Original article

Trends in occurrence of takotsubo syndrome and association with SARS-CoV-2 infection and COVID-19 vaccination

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Aims Takotsubo syndrome (TTS) is a serious heart disease associated with significant morbidity and mortality. TTS has been related to SARS-CoV-2 infection and COVID-19 vaccine; however, the current data are scarce. We aimed to examine the associations between SARS-CoV-2 infection and its vaccine with TTS.

Methods We conducted a nested case–control study in a cohort of 3 237 909 adults from the largest healthcare provider in Israel. Patients were followed from 1 March 2020 until 31 December 2021 for the occurrence of TTS. Ten randomly selected controls were matched to each case of TTS on age, sex, and duration of follow-up. Exposure to SARS-CoV-2 infection and COVID-19 vaccine in the prior 30 days was assessed in cases and controls.

Results During the follow-up 144 patients developed TTS and were matched to 1440 controls. The mean age of cases and their matched controls was 71.4 ± 12 years, and 136 (94.4%) of them were women. Conditional logistic regression analysis showed that SARS-CoV-2 infection and COVID-19 vaccine were not associated with an increased risk of TTS; odds ratio (OR) = 2.04 [95% confidence interval (CI), 0.50–8.2] and 0.87 (0.49–1.54), respectively. The absolute number of TTS cases in the prepandemic period (March–December 2018–2019) was 82 in 2018 and 80 in 2019. The number of TTS cases decreased to 56 during the corresponding period of 2020 (first pandemic year) and increased back to 81 in 2022.

Conclusion No significant association was found between SARS-CoV-2 infection or COVID-19 vaccination and TTS occurrence.

J Cardiovasc Med 2023, 24:815–821

Keywords: COVID-19, COVID-19 vaccination, SARS-CoV-2, stress-induced cardiomyopathy, takotsubo syndrome

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Received 18 April 2023 Revised 1 June 2023
Accepted 14 July 2023

Introduction

The coronavirus disease of 2019 (COVID19) pandemic significantly affected public health, resulting in increased economic, social, and psychological stress in people's lives worldwide.[1–3]

Takotsubo syndrome (TTS), known as stress-induced cardiomyopathy, is a unique pathology that mimics acute coronary syndrome (ACS). TTS pathophysiology is not fully understood but several stressors, including emotional (negative or positive emotional stress), psychological, social, and physical may precipitate TTS resulting from myocardial catecholamine overload, inducing myocardial stunning.[4–6] Although thought to be benign, TTS has a prognosis similar to ACS and can be life-threatening, with substantial morbidity and mortality.[6,7]

Different cardiac involvements were reported in association with SARS-CoV-2 infection during the pandemic.[8–11] Occurrence of TTS during the COVID-19 pandemic was reported in three different contexts: as a direct complication of the infection; as an outcome secondary to economic stress, psychological burden of quarantine and social isolation; and recently as a complication of COVID-19 vaccine administration.[8,12–14]

Several descriptive studies, mostly case reports, case series, and systematic reviews of case reports, suggested an association between SARS-CoV-2 and TTS.[15–19] Other studies revealed that the incidence of TTS in nonactively infected individuals with SARS-CoV-2 was increased during the pandemic compared with prepandemic periods, implying a possible connection with economic, social, and psychological stressors.[16,20–22] Several reports have described TTS occurrence following COVID-19 vaccine administration. Yet, little is known regarding any association between the two.[14,23,24]

In the present population-based study, we sought to assess TTS morbidity dynamics during the pandemic, and to examine the associations between SARS-CoV-2 infection and COVID-19 vaccination with TTS, using real world data from the largest healthcare provider in Israel.

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DOI:10.2459/JCM.0000000000001541

Materials and methods

The study was approved by the institutional review board of Lady Davis Medical Center and Data Utilization committee of Clalit Health Services (CHS). Owing to the retrospective nature of the study, a waiver of informed consent was granted by the institutional review board. The current study followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data source

This study is based on data from two sources: the CHS database and the COVID-19 database. CHS provides inclusive healthcare for more than half of the Israeli population (~4.7 million). Healthcare coverage in Israel is mandatory according to the National Health Insurance Law (1995) and is provided by four groups akin to not-for-profit health maintenance organizations (HMOs), which are charged with providing a broad package of benefits stipulated by the government. The four HMOs are both healthcare insurers and providers, thus financing and supplying health services. Membership in a specific HMO is voluntary and members can freely switch to another HMO. All members of the different HMOs have similar health insurance plans and similar access to health services, including low medications copayment. CHS maintains a database that receives data from multiple sources including records of primary care physicians, community specialty clinics, hospitalizations, laboratories, and pharmacies. A registry of chronic disease diagnoses is compiled from these data sources. Diagnoses are captured in the registry by diagnosis-specific algorithms, employing International Classification of Diseases Ninth revision (ICD-9) code reading, laboratory test results and disease-specific drug usage. A record is kept of the data sources and dates used to establish the diagnosis, with the earliest recorded date from any source considered to be the defining date of diagnosis. Designed for purposes of administrative and clinical management, the database is available for clinical studies.

Since the start of the COVID-19 pandemic, the Israeli Ministry of Health (MOH) has been collecting all COVID-19-related data and activities in a national database. Among these activities are vaccination dates, active surveillance for all laboratory-confirmed SARS-CoV-2 infections with mandatory daily reporting of PCR results, and active surveillance of COVID-19-associated hospitalizations by daily updates from all hospitals, including daily status definitions during hospitalization. The collected data are transferred daily to the healthcare providers.

The cohort

The study cohort consisted of all CHS adult members aged 16 years or older and alive on 1 March 2020 (cohort entry date), the start of the pandemic in Israel. The cohort participants were followed until reaching the study outcome (TTS occurrence), death, or end of follow-up date on 31 December 2021, whichever came first.

Identification of cases and controls

All cases with TTS diagnosis during the study period were captured from hospitalization diagnosis of the CHS database by ICD-9 code (429.83). The date of TTS diagnosis was defined as the index date. We used a density-based sampling method to select controls from the source population.[25] Individuals in the cohort who were not diagnosed with TTS and were alive on the index date of each case constituted the risk set for the case. For each case of TTS, we randomly selected 10 controls from among the cohort participants in the risk set. The controls were matched to the cases by the same age, sex, and duration of follow-up. We set up the same index date for controls of their matching case; matching on calendar time allowed us to control for trends over time in the exposures to SARS-CoV-2 infection, COVID-19 vaccine and other exposures related to TTS.

Exposure data

The association of TTS was examined with both prior administration of COVID-19 vaccine (BNT162b2), and prior SARS-CoV-2 infection, defined as the documentation of positive PCR test for SARS-CoV-2 before the index date, based on data from the MOH national COVID-19 database. In the main analysis, both examined exposures were ascertained during the 30 days prior to the index date. This was done under the assumption that TTS is unlikely to be related to vaccine administration or SARS-CoV-2 infection beyond 30 days after the exposure. In addition, a sensitivity analysis was performed in which both examined exposures were ascertained during the 60 days prior to the index date.

Covariates

For each participant we extracted sociodemographic data including age, sex, population sector (Arab vs. Jews), and socioeconomic status (low, middle, high) that were based on the SES scores of the clinic neighborhood as defined by the Israeli Central Bureau of Statistics. In addition, participants' comorbidities were extracted, including history of cerebrovascular accident (CVA), diabetes, smoking, ischemic heart disease (IHD), chronic heart failure (CHF), hypertension, chronic renal failure, and liver disease.

For patients with TTS additional data were extracted, including preexistence of emotional or physical stress, psychiatric disorder, neurological disorder, coronary artery stenosis $\geq$70%, history of percutaneous coronary

intervention (PCI), ST-segment depression and prolonged QTc interval on the electrocardiogram, hypotension, arrhythmia, ejection fraction (EF) and wall motion abnormality on echocardiography and maximal serum levels of troponin, creatinine kinase and N-terminal pro b-type natriuretic peptide (NT-proBNP). Furthermore, a calculation of the interTAK diagnostic score was made using the extracted data. The interTAK diagnostic score is used to assist in differentiating the diagnosis of TTS from ACS. The score is based on data from the International Takotsubo Registry and includes seven clinical variables. A score of $\geq$50 points suggests a diagnosis of TTS with 95% accuracy, while a score of $\leq$31 points is associated with a similar accuracy for ACS diagnosis.[26] Of note, some clinical variables were missing in the hospitalization records, hence those missing variables were considered as having 'not occurred' in the score calculation.

In addition, we extracted all cases of TTS occurring between March and December, both in 2018 and 2019 (prepandemic period) and compared them to TTS cases occurring in the corresponding time period in 2020 and 2021 (pandemic period), in order to evaluate the trend in TTS occurrence before and during the epidemic.

Statistical analysis

Continuous variables are summarized as means $\pm$ standard deviation; categorical variables are presented as numbers and proportions. Comparison of baseline demographical and clinical characteristics between cases and controls was performed using conditional logistic regression. Conditional logistic regression models were also used to examine the association between TTS with SARS-CoV-2 infection and COVID-19 vaccine, and to estimate the odds ratio (OR) with 95% confidence interval (CI). To account for misclassification of TTS we preformed a sensitivity analysis that was restricted to patients with an InterTAK diagnostic score of $>$ 31. This analysis included 127 patients (3 patients with missing data and 14 with a score of $\leq$31 were excluded).

A *P*-value of $<$0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 28.0 (IBM, New York, NY) and SAS version 9.3 software (Cary, NC).

Results

A total of 3 237 909 adults aged 16 years or older were identified in the CHS database as being alive on 1 March 2020 (start of the pandemic in Israel) and constituted the study cohort. Within this cohort 144 individuals were diagnosed with TTS during the follow-up period. The interTAK diagnostic score was calculated for 141 of the 144 patients who developed TTS during the follow-up period. The remaining three patients had missing data for all the components of the interTAK score. The mean score was 47.4 $\pm$ 12.5. The score was higher than 50 points among 50 (34.7%) patients, between 31 and 50 points among 77 (53.5%) patients, and $\leq$31 points among 14 (9.7%) patients. Coronary angiography, which was performed on all 14 patients with a score of $\leq$31, revealed no significant coronary artery lesion (defined as obstruction $\geq$ 70%) and no need for percutaneous intervention.

TTS cases were matched to 1440 randomly selected controls by age and sex, using a ratio of 1 : 10. The mean age of cases and their matched controls on the index date was 71.4 $\pm$ 12 years, and 94.4% of them were women (Table 1). The two groups were comparable in terms of ethnicity and socioeconomic status. No significant differences between the two groups were found regarding the prevalence of diabetes mellitus, smoking, CHF, hypertension, CVA, chronic renal failure and liver disease. The prevalence of IHD was higher in the TTS group (23.6% vs. 12.6%, $P < 0.001$) (Table 1).

Selected clinical, electrocardiographic, and laboratory findings were extracted from hospital records of the 144 patients who developed TTS during the follow-up period and are reported in Table 2; emotional stress was documented in 33 out of 104 patients (22.9%), physical stress in 38 out of 135 patients (26.4%), psychiatric disorder in 18 out of 138 patients (12.5%), absence of ST-segment depression on electrocardiography leads (other than aVR) in 120 out of 134 patients (83.3%), neurologic disorder or pheochromocytoma in 25 out of 137 patients (17.4%) and QTc prolongation in 34 out of 80 patients (23.6%). The mean peak serum troponin T level during hospitalization was 1146.2 ng/L and the mean peak NT-Pro BNP level during hospitalization was 6691.8 pg/ml. Thirteen patients had missing data regarding troponin levels and 82 patients had missing data regarding NT-Pro BNP levels. The predominant pattern of wall motion abnormality on echocardiogram was apical (117/144), whereas 11 patients had midventricular, 7 patients had basal, and 6 patients had other focal patterns of wall motion abnormality.

Overall, two (1.4%) cases and nine (0.6%) controls had SARS-CoV-2 infection in the preceding 30 days. A total of 13 (9%) cases and 148 (10.3%) controls had received COVID-19 vaccine in the preceding 30 days. In a conditional logistic analysis, SARS-CoV-2 infection was not associated with a significant increased risk of TTS: OR, 2.04 (95% CI, 0.50–8.20). Similarly, COVID-19 vaccination was not associated with an increased risk of TTS: OR, 0.87 (95% CI, 0.49–1.54). The results were similar in a sensitivity analysis that examined exposure to SARS-CoV-2 infection and COVID-19 vaccine in the prior 60 days

Table 1 Sociodemographic and clinical characteristics of patients with takotsubo syndrome and their matched controls

	Cases ($n=144$)	Controls ($n=1440$)	*P*-value
Age	71.4 ± 12.0	71.4 ± 12.0	0.995
Female	136 (94.4)	1360 (94.4)	NA
Ethnicity			0.263
Jews	129 (89.6%)	1243 (86.3%)	
Arabs	15 (10.4%)	197 (13.7%)	
Socioeconomic status			0.089
Low	56 (38.9%)	429 (29.9%)	
Medium	51 (35.4%)	648 (45.0%)	
High	36 (25.0%)	357 (24.8%)	
Missing	1 (0.7%)	6 (0.4%)	
Diabetes	37 (25.7%)	421 (29.2%)	0.359
Smoking	53 (36.8%)	436 (30.3%)	0.103
Ischemic heart disease	34 (23.6%)	181 (12.6%)	<0.001
Congestive heart failure	11 (7.6%)	66 (4.6%)	0.100
Hypertension	85 (59.0%)	761 (52.8%)	0.110
Cerebrovascular accident	15 (10.4%)	113 (7.8%)	0.282
Chronic renal failure	11 (7.6%)	76 (5.3%)	0.224
Liver disease	0	29 (2.0%)	0.267

as well as after adjustment for IHD (Table 3). Furthermore, the results were consistent in a sensitivity analysis that was restricted to patients with InterTAK score of >31 (Table 4).

Ninety-day all-cause mortality among patients with TTS was 8.9% in those diagnosed during 2020 and 9.1% in those diagnosed in 2021 (*P*-value, 0.974). The number of new TTS cases between 1 March and 31 December during the years 2018, 2019, 2020 and 2021 was 82, 80, 56 and 81 cases, respectively (Fig. 1).

Discussion

Our study evaluated TTS occurrence before and during the COVID-19 pandemic in Israel and possible associations between TTS occurrence, SARS-CoV-2 infection and COVID-19 vaccination. We found no statistically

Table 2 Selected clinical, electrocardiographic, and laboratory findings of the patients who developed takotsubo syndrome during the follow-up period ($n=144$)

Variables	Frequency (%)
Clinical and electrocardiographic findings[a]	
Emotional stress	33/104 (22.9%)
Physical stress	38/135 (26.4%)
Psychiatric disorder	18/138 (12.5%)
Absence of ST-segment depression on electrocardiography leads (other than aVR)	120/134 (83.3%)
Neurologic disorder or pheochromocytoma	25/137 (17.4%)
QTc prolongation	34/80 (23.6%)
InterTAK diagnostic score[b]	
Mean score	47.4 ± 12.5
Score ≥50 points	50 (34.7%)
31 < Score < 50	77 (53.5%)
Score ≤ 31	14 (9.7%)
Laboratory findings	
Mean of peak troponin[c]	1146.2 ng/l
Mean of peak N-terminal pro B-type natriuretic peptide (NT-Pro BNP)[c]	6691.8 pg/ml
Pattern of wall motion abnormality on echocardiography	
Apical	117/144 (81.25%)
Midventricular	11/144 (7.64%)
Basal	7/144 (4.86%)
Focal	6/144 (4.17%)

[a] The remaining patients who are not included in the count had missing data. [b] The score was calculated for 141/144 patients who developed takotsubo syndrome. The remaining three patients had missing data for all the components of the InterTAK diagnostic score. Coronary angiography, which was performed on all 14 patients with a score of ≤31, revealed no significant coronary artery lesion (defined as obstruction ≥ 70%) and no need for percutaneous intervention. [c] Thirteen patients had missing data regarding troponin levels and 82 had missing data regarding NT-Pro BNP levels.

Table 3 Odds ratios (ORs) for the association between SARS-CoV-2 infection and COVID-19 vaccine with takotsubo syndrome

					Adjusted*	
Exposure variable	**Cases ($n=144$)**	**Controls ($n=1440$)**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Exposure in the prior 30 days						
SARS-CoV-2 infection	2 (1.4%)	9 (0.6%)	2.04 (0.50–8.20)	0.318	2.10 (0.52–8.50)	0.294
COVID-19 vaccine	13 (9%)	148 (10.3%)	0.87 (0.49–1.54)	0.637	0.88 (0.50–1.56)	0.666
Exposure in the prior 60 days						
SARS-CoV-2 infection	2 (1.4%)	13 (0.9%)	1.49 (0.37–6.00)	0.578	1.48 (0.37–6.00)	0.579
COVID-19 vaccine	24 (16.7%)	263 (18.3%)	0.90 (0.58–1.40)	0.643	0.90 (0.58–1.39)	0.622

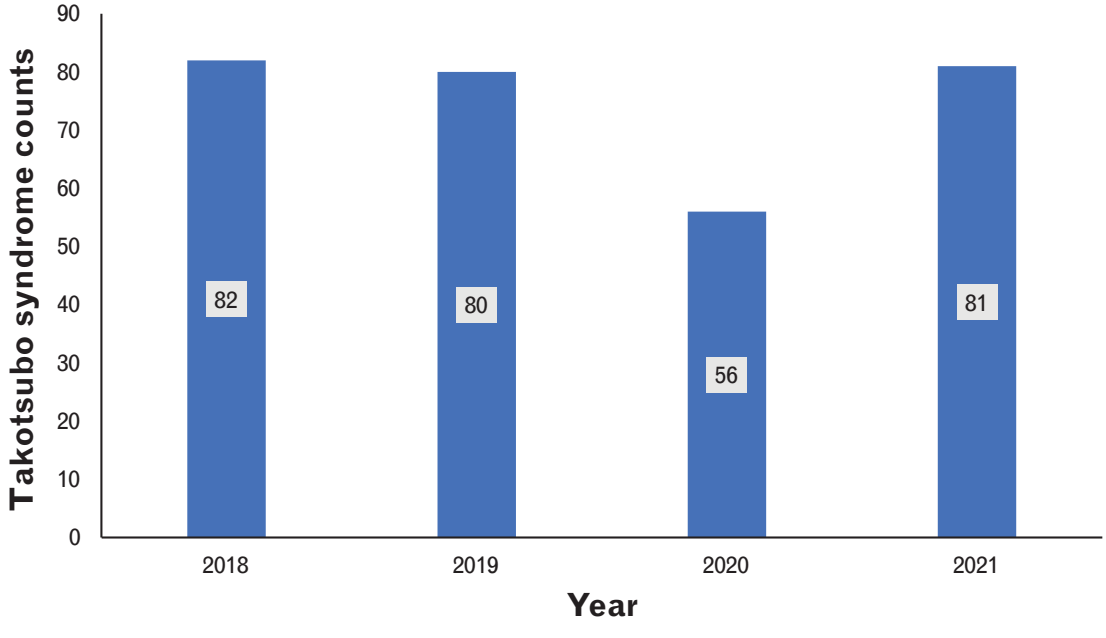
* Adjustment for IHD.

Table 4 Odds ratios (ORs) for the association between SARS-CoV-2 infection and COVID-19 vaccine with takotsubo syndrome in the prior 30 and 60 days **among patients with InterTAK score of >31**

					Adjusted*	
Exposure variable	**Cases ($n=127$)**	**Controls ($n=1270$)**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Exposure in the prior 30 days						
SARS-CoV-2 infection	2 (1.6%)	9 (0.7%)	2.04 (0.50–8.20)	0.319	2.10 (0.52–8.50)	0.297
COVID-19 vaccine	12 (9.4%)	135 (10.6%)	0.88 (0.49–1.60)	0.678	0.89 (0.49–1.61)	0.699
Exposure in the prior 60 days						
SARS-CoV-2 infection	2 (1.6%)	12 (0.9%)	1.61 (0.30–6.50)	0.503	1.58 (0.39–6.40)	0.519
COVID-19 vaccine	20 (15.7%)	241 (19.0%)	0.90 (0.50–1.31)	0.388	0.81 (0.50–1.30)	0.382

* Adjustment for IHD.

Fig. 1



Absolute number of patients with takotsubo syndrome occurring between March and December in the prepandemic period (2018 and 2019) and in the pandemic period (2020 and 2021).

significant association between SARS-CoV-2 infection or COVID-19 vaccination and TTS occurrence. The results were consistent in sensitivity analyses. In addition, compared with 2018 and 2019 (prepandemic period), we observed a decrease in the absolute number of TTS events in the first year of the pandemic (2020) that increased back to the prepandemic levels in 2021.

The decrease in TTS occurrence during 2020 and the fact that the absolute number of events remained unchanged during 2021 is in disagreement with previous studies.[12,13,21,22] Jabri *et al.*[22] evaluated two cohorts of ACS patients admitted to two hospitals in Cleveland, Ohio. The first cohort included 1656 patients, admitted during four prepandemic time periods (January and February 2019 and 2020, March and April 2018 and 2019), and the second cohort included 258 patients admitted during the pandemic (March and April 2020). They found an increased incidence of TTS per 100 ACS cases during March and April 2020 compared with prepandemic periods. Yet, their study sample was relatively small and represents only two hospitals in a single state in the United States during a considerably short period of time (2 months). Moreover, the comparison they made is not a direct parallel group comparison as we did in our study. In addition, it is plausible to estimate that people with ACS may have avoided visiting medical facilities resulting in a possible sample bias. Shah *et al.*[21] and Moady and Atar[12] suggested in their systematic review and state-of-the-art review (respectively) an increased rate of TTS diagnosis during the pandemic period. However, these reviews included only descriptive studies, mostly case reports and case series. Barbieri *et al.*[13] found 11 cases of TTS between February and May 2020 and only 3 cases in the corresponding period in 2019. However, the small sample size, short duration of the follow-up and the specific period they analyzed might have affected their results. Our findings are partially in alignment with those of Delmas *et al.*[27] They observed a relatively stable incidence of TTS between March and April 2020 in comparison to the same period in previous years, while we observed a decrease during 2020. It is plausible to assume that the decrease in the number of cases of TTS in our study is due to the general decline in hospital referrals which was observed at the beginning of the pandemic.[28–31] Notably, they had a small sample size and observed only a short and specific period during the pandemic while we evaluated a significantly longer period.

Contrary to our findings, several studies suggested possible association between SARS-CoV-2 infection and TTS.[15,16,18] Generally, approximately 2% of the patients admitted to hospitals with suspected ACS are diagnosed eventually with TTS.[32] Guglin *et al.*[15] presented in their systematic review a higher TTS proportion of approximately 36% (33 cases) among COVID-19 patients presenting with any myocardial involvement. Chang *et al.*[16] reported 123 TTS cases (between April 2020 and August 2021), of whom 82 (66.7%) had simultaneous SARS-CoV-2 infection. In a report of 12 TTS cases that developed following SARS-CoV-2 infection, the time that elapsed between the infection and the TTS diagnosis ranged between 3 and 14 days.[18]

Several reports suggested a potential association between COVID-19 vaccination and TTS during the pandemic.[14,23,24] Fazlollahi *et al.*[14] and Khalid *et al.*[24] presented a total of 14 cases (combined) of TTS following COVID-19 vaccination, occurring within 15 min to 4 days. Nonetheless, out of those 14 cases presented, only 6 had received the same vaccination as we evaluated (BNT162b2).

Strengths and limitations

To the best of our knowledge our study is the first population-based analytical study with parallel comparative groups, while previous publications on this topic were based primarily on descriptive reports. Even though case reports are an important tool for detecting novel findings, they also have significant limitations, including lack of a control group, small numbers of patients, limited generalizability, and publication bias. The present study has several limitations; recent case reports described possible occurrence of TTS as part of long COVID-19 syndrome.[33,34] However, our study evaluated TTS occurrence following the infection and vaccination within 30 and 60 days and thus did not fully address long COVID-19 syndrome. As with any retrospective study that is based on data from a clinical and administrative database, a possible limitation may be related to the completeness and the accuracy of data. In addition, this nested case–control study is observational in nature, hence residual confounding factors remain of concern.

Conclusion

TTS occurrence during the pandemic decreased initially and later returned to the prepandemic level. We found no significant association between SARS-COV-2 infection, COVID-19 vaccination and TTS occurrence.

Conflicts of interest

There are no conflicts of interest.

No financial support was received for this research.

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