BRIEF REPORT

MAYO CLINIC

Mortality Correlates in Patients With Takotsubo Syndrome During the COVID-19 Pandemic

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Abstract

We completed a systematic review of Takotsubo syndrome (TTS) cases reported during the coronavirus disease 2019 (COVID-19) pandemic and performed clustering and feature importance analysis and statistical testing for independence on the demographic, clinical, and imaging parameters. Compared with the data before the COVID-19 pandemic, TTS was increasingly diagnosed in physical stress (mostly COVID-19 pneumonia)—triggered male patients without psychiatric/neurologic disorders, warranting further investigation to establish new reference criteria to improve diagnostic specificity. In clustering analysis, sex and inpatient mortality primarily contributed to the automated classification of the TTS. Both sex and inpatient mortality had essential correlations with COVID-19 infection/pneumonia. There is effect modification of sex on outcomes in patients with COVID-19 infection and TTS, with male patients having significantly worse inpatient mortality. Meanwhile, significantly more male patients with TTS were classified as high risk according to International Takotsubo Registry prognostic scores, suggesting that male COVID-19/TTS survivors will likely have worse long-term outcome.

 ■ Mayo Clin Proc Inn Qual Out 2021;5(6):1050-1055

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The nature of the coronavirus disease 2019 (COVID-19) pandemic has increased physical and mental stress burden to an unprecedentedly large population of people.[1] While Takotsubo syndrome (TTS) has been increasingly reported during the COVID-19 pandemic, its presentation appears to diverge from the traditional archetype.[2,3] Evidence is mounting that increased mortality rates are associated with patients with TTS and COVID-19 infection.[4,5] In the present study, we completed a systematic review of published TTS cases during the COVID-19 pandemic and performed clustering and feature importance analysis on the demographic, clinical, and imaging parameters, aiming to characterize clinical/imaging features and identify mortality correlates.

PATIENTS AND METHODS

We completed a systematic review of 123 patients with TTS from 44 published case reports, 9 case series, and 3 observational cross-sectional/cohort studies published from April 1, 2020, to August 20, 2021 (PubMed). The authors and geographic and demographic information were screened to confirm the onsets of TTS within the COVID-19 pandemic time frame and avoid duplication (Supplemental Table, available online at http://mcpiqojournal.org). The COVID-19 infection was clarified to be either positive for polymerase chain reaction test only or have clinical and imaging evidence of pneumonia. In order to investigate the underlying intrinsic data structure, incorporate all features comprehensively, and elucidate factors contributing to categorization, we performed clustering analysis, which categorizes objects into different groups so that objects in the same group are more similar than those in other groups. This method does not rely on manual selection of the grouping criterion and leads to objective output.[6,7] In the present study, clustering analysis on the demographic, clinical, imaging, and inpatient mortality data of 59 patients with complete entries of all variables classified patients into 2 distinct groups.

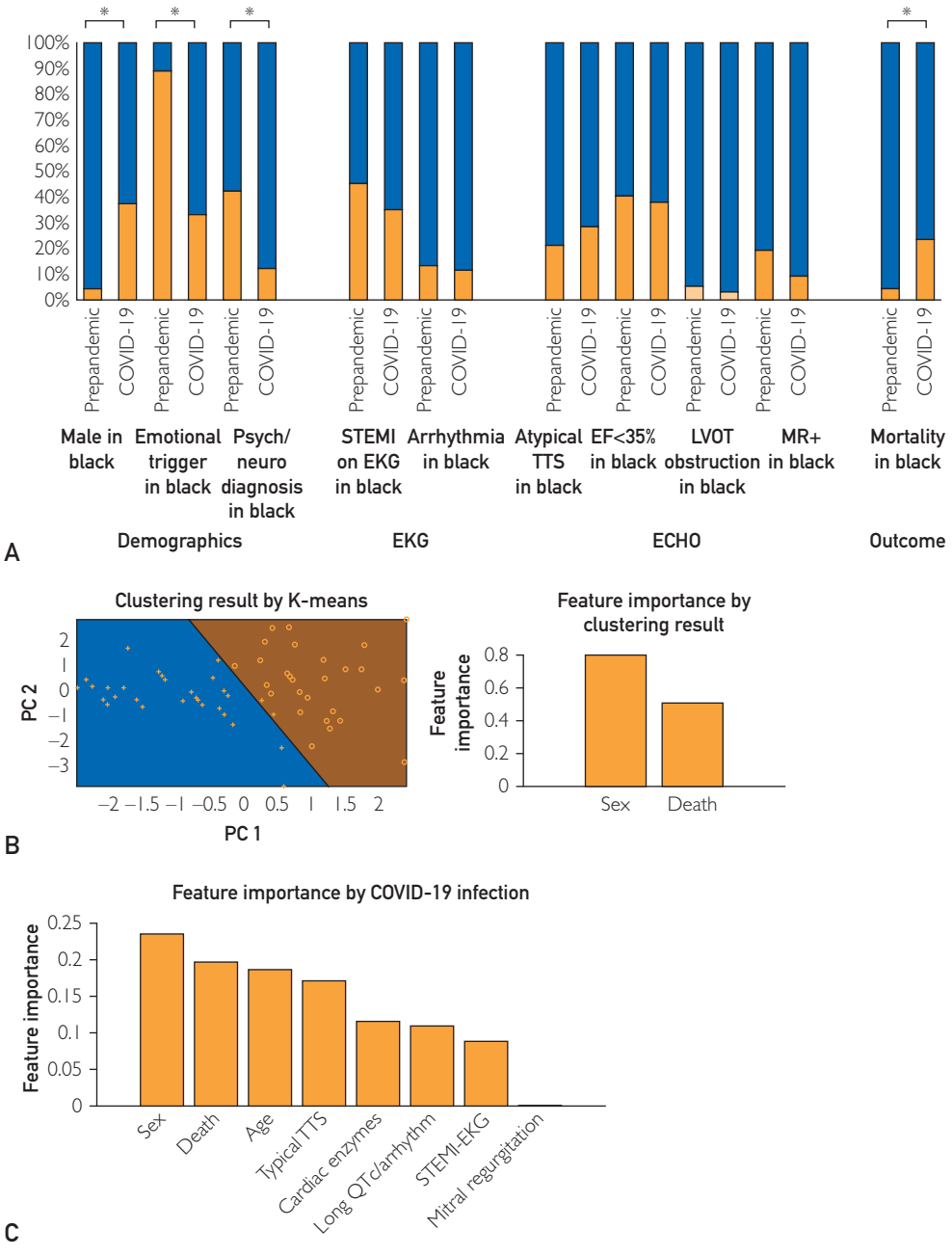
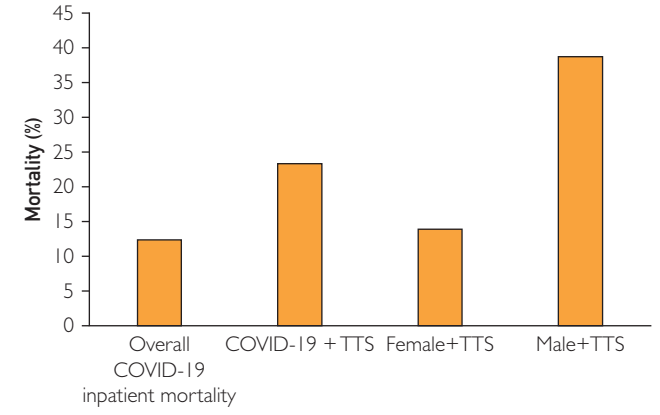


FIGURE 1. A, Demographic, clinical, and imagining characteristics of Takotsubo syndrome (TTS) before and during the coronavirus disease 2019 (COVID-19) pandemic. Compared with the prepandemic data, TTS was significantly more frequently reported in physical stress–triggered male patients (39 of 103 [37.5%] vs 6 of 130 [4.6%]; $P<.0001$) without psychiatric/neurologic disorders (87 of 99 [87.9%] vs 811 of 1525 [53.2%]; $P<.0001$). The inpatient mortality of patients with COVID-19 and TTS was higher than that reported before the pandemic (24 of 103 [23.3%] vs 72 of 1750 [4.1%]; $P<.0001$).[10] ECHO, echocardiogram; EF, ejection fraction; EKG, electrocardiogram; LVOT, left ventricular outflow tract; MR+, mitral regurgitation; Psych/neuro, psychiatric/neurologic disorder; STEMI, ST-elevation myocardial infarction; *, statistically significant with $P<.0001$. B, Clustering and feature importance analysis of the demographic, clinical, and imaging parameters in patients with TTS during COVID-19 pandemic. Left, Automated classification of the demographic, clinical, and imaging data sets. The result of a cluster analysis is shown as the coloring (orange and blue) of the squares into two clusters. PC, principal component. Right, Feature importance by clustering results shows that sex and inpatient mortality are the most important features in determining the classification of patients with TTS. C, Feature importance by clustering results shows that sex and inpatient mortality closely correlate with COVID-19 infection/pneumonia. arrhythm, arrhythmia.



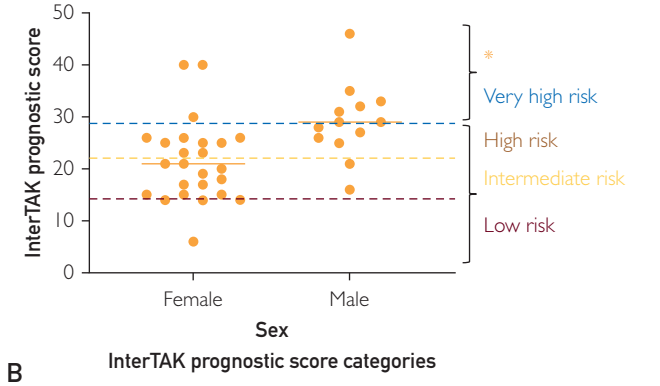


FIGURE 2. The correlation between sex and short- and long-term outcome of patients with Takotsubo syndrome (TTS) during the coronavirus disease 2019 (COVID-19) pandemic. A, Effect modification of sex on mortality in patients with COVID-19 and TTS, with male patients having significantly worse inpatient mortality (COVID-19 overall inpatient mortality, 12.0% [4612 of 38,517][16]; COVID-19 and TTS, 23.3% [24 of 103]; female and TTS, 13.9% [9 of 65]; and male and TTS, 38.7% [12 of 31]). B, Distinct risk patterns between males and females with TTS according to International Takotsubo Registry (InterTAK) prognostic scores. *, *P*=.03, Fisher exact test).

Given the clustering results, we applied feature importance analysis to find the feature(s) most relevant to the grouping. In other words, it is used to identify which feature(s) are most useful to determine the given grouping results. We validated the significance of the results by traditional statistical testing for independence (Fisher exact test) for the same demographic, clinical, and imaging data of the studied patients.

RESULTS

The mean age of the 123 patients with TTS was 67.3±14.0 years, with 39 (31.7%) males. A total of 82 patients (66.7%) had COVID-19 infection (with only one asymptomatic patient). Emotional triggers and psychiatric and neurologic disorders were identified in 41 (33.3%), 12 (12.1%), and 6 (6.1%) patients, respectively. Electrocardiography indicated ST-elevation myocardial infarction in 32 (35.2%), prolonged QTc in 11 (15.3%), and tachyarrhythmia (ventricular fibrillation, ventricular tachycardia, and atrial fibrillation/flutter) in 9 (11.1%) patients. The cardiac enzyme (troponin) levels were elevated in 59 patients (90.1%), with a median value of 0.62 ng/mL (interquartile range, 0.2 to 1.91 ng/mL; to convert value to μg/L, multiply by 1.0). A total of 78 echocardiograms revealed 53 apical, 11 middle cavity, 9 basal cavity, 3 biventricular, and 2 global ventricular TTS. The mean left ventricular ejection fraction was 33.4%±11.0%. Severe mitral regurgitation was found in 7 patients, and 2 of them had coexisting left ventricular outflow tract obstruction (Figure 1). The in-hospital mortality was 23.3% (24 of 103); 13.9% (9 of 65) in females and 38.7% (12 of 31) in males; Figure 2 A). Overall, 80.0% of mortality (8 of 10) happened in either the very high-risk or the high-risk group predicted by their International Takotsubo Registry (InterTAK) diagnostic scores.[8] The male and female patients with TTS also had different risk distribution patterns according to their InterTAK prognostic scores[8]; there are significant sex differences in long-term prognosis prediction with regard to the risk groups (*P*=.03; Figure 2 B).

DISCUSSION

Takotsubo syndrome and acute myocardial infarction (AMI) have distinctive pathophysiology and management strategies.[9-11] During the COVID-19 pandemic, TTS was increasingly found in patients diagnosed as having AMI.[12] It is more important than ever to differentiate AMI and AMI mimickers effectively for frontline disease triage, physician protection, and hospital capacity leverage. The updated guideline requires point-of-care ultrasound or bedside echocardiography to triage patients with AMI for suspected for COVID-19 infection before cardiac catheterization.[13] Traditionally, TTS often occurs in elderly women (particularly with psychiatric and neurologic disorders) and is triggered by mental stress, which forms the basis of the

Mayo Clin Proc Inn Qual Out ■ XXX 2021;5(6):1050-1055 ■ https://doi.org/10.1016/j.mayocpiqo.2021.09.008
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commonly used diagnostic score and criteria in prepandemic times to differentiate TTS and AMI.[7] Nonetheless, during the COVID-19 pandemic, TTS was increasingly reported in the setting of physical stress (mostly COVID-19 pneumonia)—triggered male patients without psychiatric/neurologic disorders[2,4] (Figure 1 A). Meanwhile, the atypical imaging features of TTS were frequently identified on bedside echocardiograms.[2,3,14] It becomes compelling to study and validate these atypical clinical and imaging phenotypes of TTS during the COVID-19 pandemic across data sets from global health resources/registries in order to establish new reference criteria to improve diagnostic specificity and support goal-directed therapy.[2,5]

The inpatient mortality of patients with COVID-19 and TTS is much higher than its prepandemic mortality.[10] Although the exact pathologic role of TTS in the adverse outcomes of patients with COVID-19 remains poorly understood, TTS in many patients with COVID-19 infection is likely a unique illness severity marker. While not every COVID-19 infection will progress to pneumonia and systemic disorders, most of the patients with COVID-19 infection in our study (except for one symptomatic patient with COVID-19) had associated pneumonia; this finding suggests that higher-risk patients with COVID-19 are more likely to have development of TTS than asymptomatic patients with COVID-19. The increased mortality could be (at least partially) attributed to a result of the inherently higher-risk primary disease or the increased likelihood of concurrent systemic complications. From clustering and subsequent feature importance analysis by clustering results, sex and inpatient death principally contributed to automated classification of the TTS during the COVID-19 pandemic (Figure 1 B). Important correlations of COVID-19 infection with both sex and in-hospital mortality were also documented by feature importance analysis (Figure 1 C) and confirmed by Fisher exact tests (Table).

The large-scale data have revealed that there is no sex difference in the proportion of COVID-19–infected people. Instead, males are at a substantially higher disease severity and death rate than females.[15] Although overall patients with COVID-19 and TTS had higher inpatient mortality than those without

TABLE. Fisher Exact Test Results for Demographic, Clinical, and Imaging Characteristics of Patients With TTS During the COVID-19 Pandemic

Variable	Age	Sex	COVID-19 infection	STEMI- EKG	Long QTc/ arrhythmia	Cardiac enzymes	Typical TTS	Mitral regurgitation	Death
Age	0.000	0.866	0.154	0.627	0.678	0.187	0.256	0.155	0.328
Sex	0.866	0.000	0.011	0.775	0.228	1.000	0.402	0.679	0.132
COVID-19 infection	0.154	0.011	0.000	1.000	0.484	0.572	1.000	1.000	0.026
STEMI-EKG	0.627	0.775	1.000	0.000	0.033	0.653	0.402	0.679	1.000
Long QTc/ arrhythmia	0.678	0.228	0.484	0.033	0.000	1.000	1.000	1.000	0.759
Cardiac enzymes	0.187	1.000	0.572	0.653	1.000	0.000	0.388	1.000	1.000
Typical TTS	0.256	0.402	1.000	0.402	1.000	0.388	0.000	0.689	0.152
Mitral regurgitation	0.155	0.679	1.000	0.679	1.000	1.000	0.689	0.000	0.078
Death	0.328	0.132	0.026	1.000	0.759	1.000	0.152	0.078	0.000

COVID-19, coronavirus disease 2019; EKG, electrocardiography; STEMI, ST-elevation myocardial infarction; TTS, Takotsubo syndrome.

TTS,[16] our study also found that male patients with TTS had nearly 2.8-fold higher inpatient mortality compared with female patients with TTS. There is effect modification of sex on outcomes in patients with COVID-19 infection and TTS, with male patients having substantially worse inpatient mortality (Figure 2 A). Moreover, according to InterTAK prognostic scores,[8] male and female patients with TTS had distinct future risk patterns, with considerably more males classified in the very high-risk group (Figure 2 B). Whether male COVID-19/TTS survivors will have more persistent myocardial injuries and worse long-term outcome requires longitudinal and prospective investigations. Nevertheless, our results highlight sex as an important TTS research variable during the COVID-19 pandemic.

Physical and mental stress has constantly increased during the COVID-19 pandemic, resulting in major neurologic and psychiatric conditions even after COVID-19 infections.[1,16,17] As a consequence, the increased incidence of TTS may possibly rise as a long-term sequala.[2,5] While the interplay between COVID-19 infection at presentation and potential hidden long-term effects remains a general curiosity, the investigation on TTS pathophysiology during and after the COVID-19 pandemic may contribute to the development of effective risk stratification and reduction strategies in future public health crises. Since our study is limited by a relatively small sample size and incomplete data in some studied patients, further investigation on large-scale data sets is needed to validate the importance of atypical clinical phenotypes and elucidate novel prognostic markers during the COVID-19 pandemic.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AMI,** acute myocardial infarction; **COVID-19,** coronavirus disease 2019; **InterTAK,** International Takotsubo Registry; **TTS,** Takotsubo syndrome

Grant Support: This work was supported by grants from the Obermann Center for Advanced Studies and the Institute for Clinical and Translational Science (X.W., K.L .).

Potential Competing Interests: The authors report no competing interests.

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