Sex Differences in Stress-Induced (Takotsubo) Cardiomyopathy

Waddah Maskoun, MD, FHRS, FACC, Bilal Alqam, MD, Fuad Habash, MD, Zaid Gheith, MD, Stephen G. Sawada, MD, Srikanth Vallurupalli, MD

PII: S2589-790X(22)00249-9

DOI: https://doi.org/10.1016/j.cjco.2022.11.012

Reference: CJCO 604

To appear in: *CJC Open*

Received Date: 18 October 2022

Revised Date: 11 November 2022

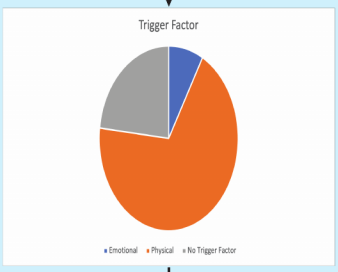
Accepted Date: 14 November 2022

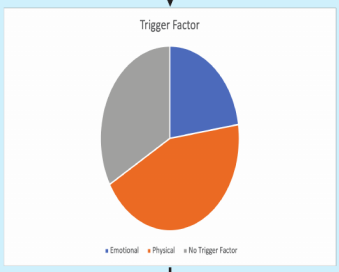
Please cite this article as: W. Maskoun, B. Alqam, F. Habash, Z. Gheith, S.G. Sawada, S. Vallurupalli, Sex Differences in Stress-Induced (Takotsubo) Cardiomyopathy, *CJC Open* (2022), doi: https://doi.org/10.1016/j.cjco.2022.11.012.

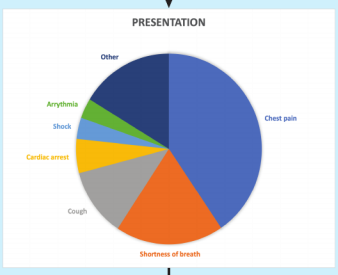
Patients diagnosed with Takotsubo cardiomyopathy in the VA healthcare system

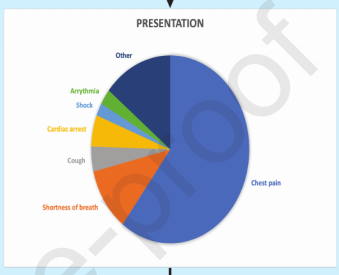
N=444

N=197



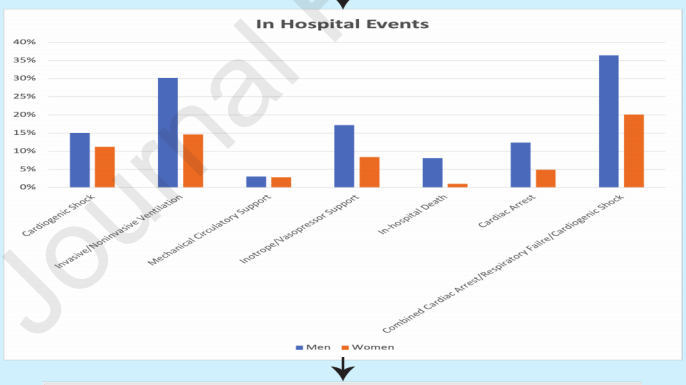


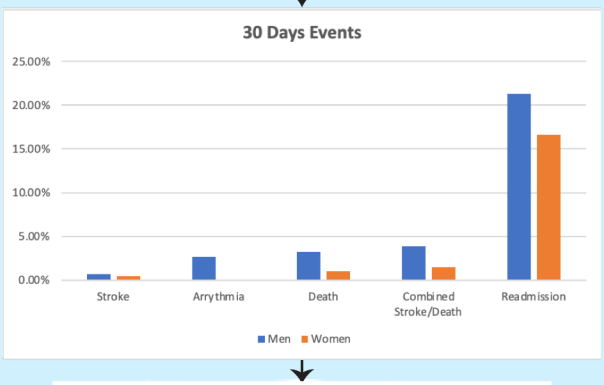


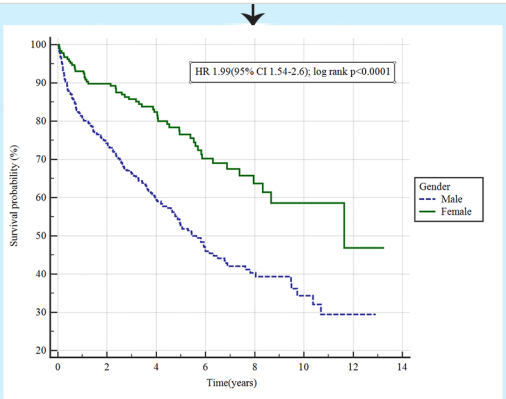


LOS median(IQR)=7(3-14) days

LOS median(IQR)=4(2-8) days







Sex Differences in Stress-Induced (Takotsubo) Cardiomyopathy

Short Title: Takotsubo Cardiomyopathy Men vs Women

Waddah Maskoun, MD, FHRS, FACC,[1,a] Bilal Alqam, MD,[1,b] Fuad Habash, MD, [c] Zaid Gheith, MD,[d] Stephen G, Sawada, MD, [e] Srikanth Vallurupalli, MD[f,g]

[a] Division of Cardiology, Department of Medicine, Henry Ford Hospital, Detroit, Michigan
[b] Department of Medicine, Presbyterian Hospital, Albuquerque, NM
[c] Division of Cardiology, Baylor Heart and Vascular Hospital, Dallas, TX
[d] Division of Cardiology, University of Texas Health Science Center at San Antonio, San Antonio, TX
[e] Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN
[f] Division of Cardiology, Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR
[g] Division of Cardiology, Department of Medicine, Central Arkansas Veterans Healthcare System, Little Rock, AR

[1]Denotes co-first authorship.

Total Word Count: 3142

Corresponding Author:
Waddah Maskoun, MD, FHRS, FACC
Division of Cardiology, Department of Medicine
Henry Ford Hospital
2799 W. Grand Blvd, Detroit, MI 48202
Tel: (313) 916-2417
Fax: (313) 916-8416
Email: wmaskou1@hfhs.org

Abstract:

Background:
Takotsubo cardiomyopathy (TC) predominantly affects women. Prior studies have suggested that men might have worse short-term outcomes, but limited data is available regarding long-term outcome. We hypothesized that men with TC have worse short and long-term outcomes when compared to women.

Methods
Retrospective study of patients diagnosed with TC between 2005 and 2018 in the Veteran Affairs system was performed. Primary outcomes were in-hospital death, 30-day risk of stroke, death, and long-term mortality.

Results:
A total of 641 patients were included (444 [69%] men; 197 [31%] women). Men had a higher median age (65 vs 60 years; $P < 0.001$) and women were more likely to present with chest pain (68.7% vs 44.1%; $P < 0.001$). Physical triggers were more common in men (68.7% vs 44.1%, $P < 0.001$). Men had higher in-hospital mortality rate (8.1% vs 1%; $P < 0.001$). On multivariable regression analysis, female sex was an independent predictor for improved in-hospital mortality when compared to men (OR 0.25 [95% CI 0.06-1.10]; *P = 0.04).*
On 30-day follow-up, there was no difference in a combined outcome of stroke, and death (3.9% vs 1.5%; $P = 0.12$). On long-term follow-up (3.7 ± 3.1 years), female sex was identified as an independent predictor of lower mortality (HR 0.71 [95% CI 0.51-0.97]; $P = 0.032$). Women were more likely to have TC recurrence (3.6% vs 1.1%; $P = 0.04$)

Conclusions:
In our male pre-dominant study, men had less favorable short and long-term outcomes after TC when compared to women.

Introduction:

Takotsubo (stress-induced) cardiomyopathy (TC) is characterized by transient left ventricular (LV) dysfunction with distinct regional wall-motion abnormalities that is not due to obstructive coronary artery disease (CAD).[1] Although TC has been recognized for over three decades,[2] our understanding of this unique disease is still evolving. The pathophysiology of TC is not well understood, but activation of the stress regions in the brain,[3] excess catecholamines,[4] endothelial dysfunction, and estrogen deficiency may play a role in triggering this condition.[5,6] Previous studies have reported that TC predominantly affects women and is commonly preceded by intense emotional or physiological stress.[7,8] The results of prior studies comparing outcome in men and women with TC suggest that in-hospital outcomes are worse for men. However, most prior studies were limited by small numbers of men, or the sole use of ICD codes for inclusion without chart review.[7,9–12] In addition, long term outcome has not been well studied. There is also uncertainty as to whether sex is an independent predictor for in-hospital mortality after adjustment for significant difference in comorbidities between men and women.[7,9,13–15]

The United States Veteran Affairs (VA) system serves mostly male patients.[16] This dominant male population provides sufficient numbers of men for comparison of clinical characteristics and outcome in a disease that predominantly affects women. We hypothesized that men with TC have worse short and long-term outcomes when compared to women.

Methods:

Data source and study population:

Using data from Compensation and Pension Record Interchange (CAPRI) system, we identified patients who had the diagnosis of TC between January 2005 and January 2018 across all hospitals in the VA healthcare system in the United States. CAPRI is an electronic health record

system that contains national data and allows electronic search as well as review of notes, procedures, imaging reports, and lab results across various VA hospitals. We initially narrowed our search by identifying patients with the following ICD codes: Takotsubo syndrome, ICD 10 code: I51. 81, ICD 9 code 429.83. We used a combination of electronic data searching (using ICD codes) and manual verification to identify demographic data and baseline clinical variables at the time of diagnosis. We then removed any duplicate charts. We manually reviewed each medical record. Patients who did not meet the revised Mayo Clinic criteria and International Takotsubo diagnostic criteria were excluded.[1,17]. All patients were required to have a coronary angiography performed unless the procedure was deemed unnecessary by the treating cardiologist and with the reviewers' agreement (if characteristic echocardiography changes, recent coronary angiography, the risks of coronary angiography were deemed higher than the benefits, no ST abnormalities suggestive of injury, and/or no typical pattern of troponin elevation). Patient data were individually collected by at least 2 investigators. If there was any disagreement about the diagnosis between the reviewers, then consensus was reached with the rest of the investigational team. Patients with no echocardiogram or ventriculography consistent with TC were excluded.

The following information was collected: demographic data, comorbidities, medications, trigger factor, presenting symptoms, electrocardiography results, echocardiogram results (at presentation and serial echocardiography), left heart catheterization, type of TC, in-hospital events, 30-day events, and long-term outcomes (up to July 2020, which would give us about 2.5 years of follow up for last patients included in our study). In patients with missing data from echocardiogram report, diagnosis was based on ventriculography data obtained from heart catheterization. The Central Arkansas VA Health System's institutional review board approved the study.

We categorized trigger factors as physical or emotional. Physical trigger factors included acute medical/surgical illness, accidents, physical altercations, trauma, and others.

Types of TC:

Based on previously described types, TC was classified as apical, mid-ventricular, basal, or focal.[7] The type of TC was decided based on the description of wall motion abnormality in echocardiography or angiography reports.

Outcomes:

We collected data for in-hospital complications, including cardiogenic shock, arrythmias, cardiac arrest, respiratory failure, and death. We also collected data on the use of vasopressor/inotropic drugs, LV assist devices, and invasive and non-invasive ventilation. Primary outcomes of interest were: (a) in hospital mortality; (b) 30-day risk of stroke, and death; and (c) long-term mortality.

Statistical analysis:

Patients were classified into 2 groups: men and women. Categorical variables were reported as counts and percentages; differences were assessed with chi-square test. Continuous variables were presented as medians with interquartile range (IQR); and differences were compared with Mann-Whitney test. Kaplan-Meier analysis was used to compare all-cause mortality for the unadjusted data.

We performed univariate analysis for gender, comorbidities, clinical characteristics, trigger factor, labs at the time of diagnosis (hemoglobin, WBC, GFR, Troponin, BNP), ejection fraction, admission medications (beta blockers, ACE-I/ARB, antiplatelets/anticoagulants, statin), medical treatment, the presence of cardiogenic shock, and respiratory failure requiring ventilatory support to evaluate in-hospital morality. We subsequently performed multivariate logistic regression analysis on variables with a P value ≤ 0.05 to identify independent variables that predicted in-

hospital mortality. Similarly, we performed univariable analysis then multivariate analysis for 30 days combined death and stroke. We used the discharge medications instead of the admission medications.

For long-term follow-up, we performed univariable analysis for the above variables except for using discharge medications instead of admission medications. We then performed Cox regression analysis to adjust for baseline variables and calculate the adjusted hazard ratios for mortality on long-term follow-up. A two-sided *P* value $\leq$ 0.05 was considered significant. Analysis was performed using Medcalc (ver 18.11, Ostend, Belgium).

Patient and public involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Results:

Baseline characteristics:

A total of 641 patients with the diagnosis of TC were included in our analysis, 444 of whom (69%) were men and 197 (31%) were women. Table 1 compares baseline characteristics between the two groups. Men were significantly older than women (median [IQR] 65 [60-72.5] vs 60 [55-66] years; $P < 0.001$), with a higher prevalence of CAD (18.7% vs 11.2%; $P = 0.02$), chronic kidney disease (16.9% vs 7.1%, $P = 0.001$), chronic obstructive pulmonary disease (48% vs 38.1%, $P = 0.02$), and history of malignancy (19.8% vs 8.1%; $P < 0.001$). In addition, men had a higher prevalence of reported alcohol use (39.9% vs 19.8%; $P < 0.001$). Women had higher median body mass index (26 vs 24.8 kg/m^2; $P = 0.01$) and were more likely to have bipolar disease (12.7% vs 6.1%; $P = 0.005$) and fibromyalgia (20.8% vs 10.6%; $P < 0.001$). There was no significant difference in baseline medications at presentation between the two groups.

Trigger factor and presenting symptoms:

Physical stress was a more common trigger factor in men than in women (68.7% vs 44.1%; $P < 0.001$), while typical emotional stress was more likely in women than in men (22.6% vs 8.1%; $P < 0.001$). In our cohort, 26.2% had no evident trigger and was more common in women than in men (33.3% vs 23.2%; $P = 0.01$).

Chest pain was the most common presenting symptom in both groups but was more common in women (60.3% vs 40.5%; $P < 0.001$). Compared to women, men were more likely to present with shortness of breath (18.8% vs 10.9%; $P = 0.02$), weakness (6.7% vs 2.2%; $P = 0.02$), and respiratory failure or pulmonary edema (3.9% vs 0.5%; $P = 0.02$). Women were more likely to have TC as a primary diagnosis at presentation to the hospital (83% vs 65.1%; $P < 0.001$).

Electrocardiogram, Echocardiogram and Coronary angiogram on admission:

As shown in Table 2, there were no significant differences between the groups in ST-T changes by electrocardiogram. Men were more likely to present with atrial fibrillation or atrial flutter (8.9% vs 1.5%; $P = 0.004$).

On the admission echocardiogram, men had lower median (IQR) ejection fraction (32% [25-40] vs 35% [25-45]; $P = 0.03$). The most common type of TC identified was apical in both groups (94.7% in men vs 98.4% in women; $P = 0.08$).

Coronary angiogram was more likely to be performed in women than in men (81.7% vs 71.6%; $P = 0.007$). All patients who presented after a cardiac arrest underwent coronary angiography.

In-Hospital course/outcomes:

As shown in Table 3, men were more likely to require invasive or non-invasive ventilation (30.2% vs 14.6%; *P* = 0.001) and vasopressors/inotropes (17.2% vs 8.4%; *P* = 0.01). Men also had higher median (IQR) length of stay (7 [3-14] vs 4 [2-8] days; *P* <0.001) and were more likely to sustain cardiac arrest (12.4% vs 4.9%; *P* = 0.01).

Men were more likely to die during initial admission (8.1% vs 1%; *P* = 0.001).

In the total study population, patients who were already being admitted for another medical/surgical reason had higher mortality rates compared to patients who were diagnosed with TC on presentation to the hospital (12.6% vs 3.2%; *P* < 0.001)**.**

Age, male sex, presence of physical stress as trigger factor, and the use of Intubation/Non-invasive ventilation were independently associated with in-hospital mortality (Table 4). Chronic obstructive pulmonary disease, atrial fibrillation, and chronic kidney disease showed trends toward increased mortality but didn't reach statistical significance.

30 days outcomes:

At 30-day follow-up (Table 5), there was no significant difference in readmission, or a combined outcome of stroke, and death between the two groups (3.9% vs 1.5%; *P* = 0.12). Men had higher rate of arrhythmias (2.7% vs 0; *P* = 0.02

Patients who had TC while admitted for medical/surgical illness had higher mortality rates at 30 days after hospital discharge than patients who were diagnosed with TC on presentation to the hospital (5.7% vs 1.2%; *P* = 0.002). Older age at diagnosis of TC, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease, and need for intubation/non-invasive ventilation were all independent predictors for 30 days combined outcomes of stroke and death (Table 6).

Long-term outcomes:

After median ± SD follow-up of 3.7±3.1 years, mortality was higher among men than women (HR 1.99 [95% CI 1.54-2.6] p<0.001. Figure 1).

Age at diagnosis of TC, male sex, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease, history of malignancy, physical stress as a trigger factor, and receiving intubation/non-invasive ventilation were all independently associated with increased mortality on long-term follow-up (Table 7).

Patients who were discharged on ACE-I/ARB had lower mortality rates (HT 0.5[95% CI 0.57-0.98] p=0.03). However, on cox regression, discharging patients on ACE-I/ARB did not predict improved outcome during long term follow-up.

There was no significant difference in mortality between patients who were discharged on beta blockers compared to those without beta blockers. The overall incidence of recurrent TC was 1.8%. Men were less likely to have recurrence than women (1.1% vs 3.6%; *P* = 0.04).

Discussion:

The major findings in this large retrospective study of patients in a VA healthcare system are the following: (a) men had higher in-hospital mortality than women; (b) there was no significant difference in the combined outcome of stroke and death or readmission rate in men at 30 days after discharge than in women; and (c) men had worse all-cause mortality but less recurrence in long-term follow-up than women.

To our knowledge this study includes the largest cohort of men with TC (n=444).[7,9,10,18–21]

Clinical characteristics/trigger factors:

In our cohort, the men were older and had higher rates of medical comorbidities on presentation, including CAD, which is consistent with previous studies.[7,10] There were also significant

differences in trigger factors between men and women. Previous studies have shown conflicting results regarding the predominant trigger factor in patients diagnosed with TC.[7,9,10,19] In our study, physical stress was more commonly identified as the trigger factor in both men and women but it was more common in men. The reason is unclear, but in previous studies physical trigger was associated with higher levels of norepinephrine in patients with Takotsubo, which might play a role in the pathophysiology of the disease.[22] We also observed a high proportion of patients in both groups with no identifiable trigger factor, which is consistent with previous reports.[7] Similar results were obtained when we compared men above the age of 51 to women of similar age group (above the median age of menopause). More than 60% of the men in our study presented with symptoms other than chest pain; this is contrary to previous studies that showed chest pain as the presenting symptom in men in 57%-100% of patients.[7,9,19] This is likely because more men developed TC in the midst of other medical or surgical illness where symptoms elicitation is challenging. However, a true sex difference cannot be ruled out. This was consistent with a previous study that showed low rates of chest pain as the presenting symptom in patients with exacerbated underlying disorder or procedure.[18] Patients with an emotional or no trigger factor were more likely to present with chest pain than patients with a physical trigger, and this finding was similar for men and women in our study.

In-hospital outcomes:

Men with TC required higher rates of using invasive and non-invasive ventilation and catecholamines. Length of stay was longer for men, and they were more likely to sustain a cardiac arrest or die in the hospital. This is consistent with the previous large multicenter study by Templin et al.[7] A very recent published study by Arcari et al also found higher in-hospital mortality, increased frequency of cardiogenic shock, and longer length of stay in men compared

to women.[21] In addition, patients with TC who developed cardiac arrest were more likely to be men in a previous study.[23] Though the reason is unclear, higher medical comorbidities in men might be a contributing factor. In a previous small study of patients diagnosed with TC in the intensive care unit, half of the patients were men.[24] Interestingly, men were less likely to receive coronary angiography during their hospitalization, we think it might been related to the aversion of come clinicians to perform invasive procedures in patients who are more acutely ill at diagnosis such as the men in our cohort. In addition, male sex was a predictor of in-hospital mortality on multivariate analysis in our study. Prior studies have conflicting results regarding in-hospital mortality. Weidner et al and Schneider et al showed no difference for in-hospital mortality between men vs women, neither studies evaluated for independent predictors for in-hospital mortality.[9,13] Murakami et al found male sex was independent predictor of in-hospital composite cardiac events while Budnik et al found sex was not a predictor of in-hospital complications on univariate analysis,[14,15]. Brinjikji el al identified male sex as an independent predictor of in-hospital mortality, but patients included in the study and outcomes were based on chart coding only.[11] Templin et al reported male sex, physical trigger as predictors for composite endpoint (catecholamine use, cardiogenic shock, invasive/non-invasive ventilation, cardiopulmonary resuscitation, and death). But male sex was not an independent predictor on multivariate analysis. Interestingly age, above 70 was found to be an independent predictor of better outcomes in the same study.[7] Male sex was identified as an independent predictor of in-hospital mortality on multivariate analysis in the GEIST (German Italian Spanish Takotsubo) registry. [21]

Short-term Outcomes:

On 30-day follow up, male sex was not an independent predictor of mortality in our study.

Previous studies have conflicting data. Increased mortality rates in the matched cohort of men at 60 days compared to women was reported in the GEIST registry.[21] While male sex was not an independent predictor in the international takotsubo registry at 30-days.[20]

Long-term outcomes:

In our study, men were less likely to have recurrence than women on long term follow up (1.1% vs 3.6%; *P* = 0.04). Previous studies have shown conflicting data regarding recurrence rate between men and women. There was no difference in recurrence rate between men and women in the GEIST registry and in the international takotsubo registry (0.8% vs 1.9%; P=0.22) [7,21], while in a meta-analysis nearly all cases of recurrence occurred in women on 72 months followup.[25] An explanation might be the repetitive nature of emotional stress that might trigger recurrent episodes in women.

There are limited studies on long-term outcomes in patients with TC. In our study, men had higher overall mortality than women. Other independent predictors of mortality in our study, beside male sex, were age at diagnosis of TC, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease, history of malignancy, physical stress as a trigger factor, and receiving intubation/non-invasive ventilation during the hospital admission of the TC diagnosis. Weidner et al assessed long-term mortality in patients with TC and male sex and EF<35% were identified as an independent predictor for all-cause mortality, but the study had small number of men (n=16). In our study, EF <35% at diagnosis was not an independent predictor of mortality. In the recent published study involving patients in the GEIST registry, male sex, age, diabetes, pulmonary disease, malignancies, physical trigger, low EF, and cardiogenic shock were identified as independent predictors of long-term mortality.[21] Long-term mortality rate was higher in our study when compared to the GEIST registry. This could be due

to the higher number of significant lung disease and physical triggers in our study. The independent predictors of long-term mortality in the international takotsubo registry were male sex, age > 70, malignancies, EF < 45%, physical triggers, and no triggers.[20]

Limitations:

Despite its large size and multicenter cohort, our study was based on retrospective record review and thus is prone to bias. ICD codes were used to identify cases, so not all cases may have been identified. However, this limitation affects both groups and is, therefore, unlikely to affect the results. Compared to studies that used ICD codes for adjudicating outcomes, patient level data and outcomes were manually extracted. This manual review allowed us to identify outcomes when patients were admitted outside the VA system since we had access to scanned records and collect follow-up data due to the ability of tracking individual patients across the healthcare system even when they moved to a different city. However, some events could have been missed. Multivariate analysis for inpatient mortality was underpowered due to the low number of events compared to the number of variables included.

In addition, due to the male predominate population at the VA, the study cohort might not be representative of general population.

Patients were only included if they met the latest criteria for diagnosis TC, however cases of coronary spasm and myocardial infarction with non-obstructive coronary arteries (MINOCA) could have been included due to the limitation of the criteria.

Conclusion:

Men diagnosed with TC are more likely to have a physical trigger, become more acutely ill, have a more complicated hospital course, and have higher mortality rates on long-term follow-up than women. However, women were more likely to have recurrent TC and were more likely to

present with chest pain. Future prospective studies should focus on the mechanisms of these differences to elucidate how sex affects the TC clinical course, which may help physicians make better treatment decisions and more accurate prognoses.

Declarations of interest: None

Funding: None

References:

1. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *Am Heart J*. 2008;155(3):408-417. doi:10.1016/j.ahj.2007.11.008
2. Sato H, Uchida T, Dote K, Ishihara M. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. *Tokyo Kagakuhyoronsha Publ*. 1990:56-64.
3. Suzuki H, Matsumoto Y, Kaneta T, et al. Evidence for brain activation in patients with takotsubo cardiomyopathy. *Circ J*. 2014;78(1):256-258. doi:10.1253/circj.CJ-13-1276
4. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Musha H, Sasaka K. 123I-MIBG myocardial scintigraphy in patients with "takotsubo" cardiomyopathy. *J Nucl Med*. 2004;45(7):1121-1127.
5. Naegele M, Flammer AJ, Enseleit F, et al. Endothelial function and sympathetic nervous system activity in patients with Takotsubo syndrome. *Int J Cardiol*. 2016;224:226-230. doi:10.1016/j.ijcard.2016.09.008
6. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. *Circulation*. 2017;135(24):2426-2441. doi:10.1161/CIRCULATIONAHA.116.027121
7. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med*. 2015;373(10):929-938. doi:10.1056/NEJMoa1406761
8. Bybee KA, Kara T, Prasad A, et al. Systematic review: Transient left ventricular apical ballooning: A syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med*. 2004;141(11):858-865. doi:10.7326/0003-4819-141-11-200412070-00010
9. Schneider B, Athanasiadis A, Stöllberger C, et al. Gender differences in the manifestation of tako-tsubo cardiomyopathy. *Int J Cardiol*. 2013;166(3):584-588.

doi:10.1016/j.ijcard.2011.11.027

10. Agdamag AC, Patel H, Chandra S, et al. Sex Differences in Takotsubo Syndrome: A Narrative Review. *J Women's Heal*. 2020;29(8):1122-1130. doi:10.1089/jwh.2019.7741
11. Brinjikji W, El-Sayed AM, Salka S. In-hospital mortality among patients with takotsubo cardiomyopathy: A study of the National Inpatient Sample 2008 to 2009. *Am Heart J*. 2012;164(2):215-221. doi:10.1016/j.ahj.2012.04.010
12. Khera R, Light-Mcgroary KA, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for takotsubo cardiomyopathy in the United States. *Am Heart J*. 2016;172:53-63. doi:10.1016/j.ahj.2015.10.022
13. Weidner KJ, El-Battrawy I, Behnes M, et al. Sex differences of in-hospital outcome and long-term mortality in patients with Takotsubo cardiomyopathy. *Ther Clin Risk Manag*. 2017;13:863-869. doi:10.2147/TCRM.S131760
14. Murakami T, Yoshikawa T, Maekawa Y, et al. Gender differences in patients with takotsubo cardiomyopathy: Multi-center registry from Tokyo CCU Network. *PLoS One*. 2015;10(8). doi:10.1371/journal.pone.0136655
15. Budnik M, Nowak R, Fijałkowski M, et al. Sex-dependent differences in clinical characteristics and in-hospital outcomes in patients with takotsubo syndrome. *Polish Arch Intern Med*. 2019;130(1):25-30. doi:10.20452/pamw.14970
16. National Center for Veterans Analysis and Statistics. *Profile of Veterans: 2017*.; 2019. http://www.census.gov/acs/www/.
17. Ghadri J-R, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J*. 2018;39(22):2032-2046.

doi:10.1093/EURHEARTJ/EHY076

18. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. *J Am Coll Cardiol*. 2001;38(1):11-18. doi:10.1016/S0735-1097(01)01316-X
19. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress. *N Engl J Med*. 2005;352(6):539-548. doi:10.1056/nejmoa043046
20. Ghadri JR, Kato K, Cammann VL, et al. Long-Term Prognosis of Patients With Takotsubo Syndrome. *J Am Coll Cardiol*. 2018;72(8):874-882. doi:10.1016/j.jacc.2018.06.016
21. Arcari L, Núñez-Gil IJ, Stiermaier T, et al. Gender Differences in Takotsubo Syndrome. *J Am Coll Cardiol*. 2022;79(21):2085-2093. doi:10.1016/j.jacc.2022.03.366
22. Sobue Y, Watanabe E, Ichikawa T, et al. Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality rate. *Int J Cardiol*. 2017;235:87-93. doi:10.1016/j.ijcard.2017.02.090
23. Gili S, Cammann VL, Schlossbauer SA, et al. Cardiac arrest in takotsubo syndrome: Results from the InterTAK Registry. *Eur Heart J*. 2019;40(26):2142-2151. doi:10.1093/eurheartj/ehz170
24. Haghi D, Fluechter S, Suselbeck T, et al. Takotsubo cardiomyopathy (acute left ventricular apical ballooning syndrome) occurring in the intensive care unit. *Intensive Care Med*. 2006;32(7):1069-1074. doi:10.1007/s00134-006-0111-z
25. Singh K, Carson K, Usmani Z, Sawhney G, Shah R, Horowitz J. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *Int J*

Cardiol. 2014;174(3):696-701. doi:10.1016/j.ijcard.2014.04.221

Table 1: Differences in baseline characteristics between men and women

Demographic Variable	Men (N=444)	Women (N=197)	*P* Value
Age, median (IQR), y	65 (60-72.5)	60 (55-66)	<0.001
Diabetes, no. (%)	142 (32)	55 (27.9)	0.3
Hypertension, no. (%)	266 (59.9)	108 (54.8)	0.23
Hyperlipidemia, no. (%)	289 (65.1)	140 (71.1)	0.14
CKD, no. (%)	75 (16.9)	14 (7.1)	0.001
COPD, no. (%)	213 (48)	75 (38.1)	0.02
CAD, no. (%)	83 (18.7)	22 (11.2)	0.02
PVD, no. (%)	57 (12.8)	7 (3.6)	<0.001
CHF, no. (%)	47 (10.6)	16 (8.1)	0.33
Atrial fibrillation, no. (%)	41 (9.2)	12 (6.1)	0.18
History of malignancy, no. (%)	88 (19.8)	16 (8.1)	<0.001
CVA, no. (%)	96 (21.6)	30 (15.2)	0.06
Bipolar disease, no. (%)	27 (6.1)	25 (12.7)	0.005
Smoking history, no. (%)	270 (60.8)	101 (51.3)	0.02
White race, no. (%)	340 (81.3)	151 (83.9)	0.42

Black race, no. (%)	69 (15.5)	22 (11.2)	0.14
Medications on admission			
Beta Blocker, no. (%)	148 (33.8)	59 (30.3)	0.38
ACE-I/ARB, no. (%)	174 (39.7)	76 (39)	0.86
Antiplatelets, no. (%)	199 (45.4)	74 (37.9)	0.08
Anticoagulation, no. (%)	40 (9.1)	16 (8.2)	0.71
Statin, no. (%)	191 (43.6)	83 (42.6)	0.81
Calcium Channel Blocker, no. (%)	74 (16.9)	28 (14.4)	0.42
Trigger Factor			
Emotional Trigger, no. (%)	33 (8.1)	40 (22.6)	<0.001
Physical Trigger, no. (%)	281 (68.7)	78 (44.1)	<0.001
No Trigger Factor Identified, no. (%)	95 (23.2)	59 (33.3)	0.01
Location			
Initial admission for TC, no. (%)	280 (65.1)	161 (83)	<0.001
Already admitted to Inpatient general ward, no. (%)	87 (20.2)	20 (10.3)	<0.001
Already admitted to ICU, no. (%)	57 (13.3)	7 (3.6)	<0.001
Operating room, no. (%)	6 (1.4)	6 (3.1)	0.15

Abbreviations: ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blocker; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; ICU: intensive care unit; PVD: peripheral vascular disease; TC: Takotsubo Cardiomyopathy

Table 2: Differences in clinical presentation between men and women

Presentation/Symptoms	Men (N=444)	Women (N=197)	*P* Value
Chest pain, no. (%)	168 (40.5)	111 (60.3)	<0.001
Shortness of Breath, no. (%)	78 (18.8)	20 (10.9)	0.02
Cough, no. (%)	48 (11.6)	8 (4.3)	0.005
Gastrointestinal, no. (%)	8 (1.9)	6 (3.3)	0.31
Weakness, no. (%)	28 (6.7)	4 (2.2)	0.022
Respiratory failure/pulmonary edema, no. (%)	16 (3.9)	1 (0.5)	0.02
Arrythmia, no. (%)	14 (3.4)	5 (2.7)	0.67
Shock, no. (%)	15 (3.6)	4 (2.2)	0.35
Cardiac Arrest, no. (%)	24 (5.8)	10 (5.4)	0.92
ECG on Presentation			
ST-segment elevation, no. (%)	131 (39.5)	46 (36.5)	0.56
ST-segment depression, no. (%)	25 (7.5)	12 (9.5)	0.48
T wave changes, no. (%)	99 (31.9)	44 (37.9)	0.24
Lab Tests, median (IQR)			
WBC, cells/μL	9.9 (7.2-13.9)	9.2 (7-12.3)	0.41

Hemoglobin, g/dL	12.4 (10.4-14.6)	13.3 (11.3-14.4)	0.22
Troponin I, ng/mL	1.7 (0.6-4.4)	1.6 (0.7-3.8)	0.81
BNP, pg/mL	622.5 (187-1654)	615 (370-1246)	0.98
GFR, ml/min	60 (58-92.5)	64 (55-81)	0.62
Echo on presentation			
EF <=35, no. (%)	231 (63.5)	83 (54.6)	0.06
EF, median (IQR), % [no.]	32 (30-35) [364]	35 (32-40) [152]	0.03
Coronary Angiography done, no. (%)	318 (71.6)	161 (81.7)	0.007
LVEDP, median (IQR), mm Hg [no.]	20 (15-26) [76]	21.5 (16-26) [36]	0.82
Type of TC			
Apical, no. (%)	301 (95)	137 (98.6)	0.07
Mid-Ventricular, no. (%)	5 (1.6)	0	0.33
Basal, no. (%)	11 (3.5)	2 (1.4)	0.23

Abbreviations: BNP: brain natriuretic peptide; ECG: electrocardiogram; EF: ejection fraction; GFR: glomerular filtration rate; LVEDP: left ventricular end diastolic pressure; TC: Takotsubo Cardiomyopathy; WBC: white blood cell

Table 3: In-hospital events in men and women with Takotsubo cardiomyopathy

In-Hospital Events	Men (N=444)	Women (N=197)	P value
Cardiogenic Shock, no. (%)	55 (15)	16 (11.2)	0.26
Invasive/noninvasive positive pressure ventilation, no. (%)	112 (30.2)	21 (14.6)	0.001
Mechanical circulatory support (IABP/Impella), no. (%)	11 (3)	4 (2.8)	0.95
Pharmacological inotrope/vasopressor support, no. (%)	62 (17.2)	12 (8.4)	0.01
LOS, median (IQR), days	7 (3-14)	4 (2-8)	<0.001
In hospital death, no. (%)	36 (8.1)	2 (1)	<0.001
Cardiac arrest, no. (%)	46 (12.4)	7 (4.9)	0.01
Combined Cardiac arrest/respiratory failure/cardiogenic shock, no. (%)	141 (36.4)	31 (20.1)	<0.001

IABP: intra-aortic balloon pump; LOS: length of stay

Table 4: Multivariate regression for in-hospital mortality

Variable	Odd Ratios	95% CI	P Value
Age	1.04	1.00 to 1.09	0.01
Female sex	0.25	0.06 to 1.10	0.04
Diabetes Mellitus	0.80	0.37 to 1.76	0.69
Chronic kidney disease	0.33	0.10 to 1.10	0.07
Chronic obstructive pulmonary disease	0.48	0.23 to 1.04	0.06
Coronary artery disease	0.90	0.35 to 2.37	0.91
Peripheral vascular disease	1.26	0.42 to 3.76	0.80
Atrial Fibrillation	2.35	0.80 to 6.94	0.07
History of Malignancy	1.61	0.73 to 3.59	0.24
Physical stress	4.69	1.51 to 14.60	0.004
Intubation/Non-invasive ventilation	3.79	1.72 to 8.36	<0.001
Cardiogenic shock	1.98	0.86 to 4.54	0.19
Ejection Fraction <35%	1.68	0.75 to 3.79	0.17

Table 5: Events at 30 days after discharge of men and women with Takotsubo cardiomyopathy

30-days events	Men (N=408) no. (%)	Women (N=193) no. (%)	P Value
Stroke	3 (0.7)	1 (0.5)	0.75
Arrythmia	11 (2.7)	0	0.02
Death	13 (3.2)	2 (1)	0.12
Combined Stroke/ Death	16 (3.9)	3 (1.5)	0.12
Readmission	87 (21.3)	32 (16.6)	0.17

MI: myocardial infarction

Table 6: Multivariate regression for mortality and stroke at 30 days

Covariate	Odd Ratios	95% CI	P
Age at diagnosis	1.07	1.03 to 1.11	<0.001
Female sex	0.52	0.14 to 1.91	0.32
Diabetes Mellitus	0.67	0.28 to 1.62	0.38
Chronic kidney disease	2.93	1.23 to 7.00	0.02
Chronic obstructive pulmonary disease	0.40	0.18 to 0.92	0.03
Coronary artery disease	1.15	0.45 to 2.94	0.78
Peripheral vascular disease	3.08	1.17 to 8.09	0.02
Atrial Fibrillation	1.71	0.52 to 5.62	0.38
History of Malignancy	1.61	0.67 to 3.87	0.29
Ejection fraction<35%	1.08	0.47 to 2.52	0.85
Physical stress as a trigger factor	1.88	0.72 to 4.88	0.20
Intubation/Non-invasive ventilation	4.22	1.71 to 10.43	0.002
Cardiogenic shock	1.14	0.35 to 3.70	0.83

ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blocker

Table 7: Cox regression analysis of factors affecting long-term all-cause mortality of patients with Takotsubo cardiomyopathy

Covariate	Hazard ratio	95% CI	P
Age at diagnosis	1.03	1.02 to 1.04	<0.001
Female sex	0.71	0.51 to 0.97	0.03
Diabetes Mellitus	1.38	1.05 to 1.83	0.02
Chronic kidney disease	1.47	1.06 to 2.04	0.02
Chronic obstructive pulmonary disease	1.44	1.11 to 1.86	0.006
Coronary artery disease	1.30	0.94 to 1.80	0.12
Peripheral vascular disease	1.48	1.03 to 2.13	0.03
Atrial Fibrillation	1.12	0.72 to 1.75	0.60
History of Malignancy	2.05	1.52 to 2.75	<0.001
Ejection fraction<35%	1.11	0.85 to 1.44	0.44
Physical stress as a trigger factor	1.75	1.33 to 2.31	<0.001
Intubation/Non-invasive ventilation	1.66	1.14 to 2.11	0.006
Cardiac arrest	1.16	0.35 to 3.81	0.81
ACE-I/ARB on discharge	0.90	0.70 to 1.16	0.42

ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blocker

Figure 1: Long Term Mortality in Men and Women with Takotsubo Cardiomyopathy: Kaplan-Meir analysis for mortality on long-term follow up. On median±SD follow up of 3.7±3.1 years, men were found to have significantly higher mortality rates (HR 1.99 [95% CI 1.54-2.6] p<0.001).