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RESEARCH LETTER

Mortality Risk in Takotsubo Syndrome Versus Myocarditis

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Takotsubo syndrome (TTS) and myocarditis can both present with acute chest pain, reduced cardiac function, and elevated biomarkers.[1,2] Both conditions can be challenging to clinically diagnose and manage given the lack of standardized treatment strategies, although cardiac recovery is expected for most patients. Despite similarities in clinical presentation, the 2 entities represent distinct pathophysiology, with TTS being attributed to an atypical response to a catecholamine surge and myocarditis representing a diverse set of injuries stemming from infection or immune reaction.[1,2] We investigated the extent to which outcomes experienced by patients diagnosed with either of these conditions are similar or different.

The data that support the findings of this study are available from the corresponding author upon reasonable request. We identified patients newly diagnosed at our single quaternary care center between 2010 and 2021 with either TTS or myocarditis based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes (TTS: *ICD-9*, 429.83; myocarditis: codes within phecode group 420.1[3]). Recognizing the intrinsic limits of real-world patient data and their potential impact on coding accuracy, we conducted a physician-level chart review of coded diagnoses on a randomly selected 10% subset of the study sample. We found 94% agreement between coded diagnoses and manual chart review; the instances of disagreement followed no particular pattern, suggesting minimal nondifferential misclassification. We extracted diagnoses, patient-level demographics, comorbidities including diagnosis of myocardial infarction or heart failure limited to at least 30 days before TTS or myocarditis diagnosis, atherosclerotic cardiovascular disease (ASCVD) risk factors within 1 year before diagnosis, and all-cause mortality outcomes within 1 year of diagnosis from our institutional electronic health record, as previously validated.[4] We used a Wilcoxon rank sum test and Pearson χ^2 test to examine unadjusted differences between the TTS and myocarditis patient populations. We then used multivariable Cox regression to examine the relations of diagnosis with all-cause mortality within 1 year while adjusting for age, sex, ASCVD score, and prior myocardial infarction or heart failure. The proportional hazards assumption was assessed and was met in all models. The study was approved by the Cedars-Sinai Institutional Review Board, with a waiver of informed consent.

A total of 1023 patients had a diagnosis of either TTS (n=520) or myocarditis (n=503). When compared with those with myocarditis, patients with TTS were on average older (68±16 versus 46±18, $P<0.001$), more frequently women (81% versus 34%, $P<0.001$), and more often non-Hispanic (8.5% versus 15%, $P=0.002$) (Figure). In patients with nonmissing ASCVD risk score components, the ASCVD score was higher in the TTS patients than in myocarditis patients ($P<0.001$), even after accounting for age. In a limited subset with available data, left ventricular ejection fraction was slightly lower for TTS (36%±15%) versus myocarditis (40%±20%) at the time of diagnosis, but left ventricular ejection fraction was similar on follow-up of median 4 months (interquartile range, 0–22 months) (TTS: 55%±15%, myocarditis: 53%±16%). There were 68 deaths occurring 19 days (interquartile range, 6–94 days) after index diagnosis, including 52 patients (10%) from TTS and 16 patients (3.2%) from myocarditis ($P<0.001$). In models

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	Myocarditis, N = 503	Takotsubo, N = 520	p-value
Age	45 (31, 61)	68 (58, 79)	<0.001
Sex (F)	169 (34%)	421 (81%)	<0.001
Non-White Race	119 (24%)	111 (21%)	0.60
Hispanic Ethnicity	77 (15%)	44 (8.5%)	<0.01
Prior Myocardial Infarction	17 (3.4%)	18 (3.5%)	1.00
Prior Congestive Heart Failure	40 (8.0%)	35 (6.7%)	0.50
ASCVD Risk Score*	0.04 (0.01, 0.13)	0.14 (0.06, 0.24)	<0.001
Mortality	16 (3.2%)	52 (10%)	<0.001

B

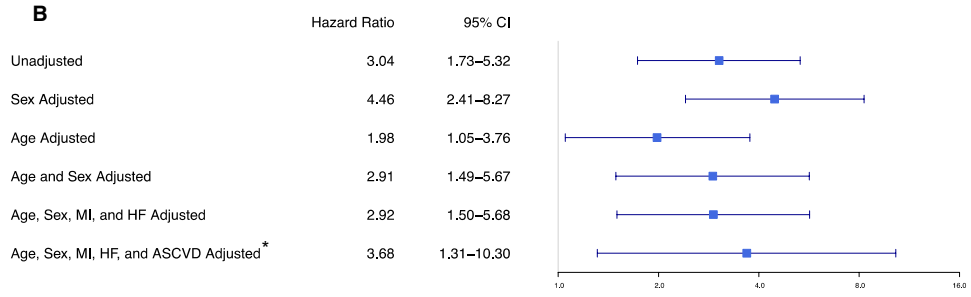

Figure. Demographic differences and excess mortality risk of Takotsubo versus myocarditis. **A**, Demographics for myocarditis and Takotsubo populations. Prior MI and congestive HF are diagnoses that preceded the diagnosis of myocarditis or Takotsubo by at least 30 days. The ASCVD risk score is from before the diagnosis of myocarditis or Takotsubo and within 1 year of the diagnosis. **B**, Forest plot of the odds ratio for Takotsubo versus myocarditis diagnosis's relation to 1-year mortality in univariable and multivariable adjusted models. *Because of missing data, analyses using the ASCVD risk score were conducted for only a subset of the total sample (N=178 with myocarditis, N=198 with Takotsubo). ASCVD indicates atherosclerotic cardiovascular disease; F, female; HF, heart failure; and MI, myocardial infarction.

adjusting for cardiac factors of age, sex, prior myocardial infarction, or prior heart failure, TTS patients had a greater 1-year mortality risk than myocarditis patients in all analyses, as well as in the subgroup with an ASCVD risk score (Figure). Results were similar after additional adjustment for noncardiac comorbidities captured by a modified Elixhauser index[5] with cardiac components removed (hazard ratio [HR], 2.21 [95% CI, 1.16–4.23]; *P*=0.02). We observed significant interaction by age (*P*=0.01) and a borderline interaction by sex (*P*=0.06), with stratified analyses demonstrating that the comparative 1-year mortality risk in TTS versus myocarditis patients was more pronounced in younger (HR, 5.03 [95% CI, 1.68–15.02]; *P*=0.004) than older patients (HR, 1.93 [0.52–4.18]; *P*=0.09), as well as more evident in men (HR, 3.73 [95% CI, 1.62–8.63]; *P*=0.002) compared with women (HR, 1.89 [95% CI, 0.72–4.95]; *P*=0.20).

Despite similar clinical presentations, we identified differences in the demographic and clinical comorbidity profiles of patients diagnosed with TTS and myocarditis. When adjusting for these factors, we found the odds of mortality at 1 year were consistently higher for patients with TTS than those with myocarditis, despite similar recovery of cardiac function. In the context of prior reports suggesting that TTS carries a more benign prognosis when compared with acute coronary syndromes, our results indicate a worse prognosis than myocarditis. Thus, our results underscore the importance of distinguishing TTS from myocarditis, not only because of relatively distinct pathophysiology, requiring differently tailored clinical management, but now also given the apparent outcomes disparity. Our findings may be of particular relevance within the context of the COVID-19 pandemic, with both myocarditis as well as TTS diagnoses being seen more frequently and in patients either directly or indirectly affected by SARS-CoV-2 exposure. Additional studies may reveal whether differences in outcomes are also relevant to these 2 conditions manifesting in relation to SARS-CoV-2. Our report was limited to retrospective chart data and *ICD-9* code diagnoses extracted from a single-center electronic health record. Future prospective studies of patients cared for in diverse settings are needed to validate our findings and clarify the mechanisms underlying differences in outcomes seen across the spectrum of acute myocardial disease conditions.

ARTICLE INFORMATION

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Disclosures

None.

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