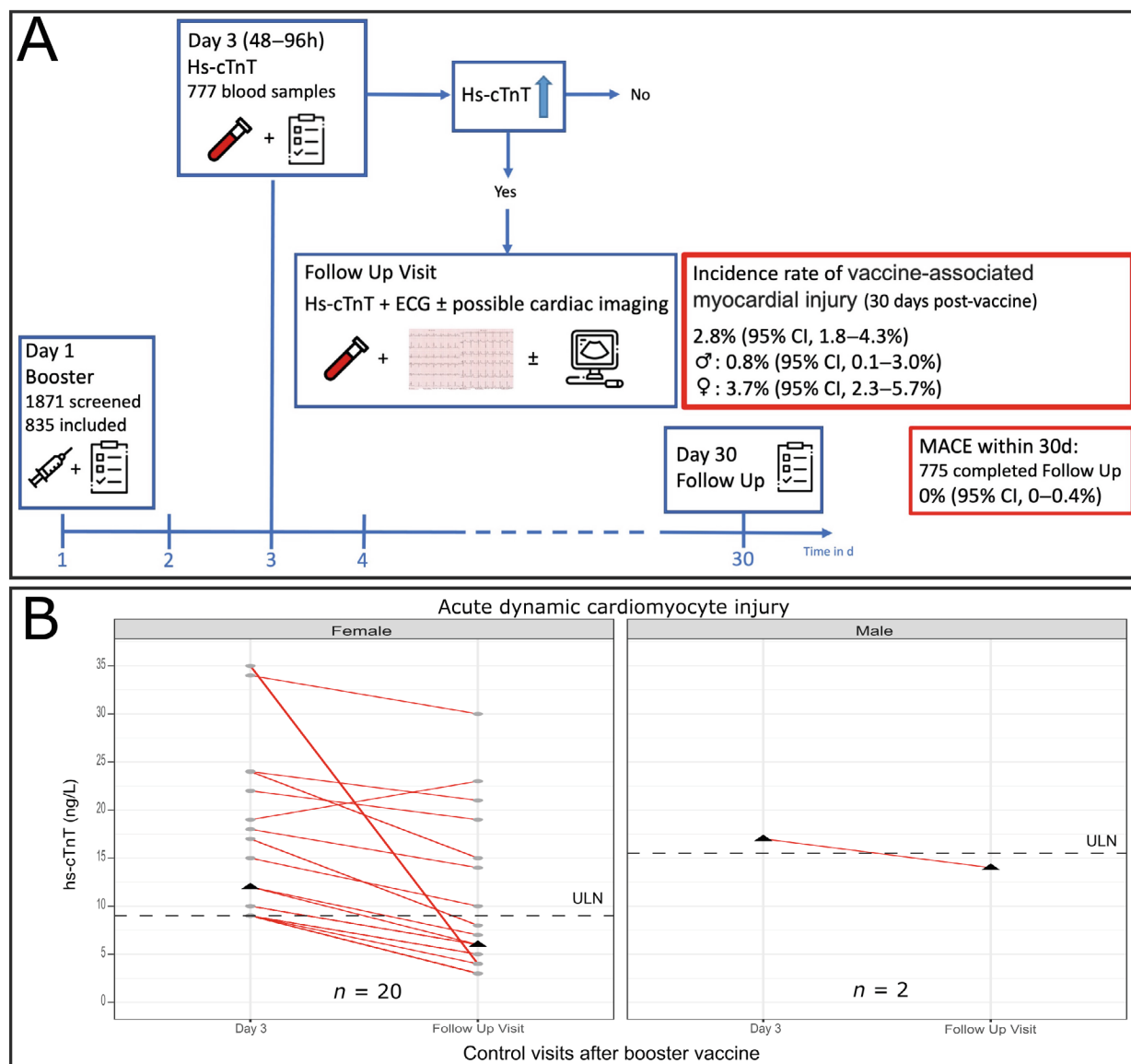


**Figure 1** Patient flowchart. Hs-cTnT, high-sensitivity cardiac troponin T; ULN, upper limit of normal.

(IQR 30–50), and 69.5% were women. Age-, sex-, and history of coronary artery disease/AMI-matched controls had comparable baseline characteristics (online supplementary Table S2 and Figures S1–S3). A flowchart of the active surveillance programme is depicted in Figure 2A and the Graphical Abstract.

## COVID-19 mRNA-1273 vaccine-associated myocardial injury

High-sensitivity cTnT concentrations (online supplementary Figure S4) above the sex-specific ULN were detected in 40 participants (5.1% [95% confidence interval, CI 3.7–7.0%]). In 18 of them (17 women, median age 59 years [IQR 57–60], median hs-cTnT concentration 10 ng/L [IQR 9–11]; online supplementary Table S3), an alternative cause was considered most likely (online supplementary Table S4). mRNA-1273 vaccine-associated myocardial injury was adjudicated in 22 patients (2.8% [95% CI 1.8–4.3%]), with 20 cases occurring in women (3.7% [95% CI 2.3–5.7%]) and 2 in men (0.8% [95% CI 0.1–3.0%]), with a median age of 46 years (IQR 33–54). This sex difference was statistically significant ( $p = 0.03$ ). On day 3, median hs-cTnT concentration of the 20 women and



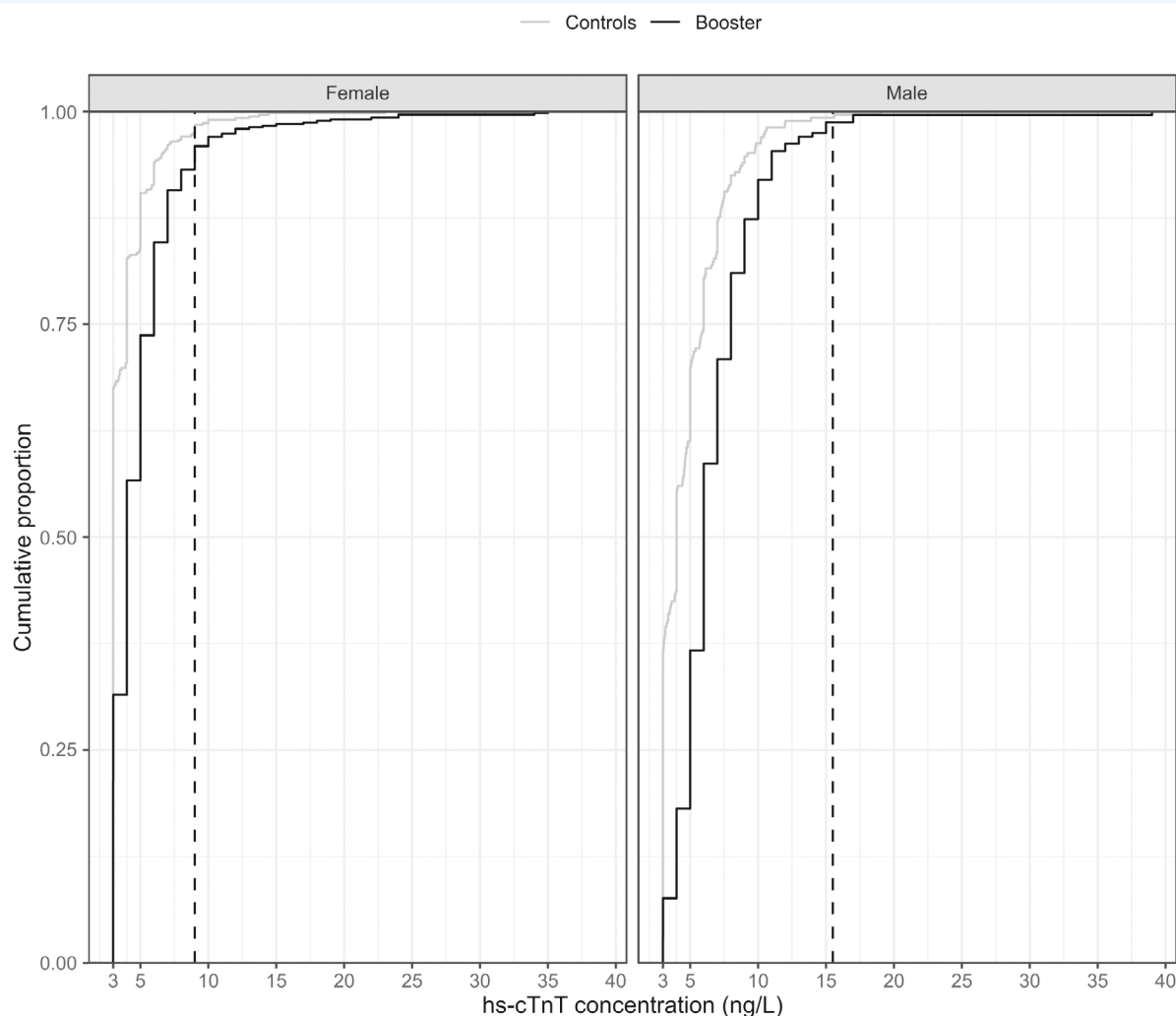
**Figure 2** (A) Flowchart of the active surveillance programme and incidence of mRNA-1273 vaccination-associated myocardial injury. (B) High-sensitivity cardiac troponin T (hs-cTnT) concentrations in patients with mRNA-1273 vaccination-associated myocardial injury. The triangles represent the median, points represent the individual patients, the dashed lines labelled ULN represent the sex-specific upper limit of normal. Both men with vaccination-associated myocardial injury had identical concentrations on day 3 (17 ng/L), therefore only one point is shown. One male patient did not have a follow-up visit, hence only one line is shown. CI, confidence interval; MACE, major adverse cardiac event.

2 men with mRNA-1273 vaccine-associated myocardial injury was 13.5 ng/L (IQR 9.0–18.8) (Figure 2B). It decreased in all but one patient on the follow-up visit to a median value of 6.0 ng/L (IQR 4.0–14.0), being again in the normal range in half of the participants.

In the overall cohort receiving the mRNA-1273 booster, hs-cTnT concentrations (day 3) were significantly higher compared to matched controls (median 5 [IQR 4–6] ng/L vs. 3 [IQR 3–5] ng/L,  $p < 0.001$ ). Figure 3 illustrates this difference, indicating an overall shift towards higher hs-cTnT concentrations in the booster

cohort versus matched controls, for both female (median 4 [3–6] ng/L vs. 2.99 [2.99–4] ng/L) and male (median 6 [5–8] ng/L vs. 4 [2.99–6] ng/L) participants.

None of the participants with elevated markers of myocardial injury related to mRNA vaccination had a history of cardiac disease (online supplementary Table S5). Eleven participants (50%) had unspecific symptoms including fever and chills, two had chest pain, and none had ST-segment depression or T-wave inversion (online supplementary Table S5). Pre-defined and prospectively recorded symptoms occurred with comparable frequency



**Figure 3** Cumulative distribution curve of cardiomyocyte injury as quantified by high-sensitivity cardiac troponin T (hs-cTnT) concentrations stratified by sex. The dashed lines indicate the sex-specific upper reference limits.

in participants developing mRNA-1273 vaccine-associated myocardial injury versus those that did not.

No definitive case of myocarditis was found. However, the two participants (both women) with vaccine-associated myocardial injury and chest pain met the Brighton Collaboration case definition Level 2, indicating probable myocarditis in those patients (0.3% [95% CI 0.1–0.9%]).<sup>13</sup>

### Sensitivity analysis

When using a uniform ULN of 14 ng/L, mRNA-1273 vaccine-associated myocardial injury was adjudicated in 14 patients (1.8% [95% CI 1.0–3.0%]), with 9 cases occurring in women (1.7% [95% CI 0.8–3.2%]) and 5 in men (2.1% [95% CI 0.7–4.9%]), with a median age of 53 years (IQR 38–56). On day 3, median hs-cTnT concentration of the 9 women and 5 men with mRNA-1273 vaccine-associated myocardial injury was 17.5 ng/L (IQR 15.5–20.5). It decreased in all but one patient on

the follow-up visit to a median value of 14.0 ng/L (IQR 10.0–19.0), being again below the uniform ULN in half of the participants (online supplementary Figure S5).

### Major adverse cardiac events

Thirty-day follow-up was completed in 775 participants (99.7%) and no participant developed MACE (0% [95% CI 0–0.4%]).

### Possible mechanisms of mRNA-1273 vaccine-associated myocardial injury

Antibodies against IL-1RA were detected with comparable and low frequency in participants with mRNA-1273 vaccine-associated myocardial injury versus those without (1 in 22 [4.5%] vs. 23/742 [3.1%]; Fisher exact test  $p=0.51$ ). The plasma levels of IL-1RA were also comparable between the two groups. There was no difference in the magnitude of the anti-S1-IgG and

**Table 2** Inflammatory biomarkers stratified by adjudicated vaccine-associated myocardial injury

Variable	Overall	No vaccine-associated myocardial injury	Vaccine-associated myocardial injury	p-value
<i>n</i>	764	742	22	
<b>Antibodies</b>				
Anti-NP (MFI)	138.2 [65.0–322.6]	139.0 [66.0–325.0]	103.5 [33.6–192.8]	0.052
Anti-S1 (MFI)	1641.0 [870.8–3254.0]	1641.0 [877.8–3281.0]	1686.5 [757.5–2614.8]	0.76
Anti-IL-1RA (MFI)	30.8 [23.0–48.1]	31.0 [23.0–48.0]	25.5 [19.5–46.9]	0.31
<b>Systemic inflammation</b>				
IL-1RA (pg/ml)	621.3 [438.0–832.0]	621.3 [440.5–829.1]	605.3 [426.5–895.2]	0.968
IL-1 $\beta$ (pg/ml)	6.8 [3.4–13.2]	6.8 [3.4–13.2]	7.0 [3.6–9.4]	0.57
IL-6 (pg/ml)	1.7 [0.5–3.4]	1.7 [0.5–3.4]	1.5 [0.5–2.7]	0.62
IL-8 (pg/ml)	4.2 [3.1–5.9]	4.3 [3.1–6.0]	3.9 [3.3–5.7]	0.65
IL-10 (pg/ml)	9.8 [3.9–25.8]	9.8 [3.9–25.6]	10.4 [3.2–31.5]	0.91
IL-12p70 (pg/ml)	10.0 [4.8–18.1]	10.1 [4.9–18.2]	8.0 [2.7–14.3]	0.289
CRP (mg/L)	5.5 [2.8–10.2]	5.4 [2.8–10.1]	6.9 [4.3–10.1]	0.28
TNF- $\alpha$ (pg/ml)	5.6 [1.7–17.6]	5.7 [1.7–17.7]	4.1 [1.7–11.9]	0.43
IFN- $\beta$ (pg/ml)	3.9 [0.8–8.9]	3.9 [0.8–9.1]	3.0 [0.8–6.4]	0.13
IFN- $\gamma$ (pg/ml)	16.9 [6.4–37.5]	16.9 [6.6–38.0]	15.5 [4.0–30.4]	0.42
IFN- $\alpha$ 2 (pg/ml)	2.5 [0.7–5.4]	2.5 [0.7–5.4]	2.0 [1.3–3.8]	0.70
IFN- $\lambda$ 1 (pg/ml)	11.4 [3.8–21.8]	11.8 [3.9–22.3]	5.3 [2.9–10.8]	0.015
IFN- $\lambda$ 2-3 (pg/ml)	7.8 [4.1–12.9]	7.9 [4.2–12.9]	5.5 [3.1–8.6]	0.052
GM-CSF (pg/ml)	2.0 [0.6–4.4]	2.0 [0.6–4.5]	0.6 [0.6–2.9]	0.039
IP-10 (pg/ml)	49.8 [25.8–120.2]	49.8 [25.4–120.8]	49.5 [31.2–78.9]	0.984

In 13 patients (without vaccine-associated myocardial injury) the volume provided to the immunology laboratory was insufficient to measure the inflammatory biomarkers. CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IP, interferon gamma-induced protein; MFI, median fluorescence intensity; NP, nucleoprotein; S1, spike; TNF, tumour necrosis factor.

the frequency of subjects positive for anti-NP-IgG (i.e. serological evidence for prior infection with SARS-CoV-2) in participants with mRNA-1273 vaccine-associated myocardial injury versus those without (Table 2). Also, most tested markers of systemic inflammation had comparable concentrations in participants with mRNA-1273 vaccine-associated myocardial injury versus those without. In contrast, levels of IFN- $\lambda$ 1 and GM-CSF were lower in cases with mRNA-1273 vaccine-associated myocardial injury versus those without (online supplementary Figures S6 and S7).

## Discussion

This prospective investigator-initiated, industry-independent study was performed to test the hypothesis that mRNA-1273 booster vaccination-associated myocardial injury may be more common than currently thought as symptoms may be unspecific, mild or even absent, escaping passive surveillance detecting only hospitalized cases. We report four main findings.

First, our findings confirmed the study hypothesis. mRNA-1273 booster vaccination-associated elevation of markers of myocardial injury occurred in about one out of 35 persons (2.8%), a greater incidence than estimated in meta-analyses of hospitalized cases with myocarditis (estimated incidence 0.0035%) after the second vaccination.<sup>14,15</sup> Elevated hs-cTnT was independent of previous COVID-19 infection or the interval since the last vaccine dose.

Among the overall group of participants, hs-cTnT concentration on day 3 after mRNA-1273 booster vaccination as a continuous variable, was significantly higher compared to a well-matched control cohort. Second, all cases were mild with only a transient and short period of myocardial injury (maximum hs-cTnT concentration 35 ng/L). No patient showed ECG changes and no patient developed MACE within 30 days. Potentially, such outcomes were averted by the safety net provided by early detection and early implementation of preventive measures for deterioration including avoidance of strenuous exercise. Notably, systemic reactogenicity (fever, chills, body aches), and chest pain occurred with comparable frequency in participants with versus without mRNA-1273 booster vaccine-associated hs-cTnT elevations. Third, when using sex-specific ULN cut-offs for myocardial injury adjudication, mRNA-1273 booster vaccine-associated myocardial injury occurred significantly more often in women versus men (3.7% vs. 0.8%). This is in striking discrepancy to the sex distribution of vaccine-associated myocardial injury in the setting of clinical myocarditis following the first and second vaccinations detected by passive surveillance, which occurred predominately in young men.<sup>2,3,16</sup> Median age of participants developing mRNA-1273 vaccine-associated myocardial injury was 46 years. Thereby, also the age distribution is different to that of most reported vaccine-associated clinical myocarditis cases.<sup>2,3</sup> When using a uniform (and thereby higher in women and lower in men compared to the sex-specific) ULN cut-off for adjudication, the incidence rate

of vaccine-associated myocardial injury declined in women and increased in men. Fourth, the predominate mechanisms underlying mRNA-1273 booster vaccination-associated myocardial injury did not seem to include antibodies neutralizing IL-1RA, which were suggested to be involved in the pathophysiology of severe COVID-19 mRNA vaccine-associated myocarditis in young male patients,<sup>8</sup> pre-existing vaccine/infection-induced immunity against SARS-CoV-2, nor systemic inflammation. In contrast, levels of IFN- $\lambda$ 1 and GM-CSF, both modulators of the immune responses to acute viral infection, vaccination, and tissue inflammation, were lower in cases with mRNA-1273 vaccine-associated myocardial injury versus those without.<sup>17–19</sup> However, we did not adjust for multiple testing nor for potential confounders for the evaluation of different potential immunological mechanisms underlying COVID-19 mRNA-vaccine-associated myocardial injury due to the exploratory nature of the analysis and should thus be considered as a hypothesis-generating analysis. IFN- $\lambda$  limits inflammation-induced tissue damage in viral infections<sup>20</sup> and in models of ischaemic myocardial injury.<sup>21</sup> Whether IFN- $\lambda$ 1 deficiency may reduce myocardial protection and thereby promote vaccine-associated myocardial injury needs to be further investigated. In a phase 3 trial, pegIFN- $\lambda$  reduced hospitalizations and emergency visits in patients with COVID-19<sup>22</sup> and in a phase 2 study, pegIFN- $\lambda$  accelerated viral decline in outpatients with COVID-19,<sup>17,18</sup> thereby further strengthening the rationale of the hypothesis that IFN- $\lambda$ 1 deficiency may be involved in vaccine-associated myocardial injury. GM-CSF exerts pro-inflammatory effects, and both administration and inhibition of GM-CSF are tested as potential therapeutics in COVID-19.<sup>19</sup> Whether low GM-CSF blood levels are a risk factor for immune-mediated cTnT elevations remains to be further elucidated. The significantly higher rate of mRNA-1273 booster vaccination-associated myocardial injury in women versus men may at least partly be related to the higher vaccine dose per body weight or myocardial mass in women and therefore dose-dependent toxic effects. Clinically overt severe vaccination-associated myocarditis may then occur following a second hit, possibly mediated by neutralizing autoantibodies targeting IL-1RA, microvascular thrombosis, or direct cardiac myocyte injury unrelated to inflammation.<sup>8,23</sup>

Our findings following mRNA-1273 booster vaccination extend and corroborate observations in two recent active surveillance studies after BNT162b2 vaccination.<sup>24,25</sup> Among 324 healthcare workers (mean age 51 years, 59.2% women) who received a fourth dose of BNT162b2 in Israel, two participants (one woman and one man) developed vaccine-related myocardial injury on day 3 (incidence 0.6%, maximum hs-cTnI concentration 22.1 ng/L). One had mild symptoms including fever and chest pain, one was asymptomatic. Both had a normal ECG and echocardiography.<sup>24</sup> Among 301 adolescents in Thailand (mean age 15 years) receiving the second dose of BNT162b2, five participants (incidence 1.7%), all boys, developed vaccine-related myocardial injury on either day 2 or day 3.<sup>25</sup> One of them had very high hs-cTnT concentrations (593 ng/L) and late gadolinium enhancement indicating myocarditis on cardiac magnetic resonance (CMR) imaging. When comparing these studies, it is important to highlight major differences in the study population and study methodology.

Therefore, the main finding of this study, that subclinical mRNA vaccine-associated myocardial injury is much more common than estimated based on passive surveillance, has been confirmed and generalized in these complimentary cohorts of slightly older health-care workers in Israel and adolescents in Thailand. Additional active surveillance studies are needed to externally validate two specific findings of this study: the even higher rate of mRNA-1273 booster vaccination-associated myocardial injury overall, and particularly in women. At least in part, these findings seem explained by the use of sex-specific ULN for hs-cTnT in this versus a uniform ULN in the two other studies, as well as using mRNA-1273, which also had resulted in a higher rate of hospitalizations due to clinical myocarditis versus BNT162b2 in prior passive surveillance studies.<sup>2,3,26,27</sup> Of note, mRNA-1273 had also resulted in higher immunogenicity and protection from COVID-19 versus BNT162b2 in large observational studies.<sup>28,29</sup>

Vaccine-related myocarditis has previously been reported following smallpox vaccination with an observed incidence of 16.11/100 000, which was nearly 7.5-fold higher than the expected background incidence.<sup>30</sup> In contrast, myocarditis following other vaccines is rare.<sup>31</sup> Similar to our finding with mRNA vaccination, there is evidence that the frequency of subclinical myocardial injury may also be higher after smallpox vaccination. A study on US military personnel found subclinical cTnT elevations in 2.87% of 1081 smallpox vaccinated subjects, or a 60 times higher rate than overt clinical cases.<sup>32</sup> The same study found no cTnT elevation in 189 subjects vaccinated with the inactivated influenza vaccine. This suggests that vaccine characteristics are relevant for the observed cTnT increase.

The long-term consequences of vaccine-related myocardial injury detected by transient and mostly mild hs-cTnT/I elevations on day 2 or 3 are unknown. Given the small extent of acute cardiomyocyte injury in our study, that is, cTnT levels of about one-fourth of those observed in patients with spontaneous myopericarditis,<sup>10</sup> and its transient nature, good long-term outcomes can be expected. COVID-19 associates with a substantially higher risk for myocarditis than mRNA vaccination,<sup>33</sup> and myocarditis related to COVID-19 infection has shown a higher mortality than myocarditis related to mRNA vaccination.<sup>34,35</sup> Thus, for the majority of individuals, the overall very favourable risk–benefit ratio of booster immunizations persists.<sup>14,15,36–39</sup> However, further studies are needed to assess the impact of mRNA vaccine-associated myocardial injury on the long-term risk of cardiac arrhythmias and heart failure. Also, evidence generated in the perioperative setting should help avoid the over-simplistic assumption that the absence of typical chest pain on day 3 after vaccination in most cases would *per se* indicate a favourable prognosis: perioperative myocardial injury not associated with chest discomfort had comparable unfavourable long-term outcome versus perioperative myocardial injury with chest discomfort.<sup>40</sup>

By providing novel insights regarding the incidence, extent, duration, patient characteristics, possible mechanisms, and outcome of mRNA-1273 booster vaccination-associated myocardial injury, this study aims to help patients, physicians, and public health authorities make informed decisions regarding future booster vaccinations.<sup>4</sup> Importantly, this study also may help

manufacturers fine-tune the dose and composition of future vaccines.

It is mandatory to put our findings into perspective with the incidence and extent of myocardial injury associated with COVID-19 infection. Before the COVID-19 vaccine were available, the incidence and extent of myocardial injury associated with COVID-19 infection was much higher than observed in this active surveillance study after booster vaccination.<sup>37,41,42</sup> Data on the incidence of COVID-19-associated myocardial injury in populations with high immunity against SARS-CoV-2 are not yet available.

Alternative, yet unlikely, contributors to the elevated cTnT in our study include cardiomyocyte injury associated with strenuous exercise, or in the context of a high inflammatory response to the vaccination or a non-cardiac source. While exercise was not restricted between vaccination and first hs-cTnT measurement, none of the detected cases reported strenuous exercise preceding the blood draw on day 3. Importantly, prior exercise was also not restricted among the matched control group, and even strong exercise typically only leads to an increase in hs-cTnT concentration of on average 1 ng/L.<sup>43</sup> Moreover, neither the clinical symptoms (i.e. fever, chills, muscle sore), nor the measured markers of systemic inflammation indicated an overshooting inflammatory response in subjects with hs-cTnT elevation. In contrast to some rather rare chronic active skeletal muscle diseases such as muscle dystrophies, acute skeletal muscle injury, even when as extensive as in patients with rhabdomyolysis, has been found not to be a non-cardiac source of elevated hs-cTnT concentrations.<sup>44–46</sup> Also, interference has been reported as a possible confounding factor for cardiac troponin elevations. However, this issue seems to predominantly affect the current hs-cTnI and not the current hs-cTnT assay.<sup>47</sup> Therefore, the acute dynamic increase in hs-cTnT concentration following mRNA COVID-19 vaccination has to be considered indicating myocardial injury and not secondary to the intramuscular injection and local skeletal muscle injury. Lastly, unknown prior cardiac disease may have been contributing to some of the extent of myocardial injury observed. Therefore, conservative criteria were used for the adjudication of mRNA-1273 booster vaccination-associated myocardial injury and 18 additional patients with hs-cTnT elevation on day 3 were classified as more likely having chronic myocardial injury.

The following limitations should be considered when interpreting our findings. First, to interfere as little as possible with the motivation of the hospital staff to obtain the mRNA-1273 booster vaccination and its logistics, we restricted the study to blood draws after vaccination. Thus, baseline hs-cTnT values were not available. The lack of a baseline hs-cTnT concentration was therefore addressed threefold: (i) by requiring a relevant change in hs-cTnT concentration from day 3 to the follow-up visit as additional criteria to adjudicate mRNA vaccine-associated myocardial injury; (ii) by conservative adjudication in that 18 participants with mild hs-cTnT-elevations on day 3 (17 women, one man), and either no available hs-cTnT concentration at follow-up visit or one with no relevant change, were considered to reflect pre-existing known or assumed cardiac disease rather than mRNA-1273 booster vaccine-associated myocardial injury

(although the differential diagnosis in these 18 patients includes persistent vaccine-associated myocardial injury); Thereby, among the 40 participants (5.1%) detected to have increased hs-cTnT concentration on day 3 after mRNA-1273 booster vaccination, only 22 participants (2.8%) were adjudicated to have mRNA-1273 vaccine-associated myocardial injury. For comparison, using the sex-specific 99th percentile as the ULN, among presumably healthy individuals only 1% of persons are expected to have increased levels; (iii) by adding an age-, sex-, and history of coronary artery disease/AMI-matched control group. Despite our efforts to address the lack of baseline hs-cTnT concentration, we may have still misclassified a small number of participants. Future studies using baseline values for adjudicating acute dynamic high-sensitivity cardiac troponin elevation above the sex-specific ULN are warranted to confirm our findings. Second, the time-course of mRNA-1273 vaccine-associated myocardial injury is incompletely understood. Accordingly, by measuring hs-cTnT on day 3 after mRNA-1273 booster vaccination, which was in line with other studies,<sup>24</sup> we might have missed cases that peaked earlier and had already returned to normal on day 3. Third, the 4th universal definition of myocardial infarction states that 'elevated cTn levels may be indicative of acute myocardial injury if the pattern of values is rising and/or falling'.<sup>48</sup> No specific percentage change was proposed, thus in some patients the distinction between acute and chronic was challenging. In those cases, we adjudicated those patients as chronic injury, thus choosing the more conservative approach. Fourth, this study recruited unselected healthcare workers of a university hospital. Thereby, the study population was relatively young and 70% women. Further studies are warranted to extend the findings regarding incidence of mRNA-1273 booster vaccination-associated myocardial injury and 30-day MACE to other populations. Both may differ particularly in older persons with a higher preexisting burden of cardiovascular disease. Fifth, no CMR imaging was performed, as the amount of vaccine-induced cardiomyocyte injury in this study was below the expected limit of detection of CMR for late gadolinium enhancing myocardial lesions indicative of myocarditis (usually a hs-cTnT concentration of about 50–100 ng/L).<sup>10,11</sup> These thresholds were pre-defined in collaboration with imaging experts, but are based on expert opinion rather than large prospective studies. Sixth, it is unknown whether and to what extent early detection and management, such as asking cases to avoid strenuous exercise, contributed to the excellent outcomes at 30 days. Seventh, given the absence of another *in-vivo* technique with comparable sensitivity to hs-cTnT/I regarding acute cardiomyocyte injury, it remains unknown whether mRNA-1273 vaccine-induced myocardial injury resulted in cardiomyocyte cell death and thereby irreversible loss of cardiomyocytes, or sublethal injury.

In conclusion, using active surveillance, mRNA-1273 vaccine-associated mild transient myocardial injury was found to be much more common than previously thought. It occurred in one out of 35 persons, was mild and transient, and more frequent in women versus men. Neither anti-IL-1RA, nor pre-existing vaccine/infection-induced immunity or systemic inflammation seemed to be dominant mechanisms of myocardial injury. No participant developed MACE within 30 days.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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