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Transient elevation of NT-proBNP after mRNA COVID-19 vaccination in healthy adults: A longitudinal biomarker analysis

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ABSTRACT

Background: Cardiovascular complications such as myocarditis and pericarditis have been reported following mRNA COVID-19 vaccination, particularly after the second dose. However, little is known about the cardiac biomarker response in otherwise healthy individuals after mRNA COVID-19 vaccination.
Methods: This study aimed to investigate the dynamics of high-sensitivity cardiac troponins (hs-cTnI, hs-cTnT) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) following mRNA COVID-19 vaccination. We analyzed serum samples collected at multiple time points between April and December 2021 from 83 healthy adult military personnel vaccinated with two doses of mRNA COVID-19 vaccines. Statistical analyses included mixed-effects ANOVA with Geisser-Greenhouse correction and logistic regression to assess the influence of covariates.
Results: NT-proBNP levels showed a significant but transient increase, particularly within 14 days after the second vaccine dose (geometric mean 36.2 pg/mL; $p < 0.0001$). Nearly 49% of participants exhibited a relative increase exceeding 1.5 times their individual baseline. No participant surpassed the 450 pg/mL threshold indicative of cardiovascular complications, and troponin levels remained unchanged across all assessed 14-day intervals. The observed NT-proBNP elevation was not significantly associated with any of the assessed covariates. However, non-significant trends were noted among men, individuals without prior COVID-19 infection or comorbidities, and those vaccinated with the mRNA-1273 (Moderna) vaccine.
Conclusions: In healthy adults, mRNA COVID-19 vaccination was associated with a short-term, subclinical elevation in NT-proBNP, particularly after the second dose. While not indicative of overt cardiovascular injury, this biomarker response may reflect transient myocardial stress and warrants further research.

1. Introduction

The COVID-19 pandemic presented an unprecedented global challenge demanding the rapid development of effective protection in the form of vaccination against the novel coronavirus. As a result, vaccines were developed not only using traditional technologies but also

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with a new generation of mRNA-based platforms. Although the authorized vaccines underwent accelerated clinical trials, their large-scale implementation in immunization programs required continued safety monitoring. [1] Consequently, numerous studies were published, focusing particularly on the safety profile of COVID-19 vaccines.

Within the first year, cardiovascular complications following mRNA vaccination—such as myocarditis, myopericarditis, arrhythmia, and ischemic heart disease—were rarely documented, particularly among young males. These observations prompted extensive research aimed at evaluating the potential link between vaccination and these cardiac events. [2–5] Most studies concluded that while an association could exist, the risk of developing such cardiac events is considerably higher following COVID-19 infection than after vaccination. [6,7]

Only a few studies have investigated cardiac biomarkers in the context of post-vaccination adverse events. In most cases, the authors adopted a conservative approach, monitoring selected parameters either before and after vaccination, or following hospitalization for a suspected post-vaccination cardiac event. [8–11]Therefore, we decided to utilize a series of nine serum samples stored and collected from each participant from a cohort study conducted in 2021, involving healthy adult soldiers aged 18–55 years who received two doses of mRNA COVID-19 vaccines. [12] Our objective was to assess the dynamics of high-sensitivity cardiac troponin I (hs-cTnI) and T (hs-cTnT), as well as N-terminal prohormone of brain natriuretic peptide (NT-proBNP). We attempted to determine the changes in these biomarkers and investigate the potential impact of vaccination on their levels.

The levels of the aforementioned cardiac biomarkers may also rise in systemic inflammatory states, even in the absence of overt structural heart disease. [13,14] Therefore, we assessed potential post-vaccination inflammation using the Systemic Inflammatory Response Index (SIRI), which integrates neutrophil, monocyte, and lymphocyte counts into a composite index of inflammatory burden. [15]

2. Methods

2.1. Study design

Between April and December 2021, we conducted a prospective cohort study involving healthy adult volunteers aged 18–55 years, recruited from military personnel at the Air Transportation Base in Prague. The study protocol was approved by the Ethics Committee of the Third Faculty of Medicine, Charles University, Prague, Czech Republic. All participants provided written informed consent prior to their inclusion in the study. All participants provided written informed consent prior to their inclusion in the study. None had a personal history of heart disease, dyspnea, edema, or renal insufficiency, and individuals with any acute condition such as sepsis, pulmonary embolism, or acute coronary syndrome were not enrolled. All participants received two doses of an mRNA COVID-19 vaccine—either BNT162b2 (Comirnaty, Pfizer–BioNTech) or mRNA-1273 (Spikevax, Moderna). While the complete study design and procedures have been described previously, here we specifically focused on the evaluation of cardiovascular biomarkers measured in serum samples stored at approximately −80 °C throughout the study. [12] In the original study, serum was collected from 83 participants over a period of approximately 130 days, covering both pre- and post-vaccination periods for the first and second doses. Additionally, a complete blood count was obtained at each blood draw for every participant. A total of nine samples per participant were planned, and the biomarker data were organized into 14-day intervals before and after each vaccination, according to the original protocol.

2.2. Study endpoints

The analysis of three cardiac markers—hs-cTnT, hs-cTnI, and NT-proBNP—was performed at the Central Laboratory of the Institute for Clinical and Experimental Medicine (IKEM, Prague, Czech Republic) between December 2024 and February 2025. Levels of hs-cTnI were measured on the Abbott Architect i2000 (FSA) using the STAT High Sensitive Troponin-I assay (Abbott, Ireland). Concentrations of hs-cTnT and NT-proBNP were determined on the Roche Diagnostics cobas e801 analyzer with Elecsys Troponin T hs (Roche Diagnostics GmbH, Germany) and Elecsys proBNP II (Roche Diagnostics GmbH, Germany), respectively.

The threshold limits for elevated troponins were adopted according to the manufacturer's instructions: the cut-off values for hs-cTnI were 15.6 pg/mL in women and 34.2 pg/mL in men; for hs-cTnT, 9.0 pg/mL in women and 16.0 pg/mL in men. For NT-proBNP, two thresholds were evaluated regardless of sex: 125 pg/mL, commonly used to indicate heart failure [16], and 88.6 pg/mL, associated with increased mortality in patients with COVID-19. [8]

It was also assumed that cardiac marker concentrations should remain approximately consistent across all samples collected at different time points for each participant, as none exhibited clinical signs of heart failure. Therefore, the median concentration for each participant was used as the individual baseline, and any value exceeding 1.5 times this median was classified as a relative increase in the respective marker. The proportion of participants exhibiting such increases was then evaluated as the relative increase rate.

Since some sera were missing due to lack of collection, thawing, or prior use in previous analyses, the measured concentrations were reorganized into 14-day intervals after vaccination and a 7-day interval before vaccination. A quasi-longitudinal dataset was assembled, comprising paired observations from the first 28 days after each vaccine dose, structured into two 14-day intervals. The remaining study intervals were represented by outcomes aligned with this set. To assess the robustness of the findings, the analysis was conducted on the full analysis set, which included all data obtained from the available sera.

Complete blood counts were analyzed immediately after collection in the central laboratory using an XN-10 analyzer (Sysmex Corporation, Kobe, Japan), integrated into the XN-9100DI hematology line with SP-50 and DI-60 modules. At each corresponding time point, SIRI was calculated from the respective complete blood counts as (neutrophil count × monocyte count) / lymphocyte count.

2.3. Statistical analysis

Demographic characteristics and study variables were reported as proportions, means with standard deviations (SD), or medians with interquartile ranges (IQR), unless stated otherwise. Geometric means were used for concentrations of cardiac markers, as their log-transformed values followed a normal distribution.

The statistical significance of cardiac marker concentrations across different time intervals was assessed using a mixed-effects ANOVA with the Geisser-Greenhouse correction, followed by Tukey's multiple comparisons test. The presence of an increased relative risk or a higher risk of potential cardiac insufficiency in any of the monitored intervals was evaluated using the odds ratio (OR) derived from McNemar's test for paired proportions within the same fixed intervals (14- or 7-day periods).

The influence of covariates—including sex, age, BMI, smoking status, comorbidities, prior COVID-19 infection, and the type of commercial mRNA vaccine—on the relative increase rate was assessed using odds ratios (ORs) derived from logistic regression. Correlations between cardiac marker concentrations were assessed using Spearman's rank correlation test.

All tests were two-tailed, with the significance level set at 0.05. Statistical analyses were performed using Prism 10 (GraphPad Software, Inc., San Diego, CA, USA) and STATA version 18 (StataCorp, College Station, TX, USA).

3. Results

Of the 83 subjects initially enrolled in the study, 67 had their parameters measured at two consecutive 14-day intervals following both the first and second vaccine doses (i.e., at 1–14 days and 15–29 days after each dose). A total of 59 samples were collected during the week before vaccination (from day −6 to day 0), 49 samples were collected 30–45 days after the first dose, and 47 samples 66–79 days after the second dose.

The mean age of the study population was 39.1 years ±7.5 years (±SD), and the mean BMI was 26.2 ± 3.6 kg/m^2. The quasi-longitudinal dataset included 56 men (84%), 11 current smokers (16%), and 22 participants (33%) with a confirmed history of COVID-19 infection prior to vaccination. All participants received both the first and second doses of the same commercial vaccine: 56 were vaccinated with Comirnaty (83.6%) and 11 with Spikevax (16.4%). The mean interval between the two doses was 40.8 ± 5.9 days.

The geometric mean NT-proBNP concentration increased significantly to 28.7 pg/mL ($p = 0.021$) within the first 14 days after the first vaccine dose to rise significantly to 36.2 pg/mL ($p < 0.0001$) after the second dose, compared with pre-vaccination levels (Fig. 1). Moreover, NT-proBNP levels following the second vaccine dose were significantly higher than the levels measured at 15–29 and 30–44 days after the first dose, as well as at 15–29 and 66–79 days after the second dose.

NT-proBNP levels exceeding the cut-off of 125 pg/mL were observed in seven participants, with no recurrences and a maximum recorded level of 212 pg/mL. These elevated levels occurred most frequently within the first 14 days of vaccination, in two participants after the first dose and three participants after the second dose.

Furthermore, the 88.6 pg/mL cut-off was exceeded more frequently after both the first and second vaccine doses, with rates of 10.5% and 14.9%, respectively. While the rate observed after the first dose was not statistically different from those at other 14-day intervals, the rate following the second dose was significantly higher compared with later time points—4.5% at 15–29 days ($p = 0.035$) and 2.1% at 66–79 days ($p = 0.008$) post second dose (data not shown).

Within two weeks of the second vaccine dose, the relative increase rate—defined as NT-proBNP levels exceeding 1.5 times the individual baseline—reached 49% (Fig. 2). This elevation was observed as early as the first week in 45% of participants and was statistically significant compared with the pre-vaccination rate of 8.5%, with an odds ratio (OR) of 13.5 (95% CI: 3.4–117.1).

Although an elevated rate of relative NT-proBNP increase was observed in 19.4% of participants within 7 days of the first dose, this rate did not significantly differ from the pre-vaccination level (OR = 2.2, $p =$ 0.134). In contrast, the second dose significantly increased this rate within the first 14 days compared with that observed after the first dose (OR = 3.0, 95% CI: 1.3–7.7). Beyond 14 days following vaccination with either one or two doses, the rates declined and were no longer significantly different from the pre-vaccination level. The consistency of NT-proBNP levels and relative increase rates in the full analysis set supports the reliability of the findings from the quasi-longitudinal dataset (Supplemental Fig. 1).

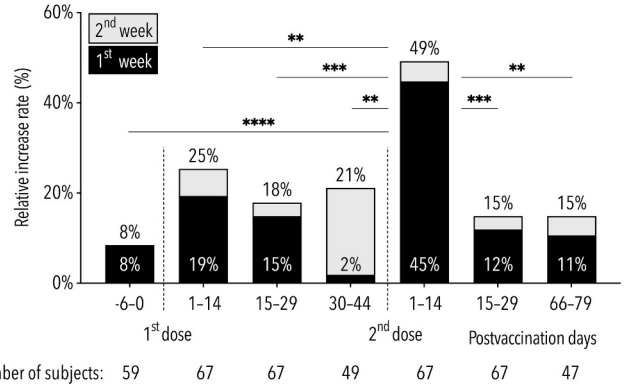

Fig. 2. Time-related changes in relative NT-proBNP increase rates before and after the first and second doses of an mRNA COVID-19 vaccine (quasi-longitudinal dataset).
* – p < 0.05; ** – p < 0.01; *** – p < 0.001; **** – p < 0.0001.

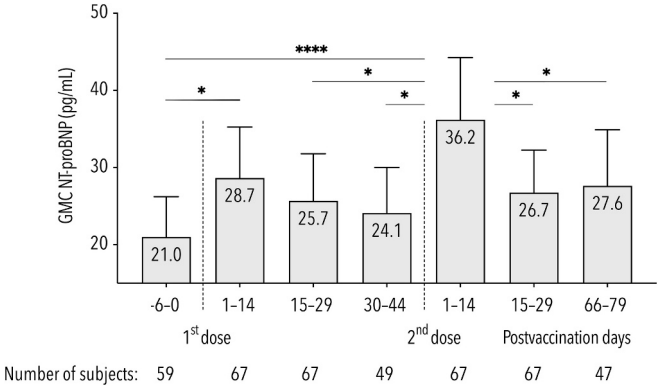

Fig. 1. Time-related changes in NT-proBNP concentrations before and after the first and second doses of an mRNA COVID-19 vaccine (quasi-longitudinal dataset).
GMC – geometric mean concentration; * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$; **** – $p < 0.0001$.

Levels of both troponins, hs-cTnI and hs-cTnT, remained unchanged after the first and second vaccine doses compared with pre-vaccination values (Supplemental Fig. 2). Similarly, the number of participants with levels exceeding 1.5 times their baseline did not differ significantly across any of the time points. While NT-proBNP levels showed no correlation with either hs-cTnI or hs-cTnT at any interval, a consistent correlation between the two troponins was observed across all time points (Supplemental Table 1).

SIRI showed a significant increase during the first 14 days after both doses, similar to NT-proBNP levels, and this increase was only transient (Supplemental Fig. 3). Nevertheless, no correlation was observed between SIRI and cardiac biomarkers (Supplemental Table 2).

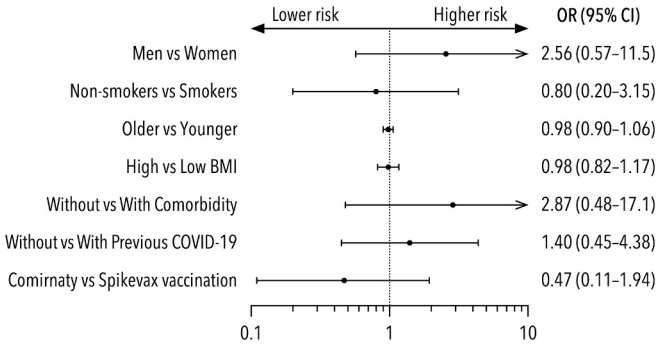

Fig. 3. Odds ratios for NT-proBNP relative increase rates within 14 days of the second mRNA vaccine dose, stratified by study covariates.
OR – odds ratio; 95% CI – 95% confidence interval.

4. Discussion

The dynamics of NT-proBNP levels in relation to the administration of the first and second doses of an mRNA COVID-19 vaccine demonstrated a significant early increase following both doses, administered 4–5 weeks apart. The elevation was particularly pronounced after the second dose. This increase was short-term and transient, as NT-proBNP levels began to decline more than 14 days after both the first and second doses, ultimately showing no significant difference from pre-vaccination levels. This approach allowed for the observation of an early NT-proBNP elevation following vaccination, a pattern not documented in prior research. [17]

Although the NT-proBNP threshold of 125 pg/mL was exceeded in three participants following the second dose, none of the individual values surpassed 450 pg/mL—the diagnostic threshold for heart failure. [16,18] This finding is consistent with the absence of any clinical signs or symptoms suggestive of cardiovascular complications in the study participants.

Surprisingly, the number of individuals with NT-proBNP levels >88.6 pg/mL—a prognostic threshold associated with increased risk of death from COVID-19—mirrored the rise in geometric mean concentrations observed during the first 14 days following the first (10%) and especially the second (15%) dose of the mRNA vaccine. Nevertheless, this proportion declined significantly thereafter and was no different from that observed prior to vaccination.

The relative increase rate in NT-proBNP levels—defined as a 1.5-fold rise over the individual baseline—also followed a dynamic similar to that of the geometric mean concentrations. Notably, nearly half of the participants reached this threshold shortly after the second mRNA dose, further supporting the assumption that the observed increase was obviously associated with vaccination. Elevated NT-proBNP levels, as well as the relative increase rate observed after the second—rather than the first—dose of the mRNA vaccine, are consistent with the increased risk of myocarditis and pericarditis, which has been more frequently reported following the second dose. [8,19]

Furthermore, this rate was not associated with any of the assessed covariates, although a slightly higher increase was observed in men, in participants without comorbidities, and in those vaccinated with the commercial Spikevax vaccine. Notably, myocarditis and pericarditis have also been reported more frequently in men, particularly following Spikevax vaccination. [20,21] Whether the presence of comorbidities may mitigate the risk of such increases remains speculative and would likely require further research, particularly focusing on concurrent medication use. Nonetheless, a similar effect has been documented in other studies. [8,19,22]

Immunization with mRNA vaccines against COVID-19 has been shown to induce a range of pro- and anti-inflammatory cytokines, as demonstrated in several original studies. [23,24] The cytokine-mediated inflammatory cascade may stimulate the renin-angiotensin-aldosterone system, thereby contributing to increased blood pressure and fluid retention. [25,26] These changes could result in atrial or ventricular wall stress, stimulating cardiac secretion of NT-proBNP even in otherwise healthy individuals. [27] Although it remains unclear whether vaccination against other infectious diseases can similarly elevate NT-proBNP levels, in the case of SARS-CoV-2 infection, the binding of the viral spike protein to angiotensin-converting enzyme 2 may contribute to dysregulation of this pathway—resulting in elevated blood pressure and potentially promoting cardiac NT-proBNP secretion. [28]

Importantly, circulating cardiac biomarkers such as NT-proBNP are not entirely specific for primary myocardial injury. Increasing evidence indicates that their levels may also rise in systemic hyperinflammatory states, where cytokine-driven hemodynamic changes, volume overload, and cardiomyocyte stretch contribute to biomarker release, even in the absence of overt structural heart disease. [13,14] This pattern was also reflected in the dynamics of SIRI, with a transient increase observed after both the first and the second vaccine dose. The absence of a correlation between SIRI and NT-proBNP levels suggests that any relationship between them is likely indirect. Moreover, according to previous studies, a decrease in lymphocytes and an increase in monocytes occur immediately within the first 1–3 days after this vaccination, whereas NT-proBNP levels tended to increase mainly during the first week after vaccination. [29–31] During the follow-up period, neither of both troponins evaluated showed any significant changes, whether early or delayed, following vaccination. Their positive correlation suggests potential interchangeability in healthy adult participants without clinical signs of cardiovascular dysfunction. This finding aligns with previous research. While troponin levels were not found to be affected in vaccinated individuals without any heart insufficiency, abnormally elevated troponin levels have been reported in most vaccinated individuals with post-vaccination myocarditis. [32,33]

A key strength of this study was the monitoring of the investigated cardiac biomarkers at 14-day intervals both before and during mRNA COVID-19 vaccination. This approach enabled a more detailed understanding of their potential temporal variability, particularly in the period immediately following vaccination.

This study has several limitations. First, the lack of complete paired data across all planned time points necessitated the use of a quasi-longitudinal dataset for analysis. Nevertheless, the findings derived from this subset are unlikely to be substantially biased, as they were consistent with those observed in the full analysis set. Second, the study cohort consisted predominantly of men, as participants were recruited from military personnel at the Air Transportation Base in Prague. Consequently, women were underrepresented, limiting the generalizability of the results to female populations. Third, although both vaccines used in this study were mRNA-based, they may have exerted differential effects on the observed increase in NT-proBNP levels. As more than 80% of participants received only one of these vaccines, our findings primarily relate to vaccination with Comirnaty. The small number of individuals vaccinated with Spikevax did not allow for separate vaccine-specific analyses. Finally, the relatively small sample size may have reduced the statistical power to detect whether the observed increase in NT-proBNP within 14 days of the second vaccine dose was influenced by any of the assessed covariates. Future studies involving larger and more diverse populations will be essential to further clarify these associations.

5. Conclusions

In conclusion, this study demonstrated a transient, subclinical elevation in NT-proBNP following mRNA COVID-19 vaccination, particularly after the second dose. While not necessarily indicative of clinical cardiovascular complications, this biomarker response may reflect transient myocardial stress and warrants further investigation in broader populations, particularly among individuals with established cardiovascular disease. These findings may also provide a rationale for applying similar biomarker-based approaches to assess the safety of vaccines against other infectious diseases.

CRediT authorship contribution statement

Pavel Dlouhý: Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Marek Petráš:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Ivana Králová Lesná:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Roman Máčalík:** Writing – review & editing, Resources, Methodology, Conceptualization. **Jan Polák:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Antonín Jabor:** Writing – review & editing, Validation, Resources, Investigation, Data curation. **Vanda Filová:** Writing – review & editing, Validation, Resources, Investigation, Data curation. **Jan Piťha:** Writing – review & editing, Methodology, Funding

acquisition, Conceptualization. **Oliver Kuchař:** Writing – review & editing, Methodology, Conceptualization. **Jozef Rosina:** Writing – review & editing, Project administration, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128535.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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