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Systematic Review/Meta-analysis

Takotsubo Syndrome in Patients With COVID-19: A Systematic Review

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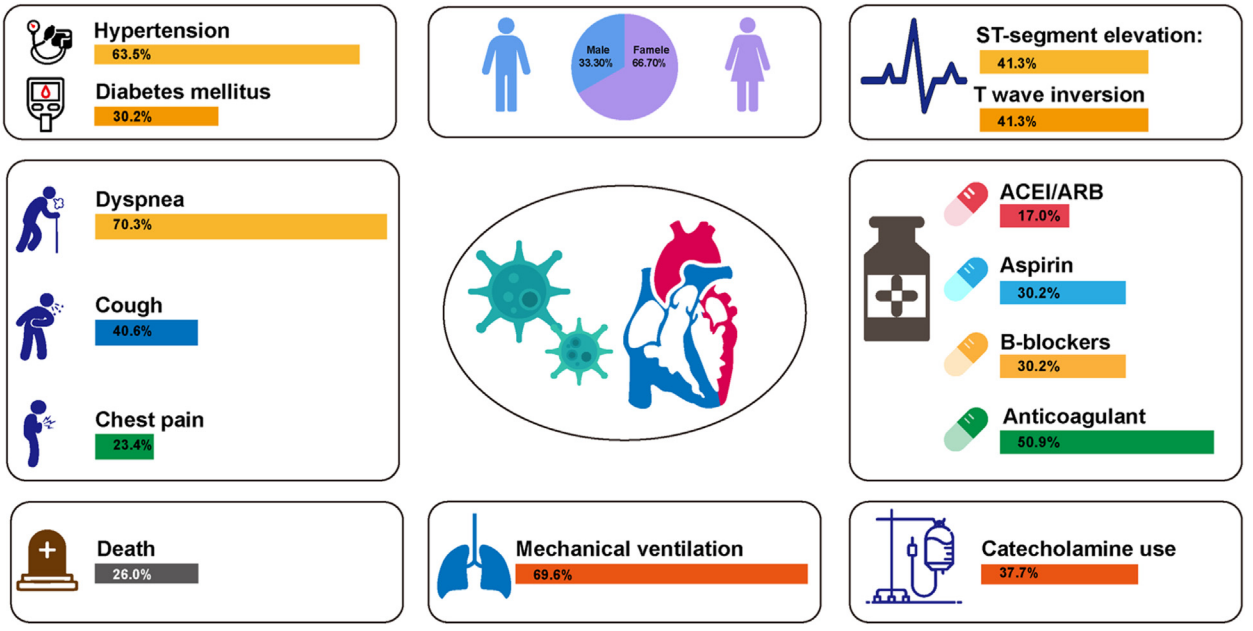

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ABSTRACT

Background: Respiratory conditions are major physical triggers of takotsubo syndrome (TTS) and portend worse outcomes. However, data on TTS in patients with coronavirus disease-2019 infection (COVID-19) are limited.

Methods: We searched PubMed, Embase, and Cochrane Library databases for case reports for the period 2019-2022 describing TTS in patients with COVID-19 pneumonia (TTS-COVID). We summarized the clinical data and outcomes and compared them to those in patients with TTS with an acute respiratory disease other than COVID-19 as a trigger (TTS-acute respiratory disease) and those with TTS with no respiratory disease (TTS-no respiratory disease).

Results: The mortality rate was higher in those with TTS-COVID (26.0%) than those with TTS-acute respiratory disease (5.7%) or TTS-no respiratory disease (4.2%; $P < 0.001$ for both). The proportion of men was higher in TTS-COVID (33.3%) than it was in TTS-no respiratory disease (9.1%; $P < 0.001$). The manifestations of TTS in COVID patients were atypical (dyspnea [70.3%] and cough [40.6%]); few had chest pain (23.4%). Cardiovascular risk factors were common in the TTS-COVID cohort, but fewer patients were on cardioprotective medications in this group than in the other 2 groups. Level of catecholamine use was higher in the TTS-COVID group (37.7%) than it was in the TTS-no respiratory disease (10.9%; $P < 0.001$) group. Apical ballooning (72.6%) was the most common TTS subtype, and basal segment type was seen in 11.0% of TTS-COVID patients.

Conclusions: COVID-19 patients who developed TTS had high mortality rates and unique features, compared with those in the TTS-acute respiratory disease group or the TTS-no respiratory disease group. Understanding the pathophysiology of TTS in COVID-19 may help prevent TTS and direct therapy in this setting.

RÉSUMÉ

Contexte : Les troubles respiratoires sont des déclencheurs physiques importants du syndrome de Takotsubo (STT) et présagent une issue funeste. Les données sur le STT chez les personnes ayant contracté la maladie à coronavirus de 2019 (COVID-19) sont néanmoins limitées.

Méthodologie : Nous avons fait une recherche dans les bases de données PubMed, Embase et Cochrane Library pour trouver des rapports de cas signalés entre 2019 et 2022 faisant état du STT chez des patients ayant contracté une pneumonie associée à la COVID-19 (STT-COVID). Nous avons synthétisé les données cliniques et les résultats pour les comparer à ceux de patients atteints du STT déclenché par une autre maladie respiratoire aiguë que la COVID-19 (STT-maladie respiratoire aiguë) et de patients atteints du STT sans maladie respiratoire (STT-sans maladie respiratoire).

Résultats : Le taux de mortalité a été plus élevé chez les patients atteints du STT-COVID (26,0 %) que chez ceux atteints du STT-maladie respiratoire aiguë (5,7 %) ou du STT-sans maladie respiratoire (4,2 %; $p < 0{,}001$ dans les deux cas). La proportion d'hommes était plus élevée dans le groupe STT-COVID (33,3 %) que dans le groupe STT-sans maladie respiratoire (9,1 %; $p < 0{,}001$). Les manifestations du STT chez les patients atteints de la COVID étaient atypiques (dyspnée [70,3 %] et toux [40,6 %]); quelques patients présentaient une douleur thoracique (23,4 %). Les facteurs de risque cardiovasculaires étaient courants dans la cohorte STT-COVID, mais les patients qui prenaient des médicaments cardioprotecteurs étaient moins nombreux dans ce groupe que dans les deux autres groupes. Le taux d'utilisation de la catécholamine était plus élevé dans le groupe STT-COVID (37,7 %) que dans le groupe STT-sans maladie respiratoire (10,9 %; $p < 0{,}001$). La ballonisation de l'apex (72,6 %) était le sous-type de STT le plus courant, et le type caractérisé par un trouble du segment basal a été observé chez 11,0 % des patients atteints du STT-COVID.

Conclusions : Les patients atteints de la COVID-19 ayant développé un STT présentaient des taux de mortalité élevés et des manifestations singulières, comparativement à ceux du groupe STT-maladie respiratoire aiguë ou du groupe STT-sans maladie respiratoire. Comprendre la physiopathologie du STT chez les patients atteints de la COVID-19 pourrait contribuer à prévenir le STT et à orienter le traitement dans ce contexte.

COVID-19 infection poses significant cardiovascular risks,[1,2] including myocarditis/myopericarditis,[3] myocardial infarction,[4] atrial fibrillation,[5] and cardiac arrest.[6,7] Myocardial injury frequently is seen in patients hospitalized with COVID-19 (~62.3%).[2] The in-hospital mortality rate is reported to be 31.7% in patients with biomarker evidence of myocardial injury and wall-motion abnormalities—a mortality rate much higher than the death rate from COVID-19 alone.[2]

Takotsubo syndrome (TTS) is a type of myocardial injury in which the presentation is characterized by acute coronary syndrome and transient global left ventricular systolic dysfunction without evidence of acute coronary artery blockage.[8] Previously thought to be rare and benign, TTS is reported to make up 0.7% to 2.2% of all acute coronary syndrome cases,[9,10] and it has a short-term mortality rate similar to that of acute myocardial infarction (4.5% to 7%),[11] and a long-term 10-year mortality rate of up to 25%.[12]

Respiratory diseases have long been known to coexist with TTS[13-16]; studies suggest that respiratory conditions are a major physical trigger of TTS and are independently associated with worse outcomes.[13-15,17] Respiratory disease not only can alter the clinical course of TTS, but also can affect the management of TTS. Data on patients with COVID-19 who develop TTS are limited,[18] and the coexistence of the 2 (TTS-COVID) is likely

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See page 824 for disclosure information.

underreported. Whether the features of TTS-COVID differ from those in cases of TTS triggered by other respiratory diseases or of TTS with no respiratory disease is unknown. In this study, we have reviewed the current literature and summarized the available evidence on the characteristics and outcomes of TTS in the setting of COVID-19. In addition, we compared characteristics in the TTS-COVID group with those in patients with TTS who had an acute respiratory disease other than COVID-19 as a trigger (TTS-acute respiratory disease), and those with TTS who had no respiratory disease (TTS-no respiratory disease). For information on patients with TTS-acute respiratory disease and TTS-no respiratory disease, we used data from a subgroup analysis of the International Takotsubo Registry (InterTAK Registry) of patients with TTS.[17]

Methods

We searched PubMed, Embase, and the whole Cochrane Library database for case reports and case series published from January 2019 to November 2023, using the following keywords: ("corona" OR "covid*" OR "sars" OR "severe acute respiratory syndrome" OR "ncov*" OR "severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR "coronavirus" OR "COVID19" OR "COVID 19" OR "coronavirus 2019" OR "SARS-CoV-2" OR "SARS2" OR "SARS 2" OR "severe acute respiratory syndrome 2" OR "2019-nCoV" OR "novel coronavirus") AND ("stress induced cardiomyopathy" OR "neurogenic pulmonary edema" OR "ampulla cardiomyopathy" OR "takotsubo" OR "takotsubo cardiomyopathy" OR "takotsubo syndrome" OR "takotsubo cardiomyopath*" OR "stress cardiomyopathy" OR "broken heart syndrome" OR "apical ballooning syndrome"). All published cases included in the final analysis were written in English. After the electronic and manual searches, we exported the identified studies into EndNote 20 (Clarivate Analytics, Philadelphia, PA) and removed duplicate publications. Two authors (C.T. and X.L.) independently screened the title and abstract of the papers and excluded those deemed to be irrelevant. After the initial screening, both authors reviewed the full text of the remaining articles. All steps of the screening process were conducted using EndNote 20 software. A third author (P.L.) was consulted to resolve any discrepancies during the screening process. Because all data were collected from previous publications, no ethical or institutional review board approval was required.

The inclusion criteria for this study were as follows: (i) the papers must be case reports or case series; (ii) the cases of TTS must have occurred after a diagnosis of COVID-19; and (iii) adequate clinical information (demographics and outcomes) must be reported.

Data from the articles were curated and summarized in the order of the year of publication. We gathered the following data: age and sex of the patient, presentation, medical history, diagnosis time between COVID-19 and TTS, electrocardiogram (ECG) changes, left ventricular ejection fraction, coronary angiography, computed tomography coronary angiography, cardiac magnetic resonance, mechanical circulatory and/or respiratory support interventions during hospitalization, cardiac and inflammatory markers, drugs, and outcomes. Furthermore, to evaluate the effect of variant predominance on TTS outcomes, we aimed to identify the specific severe acute respiratory syndrome (SARS)-CoV-2 variants in all reported cases; however, the variant information was not disclosed in most cases. In regard to the changing epidemiologic trends of COVID-19, earlier variants have exhibited a higher degree of virulence than the Omicron variant.[19] As a result, we divided the cases of TTS associated with COVID-19 into 2 cohorts, as follows: those identified before 2022 and those identified after 2022. This categorization allowed us to analyze and compare the clinical outcomes across the 2 timeframes. We further compared the characteristics of the TTS-COVID group with those of the TTS-acute respiratory disease (other than COVID-19) and the TTS-no respiratory disease groups. Data on the 2 comparator groups were obtained from a subgroup analysis study of a well-characterized dataset (InterTAK Registry) describing the characteristics of 1670 patients with TTS.[17]

Finally, we used the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) 2020 database for a propensity-score matching analysis to compare COVID-19 patients with vs without TTS, focusing on variables such as patient demographics, chronic comorbidities, and acute organ failure indicators (eg, acute kidney injury and acute respiratory failure). This approach compensated for the lack of direct laboratory data, using these variables as proxies for disease severity.

We used the mean and standard deviation to express continuous variables and percentages to express categorical variables. Continuous variables were examined by using a t test, and categorical variables were tested using χ^2 tests. Bonferroni correction for multiple comparisons was not applied because of the exploratory nature of this study.[20] P values < 0.05 were considered significant. All data extraction and descriptive analysis were performed using R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 1024 articles in our search; 220 duplicates were removed. An additional 618 articles were excluded after initial screening of the abstract, because they did not meet the inclusion criteria. After examining the eligibility of the remaining 186 articles in detail, we excluded 127 articles that were deemed to be irrelevant to the topic of interest. Ultimately, 59 articles were selected for study; 78 patients met the inclusion criteria and were included in the study (Supplemental Fig. S1; Supplemental Table S1).

To examine whether TTS-COVID had unique characteristics, we compared our data on patients with TTS-COVID with data from 2 groups—the TTS-acute respiratory disease and the TTS-no respiratory disease cohorts. The data on the comparator groups were obtained from the reported subgroup analysis using the InterTAK Registry.[17] Table 1 shows the details of patient demographics, presentations, laboratory tests, ECGs, and imaging results. Table 2 shows the treatment regimen and mortality rate in the 3 cohorts—TTS-COVID, TTS-acute respiratory disease, and TTS-no respiratory disease.

Patient age was similar among all 3 groups (Table 1). Of the 78 patients with TTS-COVID, 33.3% were men, which is a higher proportion than that seen in the TTS-no respiratory disease (9.1%; $P < 0.001$) group. Dyspnea (70.3%) and cough (40.6%) were the most common presenting symptoms in the TTS-COVID group. Chest pain, a more typical symptom of TTS, was seen in only 23.4% of TTS-COVID patients, compared with 52.3% in the TTS-acute respiratory group, and

Table 1. Demographics and clinical features in patients with takotsubo syndrome with COVID-19 (TTS-COVID), TTS with an acute respiratory disease other than COVID-19 as a trigger (TTS-acute respiratory disease), and TTS with no respiratory disease (TTS-no respiratory disease)

Demographics and features	TTS-COVID (n = 78)	TTS-acute respiratory disease (n = 123)	TTS-no respiratory disease (n = 1353)	P*	P†
Demographics					
Age, y	65.13 ± 15.5	67.3 ± 11.5	66.4 ± 13.3	0.29	0.48
Males	22 of 78 (33.3)	20 of 123 (16.3)	123 of 1353 (9.1)	0.06	< 0.001
Presenting symptoms					
Dyspnea	45 of 64 (70.3)	100 of 115 (87.0)	523 of 1265 (41.3)	0.01	< 0.001
Chest pain	15 of 64 (23.4)	56 of 107 (52.3)	1002 of 1274 (78.6)	< 0.001	< 0.001
Cough	26 of 64 (40.6)	—	—	—	—
Comorbidities					
Hypertension	40 of 63 (63.5)	85 of 123 (69.1)	869 of 1343 (64.7)	0.54	0.950
Diabetes mellitus	19 of 63 (30.2)	17 of 122 (13.9)	191 of 1348 (14.2)	0.01	0.001
Hyperlipidemia	13 of 63 (20.6)	42 of 122 (34.4)	420 of 1342 (31.3)	< 0.001	< 0.001
Takotsubo type					
Apical	53 of 73 (72.6)	92 of 123 (74.8)	1110 of 1353 (82.0)	0.87	0.06
Midventricular	6 of 73 (8.2)	—	—	—	—
Basal	8 of 73 (11.0)	—	—	—	—
Focal	1 of 73 (1.4)	—	—	—	—
Biventricular	5 of 73 (6.8)	—	—	—	—
Elevated cardiac biomarkers					
BNP‡	38 of 41 (92.7)	40 of 123 (32.5)	324 of 1353 (23.9)	< 0.001	< 0.001
Creatine kinase	14 of 18 (77.8)	75 of 123 (61.0)	959 of 1353 (70.9)	0.20	0.61
C-reactive protein	44 of 45 (97.8)	—	—	—	—
D-dimer	38 of 40 (95.0)	—	—	—	—
Troponin§	61 of 65 (93.8)	101 of 123 (82.1)	1107 of 1353 (81.8)	0.03	0.01
Lactate	6 of 6 (100.0)				
Creatinine	13 of 13 (100.0)				
ECG changes					
ST-segment elevation	31 of 75 (41.3)	40 of 106 (37.7)	548 of 1238 (44.3)	0.74	0.71
T-wave inversion	31 of 75 (41.3)	47 of 106 (44.3)	509 of 1238 (41.1)	0.80	1.00

Values are n of n (%), or mean ± standard deviation, unless otherwise indicated.
ECG, electrocardiogram.
*TTS-COVID cohort compared with TTS-acute respiratory disease cohort.
†TTS-COVID cohort compared with TTS-no respiratory disease cohort.
‡Includes brain natriuretic peptide (BNP) and the N-terminal of prohormone brain natriuretic peptide.
§Includes troponin T, high-sensitivity troponin T, and troponin I.

78.6% in the TTS-no respiratory group (Table 1). The most common comorbidities in the TTS-COVID cohort were conventional cardiovascular risk factors, such as hypertension (63.5%) and diabetes mellitus (30.2%). Hypertension rates were similar among the 3 groups, but diabetes was more common in the TTS-COVID group.

Biomarkers that indicate myocardial injury or inflammation were elevated in most patients with TTS-COVID (Table 1; Supplemental Table S2). Troponin and creatinine kinase-muscle/brain (CK-MB) similarly were increased in all groups. However, a higher proportion of patients in the TTS-COVID cohort had elevated brain natriuretic peptide levels (92.7%) than that seen in the TTS-acute respiratory group (32.5%) and the TTS-no respiratory group (23.9%; $P < 0.001$ for both comparisons). The ECG presentation was similar across all 3 groups, with ST-segment elevation and T-wave inversion being the most frequent findings (Table 1).

Table 2. Treatment and outcome in patients with takotsubo syndrome with COVID-19 (TTS-COVID), TTS with an acute respiratory disease other than COVID-19 as a trigger (TTS-acute respiratory disease), and TTS with no respiratory disease (TTS-no respiratory disease)

Treatment and outcome	TTS-COVID (n = 78)	TTS-acute respiratory disease (n = 123)	TTS-no respiratory disease (n = 1353)	P*	P†
Treatment					
ACEI and/or ARB	9 of 53 (17.0)	82 of 109 (75.2)	952 of 1189 (80.1)	< 0.001	< 0.001
Beta-blockers	16 of 53 (30.2)	76 of 109 (69.7)	948 of 1189 (79.7)	< 0.001	< 0.001
Statin	8 of 53 (15.1)	54 of 109 (49.5)	616 of 1189 (51.8)	< 0.001	< 0.001
Anticoagulant	27 of 53 (50.9)	9 of 109 (8.3)	104 of 1189 (8.7)	< 0.001	< 0.001
Aspirin	16 of 53 (30.2)	71 of 109 (65.1)	794 of 1189 (66.8)	< 0.001	< 0.001
$P2Y_{12}$ antagonist	8 of 53 (15.1)	15 of 109 (13.8)	128 of 1189 (10.8)	1.00	0.45
Mechanical ventilation	37 of 56 (69.6)	55 of 122 (45.1)	183 of 1349 (13.6)	0.02	< 0.001
Catecholamine use	20 of 53 (37.7)	29 of 122 (23.8)	147 of 1349 (10.9)	0.09	< 0.001
Outcome					
Death	20 of 77 (26.0)	7 of 123 (5.7)	57 of 1353 (4.2)	< 0.001	< 0.001

Values are n of n (%), unless otherwise indicated.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; $P2Y_{12}$, adenosine diphosphate receptor.
*TTS-COVID cohort compared with TTS-acute respiratory disease cohort.
†TTS-COVID cohort compared with TTS-no respiratory disease cohort.

The most common type of TTS in all groups was apical TTS. The rate was similar across all 3 groups. In the TTS-COVID cohort, the second-most-common type was basal TTS, which was seen in 11.0% of patients; this rate is higher than the 2.2% rate reported in the InterTAK registry for all patients with TTS.[17] The average left ventricular ejection fraction in the TTS-COVID group was 34.6% (Supplemental Table S3).

Despite having high rates of cardiovascular risk factors, few TTS-COVID patients were being treated for them. The treatment regimen of this cohort differed significantly from those of the other 2 comparator groups (Table 2). Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) use was lower in the TTS-COVID group (17.0%) than in the TTS-acute respiratory disease group (75.2%) and the TTS-no respiratory disease group (80.1%; $P < 0.001$ for both comparisons). Similar results were seen for beta-blocker (30.2%, 69.7%, and 79.7%, respectively), aspirin (30.2%, 65.1%, and 66.8%, respectively), and statin (15.1%, 49.5%, and 51.8%, respectively) use ($P < 0.001$ for all comparisons). Catecholamine use was reported in 37.7% of the TTS-COVID cases; norepinephrine was most commonly used (Supplemental Table S4). TTS-COVID cases often were complicated by undifferentiated shock requiring catecholamines, as indicated by their higher level of use in that group (37.7%) compared to that in the TTS-no respiratory disease cohort (10.9%; $P < 0.001$). The rate of mechanical ventilation use was significantly higher in the TTS-COVID group than it was in the TTS-acute respiratory disease group (69.6% vs 45.1%, respectively; $P = 0.02$) and the TTS-no respiratory disease group (69.6% vs 13.6%, $P < 0.001$). In the TTS-COVID cohort, mechanical circulatory support was required in 6 patients (4 extracorporeal membrane oxygenation, 2 systemic hemodynamic support; Supplemental Table S4).

Finally, the mortality rate in patients with TTS-COVID was high, at 26.0%. This rate was significantly higher than the rates in the TTS-acute respiratory disease group (5.7%) and the TTS-no respiratory disease group (4.2%; $P < 0.001$ for both comparisons).

In the sensitivity analysis comparison of TTS patients who had COVID-19 after 2022 vs those who had it before 2022, no significant differences were observed in age, sex, presenting symptoms, comorbidities, types of TTS, or ECG changes. Furthermore, the mortality rates of TTS cases associated with COVID-19 before 2022 were not significantly different from those in cases that occurred after 2022 (30.2% vs 16.7%, $P = 0.33$; Supplemental Tables S5 and S6).

Propensity-score matching showed that COVID-19 patients with TTS had significantly higher mortality rates, compared to the rates among those without TTS, even after adjusting for variables indicative of disease severity, including acute kidney injury, acute respiratory failure, and ventricular arrhythmia. This finding underscores the profound impact of TTS on patient outcomes during the COVID-19 pandemic (Supplemental Tables S7 and S8).

Discussion

To the best of our knowledge, our study is the first to summarize the features of TTS in COVID-19 patients and compare them with those of patients with TTS triggered by another acute respiratory disease, and those with TTS and no respiratory disease. The most important finding of our study is that the mortality rate of the TTS-COVID group was higher than that among patients with TTS-acute respiratory disease (other than COVID) and TTS-no respiratory disease. More TTS-COVID patients developed cardiogenic shock requiring pressors to maintain hemodynamics. In addition, few were on medical therapy for cardiovascular disease, despite having high rates of cardiovascular risk factors.

The mortality rate of the TTS-COVID cohort (33.3%) was disproportionately higher than that in the cohort with COVID-19 infection alone. As of July 2023, the accumulative mortality rate worldwide was estimated to be 0.9%,[21] and the reported inpatient mortality rate of COVID was 15%.[22] This finding suggests that the development of TTS in hospitalized COVID-19 patients may reflect the severity of the underlying infection and may predict worse outcomes in COVID-19 infection. Hypotheses underlying this phenomenon include increased catecholamine levels due to exogenous vasopressor administration in the TTS-COVID cohort, the cytokine storm in severe COVID-19 infection, impaired myocardial perfusion and metabolism, and direct myocardial injury or stunning.[23]

The mortality rate in the TTS-COVID cohort also is significantly higher than the rate in those with TTS-acute respiratory disease (5.7%) and the rate in those with TTS-no respiratory disease (4.2%). This high mortality rate by comparison may be due in part to unique features we identified in this group, such as a higher proportion of men, which is an independent risk factor for TTS complications.[12,24] Second, the atypical presentation of dyspnea and cough in TTS-COVID, rather than chest pain, may have delayed TTS diagnosis and treatment. Third, 43.5% of patients in the TTS-COVID cohort were treated with catecholamine pressors. Because catecholamine surge is one of the proposed pathophysiologic factors in TTS development, the high proportion of catecholamine use may further increase the mortality rate. Finally, although no guideline-directed therapy is specified for TTS, cardiovascular risk factors were common in the TTS-COVID cohort, but few of the patients in this group were being treated for risk factors, which may contribute marginally to the high mortality rate.

Relatedly, a cluster analysis on TTS-COVID patients found that men with TTS triggered by COVID-19 infection had a significantly worse inpatient mortality rate than that among their female counterparts.[24] The higher percentage of men in the TTS-COVID cohort may contribute to the increased mortality rate, as men were noted to have worse outcomes in TTS and in COVID infection, respectively. Men reportedly had more severe cases of COVID-19 than did women.[25,26] Men also had worse TTS outcomes in a study of European and American TTS patients,[27] which has been confirmed in the first Chinese TTS registry.[21] Templin et al. reported that men with TTS, when compared with women with TTS, are at higher risk of in-hospital death (7.3 % vs 3.8%, $P = 0.02$), 30-day major adverse cardiac and cerebrovascular events (13.7% vs 6.3%, $P = 0.002$), and long-term all-cause death (12.9% vs5.0% per patient-year, $P < 0.001$).[12] This finding was confirmed in a recent study of the **GE**rman **I**talian **S**panish **T**akotsubo (GEIST) registry.[27] In this study, men had higher baseline rates of comorbidities. They were more likely to present with dyspnea instead of chest pain. Men also had higher rates of overall long-

term mortality (10% vs 3.8%, $P < 0.05$), in-hospital mortality (8% vs 3%, $P < 0.05$), and cardiogenic shock (16% vs 6%, $P < 0.05$) than did women.[27] In addition, sex is linked to individual risk factors and comorbidities.[27,28] For example, on a global basis, more men than women smoke (40% vs 9%),[28] which can destroy bronchial epithelial cells and weaken the airway immune response. On a molecular level, emerging evidence has shown that the mosaic loss of the Y chromosome leads to cardiac fibrosis and heart failure and is associated with increased risk of mortality in men.[29] All of the features in men combined may have contributed to higher mortality rates in the TTS-COVID cohort. Our study findings further provide a foundation to investigate the intrinsic correlations among these research variables and their possible pathophysiology correlation in TTS-COVID patients.

Patients with TTS-COVID showed atypical presenting symptoms for TTS. Only 14.8% of this cohort reported chest pain, which is the typical presentation of primary TTS.[12] Furthermore, 73.8% presented with dyspnea, and 41.0% with cough, which usually are not seen in TTS presentation. The atypical symptoms in this group could represent COVID pneumonia, decompensated heart failure, or both. Patients with TTS-COVID had an average left ventricular ejection fraction of 35.1%, and a high proportion had elevated brain natriuretic peptide levels (88.4%). The atypical presentation in the TTS-COVID cohort easily could be attributed mistakenly to COVID pneumonia and delay the diagnosis and treatment of concurrent TTS. Therefore, a proportion of the patients with dyspnea also could have had decompensated heart failure early on. Undertreating heart failure resulting from TTS also may have contributed to worse outcomes.

The high proportion of catecholamine use in the TTS-COVID cohort (43.5%) may have contributed to the worse outcomes, as catecholamines appear to play a vital role in the pathophysiology of TTS.[30] Plasma levels of catecholamine in TTS patients are substantially increased, and they are higher than those in patients with acute myocardial infarction or postmyocardial infarction heart failure.[31] Moreover, administration of catecholamines in humans has been shown to cause TTS.[32] The catecholamine surge can result in dysfunction of coronary macro- and microcirculation, abnormal myocardial metabolism, inflammation, myocardial stunning, and eventually heart failure.[30] As a result, catecholamine use may be a key factor contributing to the development and high mortality of TTS in COVID pneumonia.

Few patients in the TTS-COVID group were on conventional medical therapy for risk reduction of cardiovascular disease (ie, ACEIs and/or ARBs, beta-blockers, and statins), but cardiovascular risk factors, such as diabetes and hypertension, were common in this cohort. First, uncontrolled diabetes and hypertension can lead to chronically increased systemic inflammation.[33] Untreated cardiovascular risk factors may exacerbate inflammation and contribute to poor outcomes in TTS-COVID, as a growing body of literature suggests that inflammation is a key factor of TTS pathology; myocardial inflammation has been observed in the acute and chronic phases of TTS.[30] Second, although no treatment has proven effective for TTS, some studies suggest that use of ACEIs and/or ARBs may decrease mortality and recurrence of TTS.[16] However, hesitancy accompanies use of ACEIs and/or ARBs in COVID pneumonia, because SARS-CoV-2 shares the target receptor site with ACE2 receptors. Guidelines now suggest that patients with COVID who are receiving ACEIs and/or ARBs should continue on them, as ACEI and/or ARB use has not been associated with worse outcomes in COVID-19.[34,35] Lastly, use of ACEIs and/or ARBs and beta-blockers remains the foundation of heart failure treatment. Given that a large proportion of patients were in shock requiring catecholamines, the use of such heart failure agents was prohibited, possibly thereby contributing to higher mortality rates.

Our analysis, leveraging the National Inpatient Sample database, highlights TTS as a significant marker of disease severity and a contributor to increased mortality in COVID-19 patients. Despite the limitations posed by the absence of direct laboratory data, surrogate markers, such as acute kidney injury, acute respiratory failure, and ventricular arrhythmia, provided critical insights into the severity of disease. Future studies should explore direct markers of organ perfusion and comprehensive intensive care unit scores to clarify further the impact of TTS in COVID-19. We acknowledge that TTS may function as both an indicator of severe disease and a contributing factor to the elevated mortality rates among these patients. This dual role of TTS is critical for clinicians in the management of COVID-19, emphasizing the importance of early detection and tailored management strategies for TTS, to mitigate its potential adverse impact on patient outcomes.

The work inherently poses several unanswered questions regarding the pathophysiological links between TTS and COVID-19, optimal management strategies for affected patients, and the long-term outcomes for those who develop TTS as part of their COVID-19 illness. We call for further research in these areas, aiming to enhance our understanding and improve clinical care for patients with TTS in the setting of COVID-19.

Limitations

Our study has several limitations. First, a notable limitation of our analysis of TTS presentation in COVID-19 patients is our reliance on documented clinical symptom collection, especially in patients who were mechanically ventilated before TTS diagnosis. This reliance potentially limits the accuracy and completeness of symptom documentation, as direct patient-reported symptoms were not available for those under mechanical ventilation at the time of diagnosis. Second, our data pool was limited by the available literature on TTS in COVID and comprised mostly case reports. A large retrospective or prospective study is needed to better understand the unique features of TTS in patients with COVID pneumonia. Third, the types of patient data reported varied in individual case reports, which led to a smaller set of variables available for comparison and limited our statistical analysis. Fourth, report bias may contribute to an underreporting of TTS-COVID; therefore, the true mortality rate of this patient group may be lower than what is reported in our study. Fifth, the lack of specific variant reporting in most cases limits our ability to directly correlate COVID-19 variants with TTS outcomes. Despite this issue, our sensitivity analysis shed light on the lack of significant differences in clinical presentations and outcomes of TTS associated with COVID-19 infections before and after 2022. This period marks a significant phase in the COVID-19 pandemic, characterized by the emergence of less-virulent variants, such

as Omicron. Finally, we did not mandate coronary angiography as part of our inclusion criteria, owing to the significant restrictions imposed by the pandemic on coronary angiography, potentially introducing bias in diagnosing TTS. In addressing the diagnostic challenges posed by the COVID-19 pandemic, we acknowledge the decreased use of coronary angiography, traditionally the gold standard for diagnosing TTS, due to pandemic-related logistical and safety concerns. Consequently, we expanded our diagnostic criteria to include noninvasive methods, such as computed tomography coronary angiography, magnetic resonance imaging, echocardiography, and laboratory data. Although this approach allowed for a broader inclusion of TTS cases amid the constraints of the pandemic, it introduced variability in diagnostic practices that may affect the interpretation of our findings. This limitation underscores the need for a cautious approach in generalizing our results to all TTS populations, especially in nonpandemic settings. This decision reflects our effort to adapt to the challenging circumstances presented by the COVID-19 pandemic, ensuring our study's adaptability and relevance.

Conclusions

Not all TTS cases are the same. The mortality rate of COVID-19 patients who developed TTS was overwhelmingly high. We also found other unique features in this group, as compared with those of patients who have TTS with other acute respiratory diseases or those who have TTS with no respiratory disease. Addressing the risk factors of TTS in COVID-19 and understanding the pathophysiology are of paramount importance in both helping to prevent the occurrence of TTS in this setting and directing future targeted therapy.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article because all data were collected from previous publications.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.03.004.