

Clinical Investigation

Incidence and Impact of Takotsubo Syndrome in Hospitalized Patients With COVID-19

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Abstract

Background: Takotsubo syndrome has been reported in patients with COVID-19, although minimal data are available. This investigation assessed the incidence and impact of takotsubo syndrome on patients hospitalized with COVID-19.

Methods: A retrospective cohort study was conducted using *International Statistical Classification of Diseases, Tenth Revision*, codes to identify patients with a primary diagnosis of COVID-19 with or without takotsubo syndrome in the National Inpatient Sample 2020 database. Outcomes between groups were compared after propensity score matching for patient and hospital demographics and comorbidities.

Results: A total of 211,448 patients with a primary diagnosis of COVID-19 were identified. Of these, 171 (0.08%) had a secondary diagnosis of takotsubo syndrome. Before matching, patients with COVID-19 and takotsubo syndrome, compared with patients without takotsubo syndrome, were older (68.95 vs 64.26 years; $P < .001$); more likely to be female (64.3% vs 47.2%; $P < .001$); and more likely to have anxiety (24.6% vs 12.8%; $P < .001$), depression (17.5% vs 11.4%; $P = .02$), and chronic obstructive pulmonary disease (24.6% vs 14.7%; $P < .001$). The takotsubo syndrome group had worse outcomes than the non-takotsubo syndrome group for death (30.4% vs 11.1%), cardiac arrest (7.6% vs 2.1%), cardiogenic shock (12.9% vs 0.4%), length of hospital stay (10.7 vs 7.5 days), and total charges (\$152,685 vs \$78,468) (all $P < .001$). After matching and compared with the non-takotsubo syndrome group ($n = 508$), the takotsubo syndrome group ($n = 170$) had a higher incidence of inpatient mortality (30% vs 14%; $P < .001$), cardiac arrest (7.6% vs 2.8%; $P = .009$), and cardiogenic shock (12.4% vs 0.4%; $P < .001$); a longer hospital stay (10.7 vs 7.6 days; $P < .001$); and higher total charges (\$152,943 vs \$79,523; $P < .001$).

Conclusion: Takotsubo syndrome is a rare but severe in-hospital complication in patients with COVID-19.

Keywords: COVID-19; takotsubo cardiomyopathy; mortality

Introduction

COVID-19 had affected more than 621 million individuals by October 2022.¹ Infection with the etiologic virus SARS-CoV-2 can cause various complications, including those in the cardiovascular system. In more than 20% of hospitalized patients with COVID-19, cardiac troponin levels are elevated, suggesting acute

Citation: Li P, Shi A, Lu X, Li C, Cai P, Teng C, Wu L, Shu Y, Pan S, Dixon RAF, Liu Q, Wang B. Incidence and impact of takotsubo syndrome in hospitalized patients with COVID-19. *Tex Heart Inst J*. 2024;51(1):e238309. doi:10.14503/THIJ-23-8309

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cardiac injury.² Other COVID-19–related cardiovascular complications include myocardial infarction, cardiac arrest, atrial fibrillation, myocarditis, and pericarditis.^{3–6}

During the COVID-19 pandemic, takotsubo syndrome (TTS) was widely reported.^{7–9} Takotsubo syndrome is an acute transient heart failure syndrome characterized by transient systolic ventricular dysfunction accompanied by wall-motion abnormalities.^{10,11} It was traditionally considered rare and benign, but its hospital and long-term mortality rates are similar to those of acute coronary syndrome.¹² Although the coexistence of TTS and COVID-19 has been reported, the incidence of TTS and its effects on the prognosis of patients with COVID-19 are not well established.

This study aimed to assess the incidence and impact of TTS on patients hospitalized with COVID-19 using the latest data from the National Inpatient Sample (NIS) database.

Patients and Methods

Data Sources

The association between COVID-19 and TTS outcomes was examined by extracting data from the NIS 2020 database, which comprises more than 7 million hospital stays each year. *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* codes were used to classify in-hospital diagnoses since 2016. Starting in 2020, hospitalizations related to COVID-19 have been identified by any listed *ICD-10-CM* diagnosis code of U071 (COVID-19) on the discharge record.¹³ Supplemental Table I shows the *ICD-10-CM* codes used in this study. Institutional review board approval was not required for this study because data in the NIS database are deidentified.

Study Population and Covariates

All patients in the 2020 NIS database with the primary diagnosis of COVID-19 were studied. Patients who had no discharge status were excluded. Patient and hospital demographics (age; sex; race; geographic location; household income; primary payer; and hospital type, region, and size by number of beds); common cardiovascular comorbidities (eg, smoking, hypertension); and other reported risk factors for TTS (including hyperlipidemia,¹⁴ chronic obstructive pulmonary disease,^{15,16} anxiety,¹⁷ depression,¹⁸ obesity,¹⁹ diabetes,²⁰ and chronic kidney disease²¹) were selected as covariates.

Key Points

- Takotsubo syndrome complicates 0.08% of cases of patients hospitalized with COVID-19.
- Patients with both COVID-19 and TTS have worse in-hospital outcomes than patients without TTS.
- Takotsubo syndrome is a rare, severe in-hospital complication in patients with COVID-19.

Abbreviations and Acronyms

AKI	acute kidney injury
ICD-10-CM	<i>International Classification of Diseases, Tenth Revision, Clinical Modification</i>
LOS	length of stay
NIS	National Inpatient Sample
TTS	takotsubo syndrome

Patients with COVID-19 were then allocated into 1 of 2 groups: those with TTS and those without TTS. The detailed patient selection process is shown in Figure 1. The impact of COVID-19 on TTS was assessed by analyzing a group of patients with TTS but without COVID-19.

Outcomes

The main outcomes of interest were in-hospital mortality rate and severe in-hospital complications, including cardiogenic shock; cardiac arrest; ventricular arrhythmias (ventricular tachycardia, ventricular flutter, and ventricular fibrillation); acute respiratory failure; acute kidney injury (AKI); and mechanical ventilation. Hospital length of stay (LOS) and total admission costs were also examined.

Statistical Analysis

Mean (SD) values were used to express continuous variables, and percentages were used to express categorical variables. Continuous variables were analyzed using the *t* test, and categorical variables were analyzed using χ^2 tests. $P \leq .05$ was considered significant. All data analysis and statistical processes were performed using R, version 3.6.1, statistical software (R Foundation for Statistical Computing).

Selection bias was reduced in the unmatched cohort by conducting a propensity score matching analysis, matching patients in the TTS and the non-TTS groups in a 1:3 target ratio. A multivariate logistic regression model was adjusted for patient and hospital demographics (age; sex; race; geographic location; household income; primary payer; and hospital type, region, and

TABLE I. Baseline Characteristics of the Matched Cohort

Variable	Patients with COVID-19 without TTS ^a (n = 508)	Patients with COVID-19 and TTS ^a (n = 170)	P value
Age, mean (SD), y	68.93 (15.89)	68.94 (12.99)	.99
Sex, No. (%)			.62
Male	195 (38.4)	61 (35.9)	
Female	313 (61.6)	109 (64.1)	
Unknown	0 (0.0)	0 (0.0)	
Race, No. (%)			.85
Asian or Pacific Islander	22 (4.3)	8 (4.7)	
Black	60 (11.8)	22 (12.9)	
Hispanic	89 (17.5)	25 (14.7)	
Native American	0 (0.0)	0 (0.0)	
White	319 (62.8)	107 (62.9)	
Other	12 (2.4)	4 (2.4)	
Unknown	6 (1.2)	4 (2.4)	
Patient location, No. (%)			.99
"Central" counties of metropolitan areas with populations of ≥1 million people	172 (33.9)	60 (35.3)	
"Fringe" counties of metropolitan areas with populations of ≥1 million people	139 (27.4)	42 (24.7)	
Counties in metropolitan areas with populations of 250,000-999,999 people	77 (15.2)	27 (15.9)	
Counties in metropolitan areas with populations of 50,000-249,999 people	46 (9.1)	15 (8.8)	
Micropolitan counties	42 (8.3)	14 (8.2)	
Nonmetropolitan or micropolitan counties	28 (5.5)	11 (6.5)	
Not reported	4 (0.8)	1 (0.6)	
Mean household income, No. (%)			.87
\$1-\$42,999	115 (22.6)	40 (23.5)	
\$43,000-\$53,999	169 (33.3)	55 (32.4)	
\$54,000-\$70,999	144 (28.3)	43 (25.3)	
\$71,000 or more	75 (14.8)	30 (17.6)	
Unknown	5 (1.0)	2 (1.2)	
Primary payer, No. (%)			.49
Medicare	338 (66.5)	111 (65.3)	
Medicaid	56 (11.0)	13 (7.6)	
Private insurance, including health maintenance organizations	93 (18.3)	35 (20.6)	
Self-pay	9 (1.8)	4 (2.4)	
No charge	0 (0.0)	0 (0.0)	
Other	12 (2.4)	7 (4.1)	
Unknown	0 (0.0)	0 (0.0)	

Continued

TABLE I. Baseline Characteristics of the Matched Cohort, continued

Variable	Patients with COVID-19 but without TTS (n = 508)	Patients with and TTS (n = 170)	P value
Hospital type, No. (%)			.98
Rural	44 (8.7)	14 (8.2)	
Urban nonteaching	75 (14.8)	26 (15.3)	
Urban teaching	389 (76.6)	130 (76.5)	
Hospital region, No. (%)			.99
Northeast	101 (19.9)	36 (21.2)	
Midwest	169 (33.3)	55 (32.4)	
South	148 (29.1)	49 (28.8)	
West	90 (17.7)	30 (17.6)	
Hospital size, by No. of beds, No. (%)			.97
Small	116 (22.8)	38 (22.4)	
Medium	103 (20.3)	36 (21.2)	
Large	289 (56.9)	96 (56.5)	
Patient comorbidities, No. (%)			
Smoking	147 (28.9)	50 (29.4)	.98
Hypertension	152 (29.9)	56 (32.9)	.52
Diabetes	202 (39.8)	69 (40.6)	.92
Hyperlipidemia	261 (51.4)	83 (48.8)	.63
Obesity	122 (24.0)	40 (23.5)	.98
Anxiety	117 (23.0)	41 (24.1)	.85
Depression	91 (17.9)	29 (17.1)	.89
Obstructive sleep apnea	33 (6.5)	10 (5.9)	.92
Chronic kidney disease	122 (24.0)	39 (22.9)	.86
Chronic obstructive pulmonary disease	122 (24.0)	41 (24.1)	.99
Anemia	157 (30.9)	49 (28.8)	.68
Cancer	21 (4.1)	6 (3.5)	.90

TTS, takotsubo syndrome.

$P \leq .05$ was considered statistically significant.

^a Total percentages may exceed 100% due to rounding.

size by number of beds) and for common cardiovascular comorbidities. This method has been used in previous studies.²² In-hospital outcomes between the groups were compared before and after covariate adjustment to demonstrate the effect of TTS on in-hospital outcomes of COVID-19.

Results

Baseline Characteristics

In the NIS database, 211,619 patients with a primary diagnosis of COVID-19 were identified: 171 (0.08%)

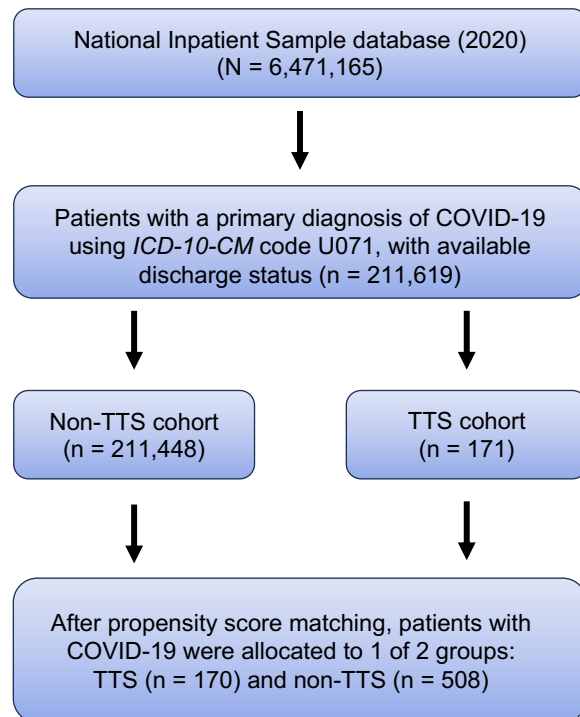


Fig. 1 Flowchart of the selection process for the final patient sample shows that inclusion criteria were applied to the National Inpatient Sample 2020 database. All eligible patients were matched 1:3 based on propensity scoring to generate the TTS vs non-TTS comparison cohorts.

ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; TTS, takotsubo syndrome.

patients with TTS and 211,448 (99.92%) patients without TTS. Baseline characteristics are provided in [Supplemental Table II](#) for the unmatched populations and in Table I for the matched cohorts.

Before propensity score matching, patients with COVID-19 and TTS were older than patients with COVID-19 who did not have TTS (mean [SD] age, 68.95 [12.95] years vs 64.26 [16.84] years; $P < .001$) and more likely to be female (64.3% vs 47.2%; $P < .001$). Patients with COVID-19 and TTS also had higher rates of comorbidities, including anxiety (24.6% vs 12.8%; $P < .001$), depression (17.5% vs 11.4%; $P = .02$), chronic obstructive pulmonary disease (24.6% vs 14.7%; $P < .001$), and anemia (29.2% vs 20.0%; $P < .001$). Hypertension was more prevalent in patients with COVID-19 who did not have TTS (41.6% vs 33.3%; $P = .03$). The distribution of smoking, diabetes, hyperlipidemia, and obesity was similar between the groups ([Supplemental Table II](#)).

Socioeconomic factors, including race, medical service primary payers, and studied hospital size, also varied substantially. There was a higher proportion of White (63.2% vs 50.9%) and Asian or Pacific Islander (4.7% vs 3.1%) patients in the TTS group than in the non-TTS group. More patients with TTS were on Medicare (65.5% vs 51.8%). Differences in hospital types were also found; midwestern hospitals had more patients with COVID-19 and TTS than they had patients with only COVID-19 (32.7% vs 23.2%), as did institutions with higher bed numbers (56.7% vs 45.5%).

Propensity score matching was used to create 2 groups matched for baseline characteristics ($P > .05$) (Table I): patients with COVID-19 but without TTS ($n = 508$) and patients with both COVID-19 and TTS ($n = 170$). All variables in this study had standardized mean differences less than 0.1 ([Supplemental Table III](#)).

In-Hospital Complications

Before matching, patients with COVID-19 and TTS had a higher incidence of complications, including cardiac arrest (7.6% vs 2.1%; $P < .001$), cardiogenic shock (12.9% vs 0.4%; $P < .001$), ventricular arrhythmia (4.1% vs 1.7%; $P = .04$), AKI (46.8% vs 25.1%; $P < .001$), and mechanical ventilation (35.1% vs 9.3%; $P < .001$), than did patients with COVID-19 who did not have TTS (Table II). These differences were also observed after propensity score matching, except in the case of ventricular arrhythmia (2.8% vs 3.5%; $P = .80$). In the matched groups, patients with COVID-19 and TTS had a higher burden of cardiac arrest (7.6% vs 2.8%; $P = .009$), cardiogenic shock (12.4% vs 0.4%; $P < .001$), AKI (46.5% vs 27.6%; $P < .001$), and mechanical ventilation (34.7% vs 10.0%; $P < .001$). The adjusted odds ratio for in-hospital complications after matching is shown in Table III. A higher incidence of TTS was found in patients who did not have COVID-19 (1.29%). Patients with TTS in the cohort without COVID-19 had a lower incidence of the following in-hospital outcomes: cardiac arrest (4.29%), cardiogenic shock (7.04%), ventricular arrhythmia (6.99%), AKI (25.21%), acute respiratory failure (32.11%), and mechanical ventilation (17.73%) ([Supplemental Table IV](#)).

Mortality, LOS, and Total Cost

In the unmatched cohort (Table II), patients with COVID-19 and TTS had a higher rate of in-hospital mortality than patients with COVID-19 only (30.4% vs 11.1%; $P < .001$) as well as a longer mean

TABLE II. In-Hospital Outcomes

Variable	Unmatched cohort			Propensity-matched cohort			Standardized mean difference
	Patients with COVID-19 without TTS (n = 211,448)	Patients with COVID-19 and TTS (n = 171)	P value	Patients with COVID-19 without TTS (n = 508)	Patients with COVID-19 and TTS (n = 170)	P value	
Outcomes							
Death, No. (%)	23,404 (11.1)	52 (30.4)	<.001	71 (14.0)	51 (30.0)	<.001	0.394
Cardiac arrest, No. (%)	4,473 (2.1)	13 (7.6)	<.001	14 (2.8)	13 (7.6)	.009	0.222
Cardiogenic shock, No. (%)	818 (0.4)	22 (12.9)	<.001	2 (0.4)	21 (12.4)	<.001	0.505
Ventricular arrhythmia, No. (%)	3,691 (1.7)	7 (4.1)	.04	14 (2.8)	6 (3.5)	.80	0.044
AKI, No. (%)	53,065 (25.1)	80 (46.8)	<.001	140 (27.6)	79 (46.5)	<.001	0.399
Acute respiratory failure, No. (%)	117,962 (55.8)	91 (53.2)	.55	299 (58.9)	90 (52.9)	.21	0.119
Mechanical ventilation, No. (%)	19,729 (9.3)	60 (35.1)	<.001	51 (10.0)	59 (34.7)	<.001	0.62
LOS, mean (SD), d	7.45 (8.07)	10.70 (12.95)	<.001	7.57 (7.40)	10.73 (12.99)	<.001	0.299
Total hospital-related cost, mean (SD), \$	78,468.44 (149,660.09)	152,685.12 (279,543.46)	<.001	79,523.29 (122,804.79)	152,942.81 (280,348.92)	<.001	0.339

AKI, acute kidney injury; LOS, length of stay; TTS, takotsubo syndrome.

$P \leq .05$ was considered statistically significant.

TABLE III. Adjusted Odds Ratios for In-Hospital Outcomes After Propensity Score Matching

Outcome	Odds ratio	95% CI	Control odds	Treatment odds	P value
Death	2.64	1.75-3.99	0.16	0.43	<.001
Cardiac arrest	35.66	8.27-153.83	0.00	0.14	<.001
Cardiogenic shock	2.92	1.34-6.35	0.03	0.08	<.001
Ventricular arrhythmia	1.29	0.49-3.41	0.03	0.04	.61
Acute kidney injury	2.28	1.59-3.27	0.38	0.87	<.001
Acute respiratory failure	0.79	0.55-1.12	1.43	1.13	.18
Mechanical ventilation	4.97	3.1-7.31	0.11	0.53	<.001

$P \leq .05$ was considered statistically significant.

[SD] LOS (10.70 [12.95] days vs 7.45 [8.07] days; $P < .001$) and higher mean [SD] total charges (\$152,685.12 [\$279,543.46] vs \$78,468.44 [\$149,660.09]; $P < .001$). As in the case of in-hospital complications, these differences remained significant after propensity matching. The TTS group had higher mortality rates (30.0% vs 14.0%; $P < .001$), a longer mean [SD] LOS (10.73 [12.99] days vs 7.57 [7.40] days; $P < .001$), and higher mean [SD] total charges (\$152,942.81 [\$280,348.92] vs \$79,523.29 [\$122,804.79]; $P < .001$) than the non-TTS group. Lower in-hospital mortality rates (7.31%), shorter mean [SD] LOS (6.98 [9.58] days), and lower mean [SD] total charges (\$112,881.40 [\$227,113.50]) were seen in patients without COVID-19 who had TTS (Supplemental Table IV).

Discussion

To the authors' knowledge, this is the first study of the incidence and impact of TTS in patients hospitalized with COVID-19. This study found that TTS is a rare complication in patients hospitalized with COVID-19 but that it results in higher rates of in-hospital mortality and complications (cardiac arrest, cardiogenic shock, and acute kidney failure), longer LOS, and higher hospitalization costs for this population than it does for hospitalized patients with COVID-19 who did not have TTS (Fig. 2).

The study's findings of higher rates of mortality, cardiac arrest, and cardiogenic shock in patients with COVID-19 and TTS support those seen in previous studies in which worse clinical outcomes were reported when patients with COVID-19 had increased cardiovascular risks, including hypertension, arrhythmia, and heart failure.^{23,24} These results are also in accordance with a previous case report–based study whose TTS cohort had a higher mortality rate (33.9%) than its non-TTS group (15%).²⁵ Although the exact mechanisms of the link between TTS and worse clinical outcomes in COVID-19 remain unidentified, 3 factors could be involved.²⁶ First, an overactive immune response exacerbates the progression of TTS. In SARS-CoV-2 infections, vascular leakage and endothelial cell death trigger a cytokine storm, resulting in the release of proinflammatory cytokines and chemokines into the circulatory system.²⁷ These inflammatory events hinder cardiac function and increase the risk of TTS onset and worse clinical outcomes.²⁸ Second, the cytokine storm can stimulate and enhance

signaling in the sympathetic nervous system, which could result in catecholamine-induced myocardial stunning, a predisposing factor for TTS.^{29,30} This perturbation in the neurologic system could help explain the unexpected higher mortality rate. Finally, microvascular dysfunction, a previously identified risk factor of TTS, has been seen in COVID-19 pathology, which may connect TTS with worse COVID-19 outcomes.³¹

A higher incidence of AKI was found in patients with COVID-19 and TTS. Coronary angiography, which is commonly used to diagnose TTS, may have adverse contrast-induced effects on kidney function.³² The bidirectional interconnections between the heart and the kidneys may also contribute to the onset of AKI.³³ During TTS, high levels of blood-borne catecholamines and uncontrolled stimulation of the autonomic nervous system can result in a sympathoadrenal attack on the secondary organs, such as the kidneys.³⁴

Patients with COVID-19 and TTS had higher total hospital-related costs and a longer LOS. Similar findings have been reported in patients with COVID-19 and other cardiovascular comorbidities.^{35,36} Because patients hospitalized with COVID-19 have more comorbidities and systemic inflammatory responses, TTS can complicate the overall treatment plan, which could increase the patient's LOS and related costs. The supportive care involved in treating TTS can add to the financial burden for patients with COVID-19.

Before propensity score matching, unique socioeconomic features among patients with COVID-19 and TTS were identified. The race of the group was predominantly White, which is consistent with analysis from the American Heart Association COVID-19 Cardiovascular Disease Registry.³⁷ The Asian population in the American Heart Association COVID-19 study notably had the worst cardiorespiratory severity of all races, which may explain the higher Asian and Pacific Islander ratio in the TTS group. As in the current study, the American Heart Association COVID-19 registry showed that Medicare was the major payer for patients with both COVID-19 and cardiovascular disorders. With regard to hospital size, findings from a Portuguese study³⁸ supported the current study by showing that hospitals with more beds handled higher numbers of patients and more complicated cases of COVID-19.

The present study has several strengths. This study used a nationwide database that has a large number of registries to adequately power its results. It also used propensity score matching to avoid confounding factors and to

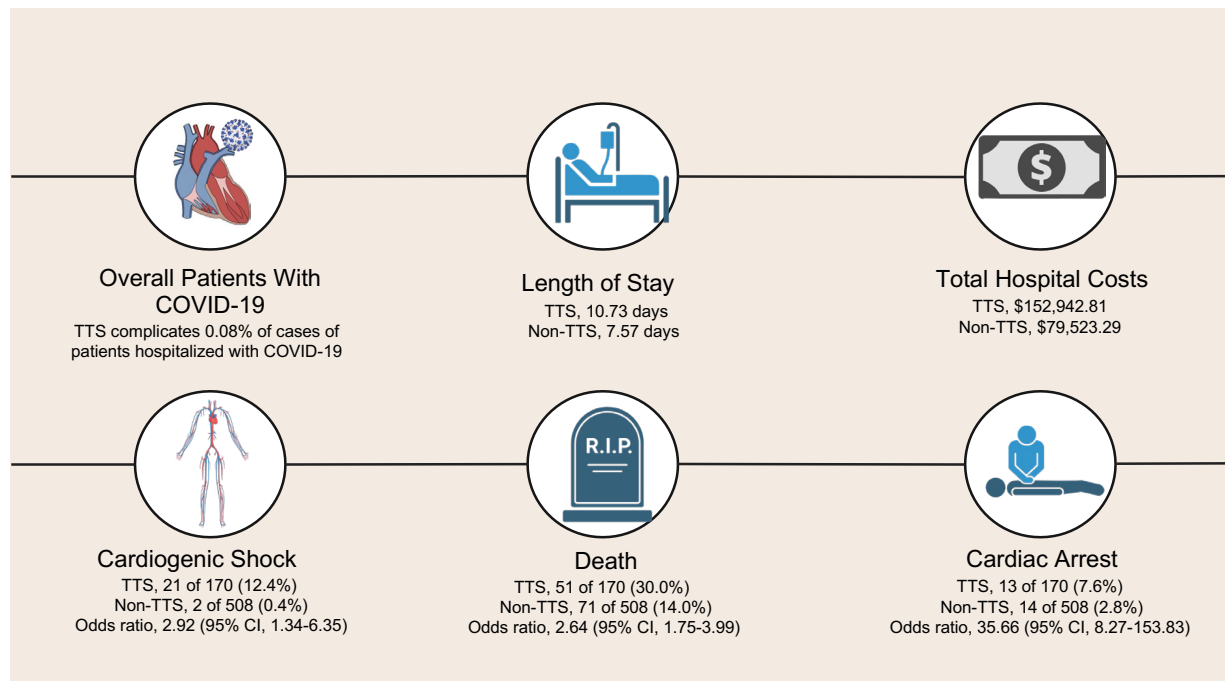


Fig. 2 This infographic shows the effects of TTS in patients hospitalized with COVID-19.

TTS, takotsubo syndrome.

minimize biased effects from baseline characteristics. The study's novel finding that morbidity and complication rates were higher in the TTS group than in the non-TTS group will help in developing considerations for the diagnosis and treatment pathway for patients with COVID-19 and different cardiovascular risks.

Study Limitations

The current study has several limitations. First, using codes from the *ICD-10-CM* to extract data may introduce bias. Second, the NIS database lacks some categories of information, such as treatment plans (eg, anti-inflammatory treatment, oxygen therapy, blood thinner prescriptions), laboratory data (including cardiac troponin levels, electrolytes, and full blood cell count), and diagnosis of disease features (symptoms, time of disease onset, and pathological presentation). The absence of this information may affect the understanding and analysis of patients with COVID-19 and TTS. Similarly, because the comorbidities in this study were assessed using *ICD-10-CM* codes in the NIS database, the severity of complications was unclear. Another limitation of this study was its potential for selection bias in covariate choice. Although the selection of covariates was based on results from the literature, the ab-

sence of specific *ICD-10-CM* codes for conditions such as history of TTS and heart failure may have led to incomplete adjustment for these factors, which may have affected the study's findings. Finally, the overlapping of clinical features between TTS and COVID-19 may result in the underdiagnosis and thus underreporting of TTS in the NIS database.

Conclusion

In this study, TTS was associated with worse in-hospital outcomes in patients with COVID-19. Patients with both COVID-19 and TTS had longer hospital LOS; higher total hospital-related costs; and higher rates of cardiac arrest, cardiogenic shock, and acute kidney failure than did patients with COVID-19 but without TTS. These findings suggest the need to optimize the current COVID-19 diagnosis plan, focusing on the early detection and prevention of TTS given the potentially atypical presentation of TTS in patients with COVID-19. The differential diagnosis of TTS and its corresponding symptoms, including shock and hemodynamic changes, should be considered in patients with COVID-19. Future studies should be

conducted to create risk stratification tools to identify high-risk patients with COVID-19 who may develop TTS and to assess whether TTS treatment can reduce in-hospital complications in patients with COVID-19. Understanding the cross-talk between the disease processes of COVID-19 and TTS may also help improve current clinical protocols and develop new therapeutics.

Article Information

Published: 6 May 2024

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Author Contributions: Pengyang Li, MD, MSc, and Ao Shi, PhD, contributed equally to the work. Pengyang Li was involved in study conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, study supervision, visualization, and the review and editing of the report. Ao Shi was involved in study conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, writing the original draft, and the review and editing of the report. Xiaojia Lu was involved in formal analysis, investigation, software, validation, and the review and editing of the report. Chenli Li was involved in formal analysis, study methodology, validation, visualization, and the review and editing of the report. Peng Cai was involved in data curation, formal analysis, investigation, study methodology, resources, software, writing the original draft, and review and editing of the report. Catherine Teng was involved in formal analysis and the review and editing of the report. Lingling Wu was involved in study investigation, methodology, validation, and the review and editing of the report. Yuan Shu was involved in procuring study resources, visualization, and the review and editing of the report. Su Pan was involved in the study investigation and the review and editing of the report. Richard A. F. Dixon was involved in the study investigation, methodology, and the review and editing of the report. Qi Liu was involved in the study conceptualization, project administration, resources, supervision, and the review and editing of the report. Bin Wang was involved in the acquisition of funds, project administration, resources, supervision, and the review and editing of the report.

Conflict of Interest Disclosure: None.

Funding/Support: None.

Acknowledgments: The authors thank Rebecca Bartow, PhD, of the Department of Scientific Publications at The Texas Heart Institute for her editorial assistance.

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