RESEARCH ARTICLE

A prospective study on myocardial injury after BNT162b2 mRNA COVID-19 fourth dose vaccination in healthy persons

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Aims	To prospectively evaluate the incidence of myocardial injury after the administration of the fourth dose BNT162b2 mRNA vaccine (Pfizer-BioNTech) against COVID-19.
Methods and results	Health care workers who received the BNT162b2 vaccine during the fourth dose campaign had blood samples collected for high-sensitivity cardiac troponin (hs-cTn) during vaccine administration and 2−4 days afterward. Vaccine-related myocardial injury was defined as hs-cTn elevation above the 99th percentile upper reference limit and >50% increase from baseline measurement. Participants with evidence of myocardial injury underwent assessment for possible myocarditis. Of 324 participants, 192 (59.2%) were female and the mean age was 51.8 ± 15.0 years. Twenty-one (6.5%) participants had prior COVID-19 infection, the mean number of prior vaccine doses was 2.9 ± 0.4, and the median time from the last dose was 147 (142−157) days. Reported vaccine-related adverse reactions included local pain at injection site in 57 (17.59%), fatigue in 39 (12.04%), myalgia in 32 (9.88%), sore throat in 21 (6.48%), headache in 18 (5.5%), fever $\geq 38°C$ in 16 (4.94%), chest pain in 12 (3.7%), palpitations in 7 (2.16%), and shortness of breath in one (0.3%) participant. Vaccine-related myocardial injury was demonstrated in two (0.62%) participants, one had mild symptoms and one was asymptomatic; both had a normal electrocardiogram and echocardiography.
Conclusion	In a prospective investigation, an increase in serum troponin levels was documented among 0.62% of healthy health care workers receiving the fourth dose BNT162b2 vaccine. The two cases had mild or no symptoms and no clinical sequela. Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT05308680.

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Graphical Abstract
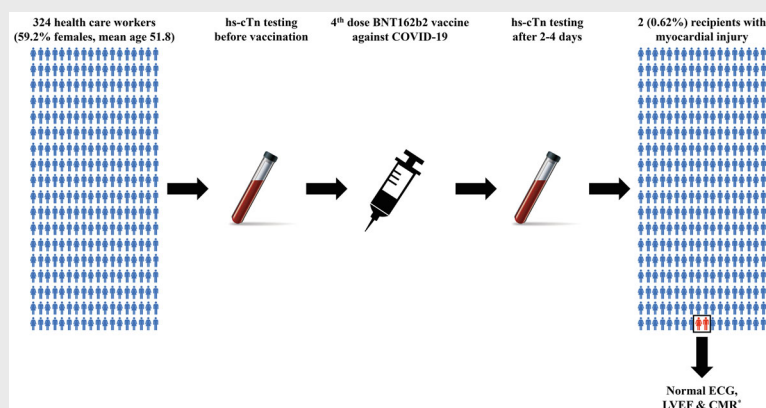
An association between the administration of mRNA vaccines against COVID-19 and myocarditis was well established in large population-based retrospective studies. In this prospective study, health care workers who received the fourth dose of the BNT162b2 (Pfizer-BioNTech) vaccine had blood samples collected for high-sensitivity cardiac troponin (hs-cTn) before and 2−4 days after vaccine administration. Of 324 recipients, 2 (0.62%) were found to have a vaccine-related myocardial injury; both had a normal electrocardiogram (ECG) and left ventricular ejection fraction on echocardiography. CMR, cardiovascular magnetic resonance; LVEF, left ventricular ejection fraction. *CMR was performed based on a clinical indication in one recipient.

Keywords COVID-19 ● mRNA ● Myocardial injury ● Myocarditis ● Vaccine

Introduction

High efficacy and safety of the BNT162b2 messenger ribonucleic acid (mRNA) vaccine (Pfizer-BioNTech) against coronavirus disease 2019 (COVID-19) were demonstrated in multiple studies.[1−3] Lately, simultaneous with the increased number of the BNT162b2 vaccines that were administered, emerging reports have suggested a possible association between vaccine administration and the occurrence of myocarditis.[4,5] Hence, in June 2021 the Advisory Committee on Immunization Practices for the Centers for Disease Control and Prevention published an update regarding myocarditis after mRNA vaccines against COVID-19.[6] This was confirmed in large studies from Israel that showed an increased incidence of myocarditis in recipients of the BNT162b2 vaccine.[7−9] In one study, the overall risk of myocarditis was estimated to be 2.13 per 100 000 persons with the highest risk observed in male recipients between the ages of 16−29 years after the second vaccine dose, with most cases reported as mild or moderate in severity and occurring 2−4 days after vaccine administration.[9] Although considered to be low, the estimated risk of myocarditis and myocardial injury in vaccine recipients is believed to be underestimated since all previous studies are retrospective and based on observational data.

The aim of this study is to prospectively evaluate the incidence of vaccine-related myocardial injury and sub-clinical myocarditis after the administration of the fourth dose BNT162b2 vaccine against COVID-19.

Methods

Study population and design

The study population included adult health care workers (≥18 years old) who received the BNT162b2 vaccine (Pfizer-BioNTech) during the fourth dose campaign conducted in two Israeli hospitals (Shaare Zedek and Shamir medical centres) during January 2022. Exclusion criteria included any of the following within 14 days prior to study enrolment: acute coronary syndrome, peri/myocarditis, cardiac catheterization, cardiac surgery, cardiac ablation, or any other invasive cardiac procedure. In addition, participants with known chronic renal failure (creatinine clearance ≤30 ml/min), or dilated or hypertrophic cardiomyopathy were not enrolled. There were no enrolment restrictions for participants' age or gender.

All participants had blood samples collected for high-sensitivity cardiac troponin (hs-cTn) I (ARCHITECT STAT High-sensitivity Cardiac Troponin I assay, Abbott Diagnostics) or T (Elecsys High-sensitivity Cardiac Troponin T assay, Roche Diagnostics) measurement at the time of vaccine administration and 2−4 days afterward (*Graphical Abstract*). Participants in whom a myocardial injury was demonstrated underwent further comprehensive cardiac assessment for possible myocarditis including electrocardiogram (ECG), blood tests including complete blood count, C-reactive protein (CRP), and hs-cTn, echocardiography. Cardiovascular magnetic resonance (CMR) was performed based on a clinical indication in recipients with suspected vaccine-related myocardial injury plus any sign or symptom suggesting the diagnosis of clinical myocarditis (e.g. chest pain, dyspnea, palpitations, new arrhythmia, etc.).

The investigation conforms with the principles outlined in the Declaration of Helsinki and has been approved by the local ethics committees. Written informed consent was obtained from all participants.

Case definition and data collection

Vaccine-related myocardial injury was defined as a hs-cTn elevation above the 99th percentile upper reference limit (URL) for the specific assay and >50% increase from the first measurement taken at the time of vaccine administration.[10,11] The diagnostic criteria, classification, and degree of certainty of myocarditis were adapted from the case definition of the Brighton Collaboration and the position statement of the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases for clinically suspected myocarditis.[12,13]

Baseline participants' characteristics including demographics, COVID-19 immunization status, prior vaccine-related adverse reactions, past medical history, and cardiovascular risk factors were obtained by self-report questionnaires completed during study enrolment. Data regarding current vaccine-related adverse reactions including the occurrence of chest pain, shortness of breath, palpitations, sore throat, or fever ≥38°C were obtained by self-report questionnaires completed 2−4 days after vaccine administration.

Statistical analysis

Characteristics were described as numbers and percentages for categorical variables and by means and standard deviations (SD) or median with interquartile (IQR) ranges for continuous variables. Paired-samples t-test was used to compare mean ± SD baseline hs-cTn with mean ± SD hs-cTn measurements taken 2−4 days after vaccine administration. Analyses were carried out using SPSS Statistics for Windows, version 25.0. (IBM Corp., Armonk, NY, USA).

Results

This study included 336 participants enrolled during vaccine administration, of them 324 (96.43%) had blood tests collected for hs-cTn 2−4 days after vaccine administration and were included in the final analysis.

Baseline characteristics

Baseline participants' characteristics are shown in *Table 1*. The mean ± SD age was 51.8 ± 15.0 years and 192 (59.2%) of the participants were female (*Graphical Abstract*). The mean ± SD number of prior vaccine doses against COVID-19 was 2.9 ± 0.4 and 32 (9.88%) participants had two or fewer prior vaccine doses. The median (IQR) time from the last vaccine dose was 147 (142−157) days and 21 (6.5%) participants had prior known COVID-19 infection. Eleven (3.27%) participants had ischaemic heart disease, 62 (18.45%) had dyslipidaemia, 58 (17.26%) had hypertension, 27 (8.03%) had diabetes mellitus, 28 (8.33%) were active smokers, 1 (0.3%) participant had prior myocarditis which was not related to prior vaccine administrations, and 1 (0.3%) had chronic kidney disease.

Table 1 Baseline participants' characteristics

| Parameter	
Patients, n	324
Age (years), mean ± SD	51.8 ± 15.0
Women	192 (59.2%)
Prior vaccine doses, mean ± SD	2.9 ± 0.4
≤2 prior vaccine doses	32 (9.88%)
Time from last vaccine dose (days), median (IQR)	147 (142−157)
Prior COVID-19 infection	21 (6.5%)
Ischaemic heart disease	11 (3.27%)
Dyslipidaemia	62 (18.45%)
Hypertension	58 (17.26%)
Diabetes mellitus	27 (8.03%)
Smoker	28 (8.33%)
Chronic kidney disease	1 (0.3%)
Prior myocarditis	1 (0.3%)

IQR, interquartile range; SD, standard deviation.

Table 2 Vaccine-related adverse reactions

Parameter	
Any adverse reaction	134 (41.35%)
Injection-site local pain	57 (17.59%)
Fatigue	39 (12.04%)
Myalgia	32 (9.88%)
Sore throat	21 (6.48%)
Headache	18 (5.5%)
Fever ≥38°C	16 (4.94%)
Chest pain	12 (3.7%)
Palpitations	7 (2.16%)
Shortness of breath	1 (0.3%)

Rates of vaccine-related adverse reactions and myocardial injury

Rates of reported vaccine-related acute adverse reactions are shown in *Table 2*. All included participants completed the self-report questionnaire of adverse events; these were reported 3.11 ± 0.74 days after vaccine administration. Vaccine-related adverse reactions (any) were reported by 134 (41.35%) participants. Reported adverse reactions included local pain at injection site in 57 (17.59%), fatigue in 39 (12.04%), myalgia in 32 (9.88%), sore throat in 21 (6.48%), headache in 18 (5.5%), fever ≥38°C in 16 (4.94%), chest pain in 12 (3.7%), palpitations in 7 (2.16%), and shortness of breath in one (0.3%) participant.

Twenty-one (6.48%) recipients had hs-cTn above the 99th percentile URL at the first measurement that was taken before vaccine administration. A second test of hs-cTn was measured 3.11 ± 0.74 days after vaccination and was elevated above the 99th percentile URL in 27 (8.33%) participants; however, only two (0.62%) participants had a >50% increase from the baseline hs-cTn measurement and hence were considered to have a vaccine-related myocardial injury (*Graphical Abstract*). Collectively, there was no
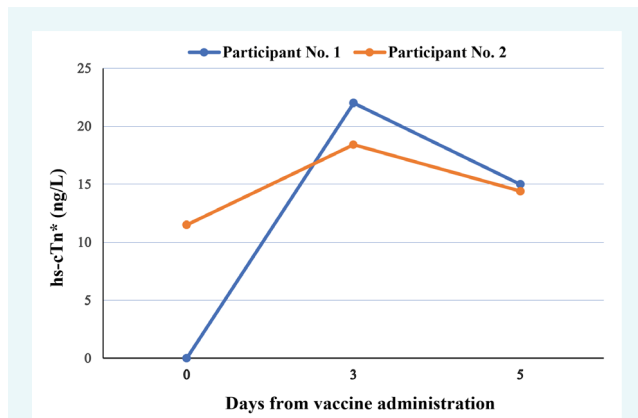
Figure 1 Changes in levels of high-sensitivity cardiac troponin (hs-cTn) in participants with vaccine-related myocardial injury. *hs-cTn I in participant no. 1 and hs-cTn T in participant no. 2.

difference between baseline hs-cTn measurements (5.52 ± 12.61) and measurements taken 2−4 days after vaccine administration (5.32 ± 8.13) (paired *t*-test $p = 0.772$). The first participant with vaccine-related myocardial injury was a 51-year-old female with a medical history of diabetes mellitus, hyperlipidaemia, and hypertension who had mild symptoms including a fever of 38°C, chest pain, and myalgia, and the second participant was a 62-year-old male with unremarkable medical history who was asymptomatic. Follow-up measurements showed a decrease in hs-cTn values in both participants, hence a typical 'raise and fall' pattern was demonstrated (*Figure 1*). Other potential causes for hs-cTn elevation including intense physical activity and systemic illness resulting in myocardial injury were ruled out in both participants. Both participants had a normal ECG and left ventricular ejection fraction on echocardiography. In addition, CMR was performed in the first participant and was normal (*Graphical Abstract*). Hence, the two participants did not fulfill the Brighton Collaboration criteria for myocarditis, but the diagnostic criteria for clinically suspected myocarditis of the ESC were met in the first participant. *Table 3* shows clinical characteristics, hs-cTn values, and diagnostic workup for the participants with vaccine-related myocardial injury.

Discussion

In this study, we aimed to prospectively assess the incidence of vaccine-related myocardial injury among generally healthy adult health care workers who received the BNT162b2 mRNA vaccine (Pfizer-BioNTech) against COVID-19 during the fourth dose campaign by using hs-cTn measurements at the time of vaccine administration and 2−4 days afterward. Vaccine-related adverse reactions were overall mild and occurred in less than half of the participants; however, two participants out of 324 (0.6%) were found to have an acute myocardial injury in the days following vaccine administration. Both participants had no evidence of clinical myocarditis and had normal ECG and echocardiography, with a normal CMR in the symptomatic participant.

Table 3 Clinical characteristics and diagnostic workup of participants with vaccine-related myocardial injury

Parameter	Participant No. 1	Participant No. 2
Age (years)	51	62
Sex	Female	Male
Medical history	DM, hypertension, hyperlipidaemia	None
No. of prior vaccine doses	3	3
Prior COVID-19 infection	No	No
Baseline hs-cTn test	0 pg/ml (hs-cTnI)	11.5 ng/L (hs-cTnT)
2−4 Day hs-cTn test	22.1 pg/ml (hs-cTnI)	18.4 ng/L (hs-cTnT)
Symptoms	Fever 38°C, chest pain, myalgia	None
Physical examination	Normal	Normal
CRP	1.68 mg/dl[a]	0.3 mg/dl[a]
WBC count, $10^3/\mu l$	10	8.2
Follow-up hs-cTn test	15 pg/ml (hs-cTnI)	14.4 ng/L (hs-cTnT)
Electrocardiogram abnormalities	None	None
Echocardiogram abnormalities	None	None
LVEF	Normal	Normal
CMR	Normal	–
Diagnosis of myocarditis[b]	Ruled out	Ruled out

CMR, cardiovascular magnetic resonance; CRP, C-reactive protein; DM, diabetes mellitus; hs-cTn, high-sensitivity cardiac troponin; LVEF, left ventricular ejection fraction; WBC, white blood cell.
[a]Normal range: 0–0.5 mg/dl.
[b]According to the case definition of the Brighton Collaboration.

Effective vaccines against COVID-19 were developed in record time and were proven in clinical trials to be both effective and safe.[2,14,15] Post-approval population-based studies after the second dose of the BNT162b2 vaccine confirm that overall side effects are mild and that serious associated events are extremely rare.[7,16] Adverse events after the fourth dose of the BNT162b2 and mRNA1273 vaccines were recently reported among health care workers.[17] When compared with previous studies,[7,16–18] systemic and local adverse reactions in the current study were generally similar, albeit less common, with the exception of chest pain and palpitations that were not reported in previous studies. In the current study, we report chest pain in 12 (3.7%) and palpitations in 7 (2.16%) participants.

Population-based retrospective studies suggest an association between mRNA-based vaccines against COVID-19 and myocarditis.[7–9,19] In these studies, most cases were observed in young male recipients after the second vaccine dose and were diagnosed mostly 2−4 days after vaccine administration. For instance, Witberg et al.[9] showed in their study that the highest incidence of myocarditis was observed after the second dose of the BNT162b2 vaccine in male recipients between the ages of 16 to 29 and was 10.69 cases per 100 000 persons, while the overall incidence after at least one vaccine dose was 2.13 cases per 100 000 persons. Currently, there are no large-scale studies to evaluate the incidence of myocarditis after the administration of the third or fourth vaccine doses, but case reports of myocarditis in recipients of the third dose were described.[20,21] Although considered to be low, the estimated risk of myocarditis and myocardial injury in vaccine recipients is believed to be underestimated. Indeed, the current

study suggests a higher incidence of myocardial injury during active monitoring for cardiac biomarkers in vaccine recipients with no clinical evidence of myocarditis. Since in our study the average age was 51 and only 40% were male with only 8 (2.47%) of them that were 30 years old or younger, it is currently unknown if a prospective evaluation among younger males will yield a higher incidence of myocardial injury.

The mechanism of vaccine-induced myocarditis is unknown but may be related to the active component of the vaccine, the mRNA sequence that codes for the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or to an unregulated immune response that follows vaccination in certain individuals with a genetic predisposition.[22,23] We can assume that in some subjects acute myocardial injury can occur by a similar mechanism without significant clinical myocarditis. Otherwise, a non-immune-mediated initial injury may trigger more significant immune-mediated myocarditis in susceptible individuals, but not in others.

Multiple studies evaluated short- and long-term analytical and biological variations of hs-cTn and defined the reference change value of different assays in healthy subjects; in these studies, the reference change value was roughly 50% for both hs-cTn I and T.[24,25] This supports the requirement for >50% increase in hs-cTn from baseline measurement in our study and supports our findings by showing that the observed changes in hs-cTn are not likely explained by analytical and biological variations alone. Although one might expect a more attenuated decline in hs-cTn values in those participants with vaccine-related myocardial injury, larger studies are needed given the small peak in hs-cTn and the low event rate of vaccine-related myocardial injury. Besides the pathophysiological implications, the clinical significance of the mild injury found in our study may be debated and should be further evaluated in larger studies. A reasonable recommendation may be to withhold strenuous physical activity for a few months. Regarding the recommendation for repeat vaccine doses in the future, there is no consensus. However, given the limited clinical utility reported recently with the fourth dose against Omicron, repeat vaccination of individuals with documented post-vaccine myocardial injury deserves a profound risk−benefit consideration.

Limitations of this study include its limited size given the fact that myocarditis following mRNA vaccination against COVID-19 is a rare event; hence, the true incidence of vaccine-related myocardial injury may not be accurate. However, this study has the merits of a prospective evaluation and can direct future studies as to the expected numbers needed for a prospective evaluation. Although spot hs-cTn 2−4 days post vaccine administration was chosen based on prior large-scale studies,[8,9] this study may have missed later occurrence of myocardial injury. Moreover, although not common, myocardial injury and myocarditis could potentially occur even in recipients without elevated hs-cTn and these recipients may have been missed in this study. By examining health care workers after the fourth dose vaccination it may be inaccurate to extrapolate the results on subjects receiving the first or second doses, or on the general population which is demographically different from our study population (e.g. vaccine-related myocarditis is more common in young male recipients). In addition, the 99th

percentile URL for hs-cTn I and T assays that were used in this study were validated in the context of ischaemic heart disease and not of myocarditis as these assays were not previously evaluated in this specific context. Lastly, previous studies have also demonstrated a cross-reaction between skeletal muscle troponin and hs-cTn I and especially T assays (e.g. in patients with rhabdomyolysis and skeletal myopathies)[26−28]; hence, it is theoretically possible that hs-cTn elevation is secondary to the intramuscular injection and local muscle injury resulting in a false-positive reaction. However, our literature review did not reveal any study to support this theory.

Conclusions

In conclusion, an increase in serum troponin levels occurred in two of 324 health care workers who received the fourth dose BNT162b2 vaccine (Pfizer-BioNTech). These increases were attended by mild or no symptoms and had no sequelae. The significance of these findings must be weighed against the overall possibility of increases in serum troponin levels in the general population and with the limitations of a relatively small study group. Larger studies are warranted to confirm this finding and evaluate the need to increase testing among mildly symptomatic individuals.

Funding

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