American Heart Journal Plus: Cardiology Research and Practice 46 (2024) 100453

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research Paper

Gender disparities in outcomes of cardiogenic shock secondary to Takotsubo cardiomyopathy

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ARTICLE INFO

Keywords:
Cardiogenic shock
Shock team
Mechanical circulatory support
Acute myocardial infarction
Acute heart failure
Systems of care

ABSTRACT

Background: Takotsubo cardiomyopathy (TTC) has a preponderance for females, particularly postmenopausal. However, recent data from multicenter registries identified a worse prognosis in male patients, particularly with cardiogenic shock. We aim to investigate gender disparities in outcomes of TTC-associated cardiogenic shock (TTC-CS).

Methods: The National Readmission Database (2016–2020) was utilized to identify TTC-CS hospitalizations. Cohorts were stratified by gender. A Propensity Score Matching (PSM) model, which utilized complete Mahalanobis Distance Matching within the Propensity Score Caliper following multivariate regression, successfully matched males and females. Pearson's χ^2 test was applied to the propensity-matched cohorts to compare outcomes.

Results: Among 12,803 TTC-CS hospitalizations, the majority (74.1 %) were females (N: 9490), and 25.9 % were males (N: 3313). On propensity-matched cohorts (2609), males were found to have higher in-hospital mortality (31 % vs. 26 %, $p < 0.001$), higher incidence of sudden cardiac arrest (14 % vs. 10.8 %, $p < 0.001$), endotracheal intubation (52.1 % vs. 48.8 %, p: 0.001), acute liver injury (18 % vs. 15.9 %, p: 0.004), acute stroke (7.2 % vs. 5.8 %, p: 0.004), cardiac arrhythmias (55.1 % vs. 49.3 %, $p < 0.001$) and acute kidney injury (63.1 % vs. 49 %, p < 0.001); while female patients were found to have higher utilization of mechanical circulatory support (MCS) modalities (16.1 % vs 13.2 %, $p < 0.001$).

Males had a higher adjusted cost of hospitalization ($54,537 vs. $42,805, p < 0.001) with a higher median length of hospital stay (10 vs. 9 days, p < 0.001). The two groups had no significant difference in 30, 90, and 180-day readmission rates ($p > 0.05$). From 2016 to 2020; mortality has not changed significantly for TTC-CS, while the use of percutaneous coronary angiogram (PCA) and MCS has down-trended (p-trend < 0.05).

Conclusion: For TTC-CS hospitalization, males have higher in-hospital mortality and complication rates, along with higher LOS and cost of hospitalization. Despite advances in the management of CS, there was no significant difference in mortality from 2016 to 2020.

1. Introduction

The clinical course of Takotsubo cardiomyopathy (TTC) can be complicated by various life-threatening conditions, with cardiogenic shock (CS) standing out as a leading cause of mortality during the acute phase. Approximately 10 % of TTC patients experience cardiogenic shock [1,2]. Prior studies involving TTC indicated ~40 % reduction in left ventricular stroke volume and ~25 % reduction in cardiac output,

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https://doi.org/10.1016/j.ahjo.2024.100453
Received 11 May 2024; Received in revised form 27 August 2024; Accepted 28 August 2024
Available online 31 August 2024
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with a further decline in stroke volume often exacerbated by tachycardia [3]. Additionally, impaired left ventricular diastolic function with elevated end-diastolic pressure contributes to the development of cardiogenic shock [4]. This condition typically arises within 72 h of admission and may necessitate pharmacologic or mechanical circulatory support, with its occurrence linked to severely reduced left ventricular ejection fraction [3,4].

Previous reports have highlighted a predominance of women, especially postmenopausal women, among individuals affected by TTC [5]. However, recent data from multicenter registries have identified male sex as a factor associated with a worse prognosis [6–8], particularly when associated with cardiogenic shock. Despite this observation, research on the outcome of male patients with TTC cases is limited and often understudied. In these investigations, male patients were noted to exhibit a higher prevalence of physical factors triggering the syndrome, a greater burden of comorbidities, and elevated rates of adverse outcomes compared to their female counterparts [9–11]. Existing studies with small sample sizes and demographic imbalances between male and female groups hinder a clear understanding of gender differences in TTC patients [12].

This study aims to systematically investigate and delineate gender-specific variations in outcomes among individuals experiencing TTC-induced cardiogenic shock. By conducting a comprehensive analysis of a diverse cohort, the objective is to identify clinical outcomes and discern differences in prognosis between male and female patients grappling with this intricate cardiac syndrome.

2. Methods

2.1. Study design and cohort selection

The Nationwide Readmission Database (NRD) from 2016 to 2020 was utilized for this study. NRD is maintained by the Agency for Healthcare Research and Quality (AHRQ) and provides data on roughly 35 million weighted hospitalizations [13]. It is a nationally representative administrative database of the United States comprising discharge and readmission records of approximately 62.2 % of all hospitalizations. International Classification of Disease, Tenth Edition, Clinical Modification (ICD-10-CM), was used to select patients admitted with TTC-induced cardiogenic shock. ICD-10 codes used to define the study population and identify the primary and secondary outcomes of the study are included in Supplemental Table 1 (Table S1). Since NRD is a publicly available deidentified database, an institutional review board approval was waived. Cohorts were created based on the gender variable given within NRD. To limit the potential bias from types of cardiomyopathies, we identified and excluded patients who underwent percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), had a simultaneous diagnosis of ischemic cardiomyopathy, or non-ischemic dilated cardiomyopathy (total N 1052). Furthermore, all duplicates and minors (<18 years) were identified and excluded. Subsequently, we classified the patient population into two groups, stratified by gender. Individual cases were identified using the unique identifier code provided within NRD. The number of days to intervention/procedure and length of stay (LOS) variables were used to calculate the readmission day of the same patient population. Data were used in its totality for analysis at index admission. Given the annualized nature of the NRD dataset and the need to identify patients admitted within the same calendar year, we iteratively incorporated data from the first 11 months, 9 months, and 6 months of each year to guarantee that all patients had 30-day, 90-day, and 180-day follow-up periods, respectively. Observations with a cell count <11 were not reported as per HCUP reporting guidelines. As the NRD database was deidentified, the Institutional Review Board (IRB) waived the requirement for IRB approval to conduct this study.

2.2. Baseline characteristics

We identified adult patients (age ≥ 18) admitted between 2016 and 2020 with TTC-CS. We analyzed baseline patient characteristics (i.e., age and various comorbidities). Hospital characteristics analyzed included bed size, teaching status, and urban-rural designation.

2.3. Study outcomes

The primary outcome was the difference in in-hospital mortality in TTC-CS patients between males and females. Secondary outcomes included other complications during the index hospitalization: acute kidney injury (AKI), sudden cardiac arrest (SCA), acute stroke, acute liver injury, MCS, respiratory complication (need for intubation); length of hospital stay, adjusted total cost of hospitalization; Propensity-matched 30, 90 and 180-day readmission rates; trends of TTC-CS related mortality, MCS use, and utilization of coronary angiogram (PCA). The definitions of study outcomes are provided in detail in the Supplementary Table S2.

2.4. Statistical analysis

Descriptive statistics were used to summarize the continuous and categorical variables of the study. Categorical variables were expressed as frequencies and percentages and compared using Pearson's χ^2 test. After assessing the distribution of data with histograms (Supplementary Fig. S1), continuous variables were compared using the independent sample *t*-test analysis (for normally distributed) or Wilcoxon rank sum test (Mann-Whitney *U* test) for non-parametric distribution. Patient demographics, comorbidities, and study outcomes were compared between male and female cohorts. The frequency of missing values was analyzed, and Little's MCAR (missing completely at random) was used to screen for missing data patterns. A *p*-value >0.05 signified randomly missing data, while a p-value <0.05 suggested missingness not at random (MNAR) [14]. Data was complete except for randomly missing data patterns in the following variables; "Primary Expected Payer" missing N 31 (0.2 %) and "Median Household Income" missing N 183 (1.4 %). As the overall, randomly missing data was minimal, we marked it missing and excluded it from the analysis.

After handling missing data, we utilized purposeful selection for building the regression model; *p*-value <0.2 was used as a cut-off for the covariates to be included in the final multivariate model [15]. The multicollinearity among independent variables was assessed by measuring the variance inflation factor (VIF) and tolerance (1/VIF). VIF >5 and tolerance value <0.2 was taken as a marker of significant correlation among independent variables [16]. After multivariate regression, the *Mahalanobis distance matching* was used with the propensity score caliper set at (0.2) to create matched cohorts for males and females. Pearson's χ^2 test was applied to the matched cohorts to compare outcomes. A graphical box plot and love plot were created to demonstrate the balance of matching variables for both cohorts (Supplementary Figs. S2 & S3). The matching variables (demographics, disease severity, mortality risk, and >15 different baseline comorbidities) used in the PSM module are listed in Supplementary Table S3. A similar propensity score matching (PSM) model was performed on 30-, 90-, and 180-day readmission analyses to calculate readmission rates on matched cohorts, respectively. Index hospitalizations alive at discharge were retained for readmission analysis to avoid mortality readmission bias. Using combined data from all years, we used a multivariable logistic regression model described above to obtain predictive margins for the adjusted trends over the years; the year was included as an independent variable. Unadjusted Trend analysis was performed using the *Cochran-Armitage* test for binary outcomes and the *Jonckheere-Terpstra* test or *Cuzick*'s test for ordered categorical or continuous variables, given the non-parametric distribution of the study population. Total cost was adjusted for national inflation and merged with cost-charge ratio (CCR)

NRD files. All analyses were conducted using appropriate clustering and weighting samples provided by Healthcare Cost and Utilization Project regulations. Stata v. 18 software (Stata Corp, College Station, TX) was used for all statistical analyses [17]. We used Biorender for the central illustration [18].

3. Results

3.1. Demographic and baseline characteristics

A retrospective analysis was conducted on a cohort of 12,803 hospitalizations for TTC complicated by CS. The majority of patients (74.1 %) were females (N: 9490), while only 3313 (25.9 %) were males. Females were found to be slightly older, with a median age of 68 years (Interquartile range, IQR:19 years) compared to a median age of 65 years (IQR: 19 years) in males ($p < 0.001$). The majority of these patients were admitted non-electively in both the males (94.7 %) & females (94 %), with no significant difference between the two groups (p: 0.377). There was also no difference in weekend vs weekday admission between the two groups (p: 0.414).

The prevalence of various comorbidities also differed between the two groups, with females having a higher prevalence of hyperlipidemia (37 % vs. 31.7 %, $p < 0.001$), pulmonary disease (24.2 % vs. 19 %, $p < 0.001$), pulmonary hypertension (7.6 % vs. 5.9 %, p: 0.032), depression (18.2 % vs. 9.7 %, $p < 0.001$), mood disorders (21.5 % vs. 11.9 %, $p < 0.001$) and hypothyroidism (16.7 % vs. 7 %, $p < 0.001$). In contrast, other comorbidities were more prevalent in males, including smoking history (24.1 % vs. 21.1 %, p: 0.037), CKD stage >3 (20.1 % vs. 16.3 %, p: 0.003), ESRD (4.5 % vs 3.1 %, p: 0.020) and history of coronary artery bypass graft (CABG) surgery (2.2 % vs 1.3 %, $p < 0.001$). Baseline demographics and comorbidities are presented in Table 1 and Fig. 1.

3.2. Gender-based outcomes of unmatched and propensity-matched cohorts of TTC-associated cardiogenic shock

On crude analysis, male patients had higher in-hospital mortality rates along with higher incidence of sudden cardiac arrest (SCA), endotracheal intubation, acute liver injury, acute kidney injury (AKI), and net adverse events (NAE), as summarized in Table 2. On a propensity-matched analysis ($N = 2609$), the majority of the crude differences remain significant, including higher in-hospital mortality (31 % vs. 26 %, $p < 0.001$) and higher incidence of SCA (14 % vs. 10.8 %, $p < 0.001$), endotracheal intubation (52.1 % vs. 48.8 %, p: 0.001), acute liver injury (18 % vs 15.9 %, p: 0.004) and AKI (63.1 % vs 49 %, $p < 0.001$) in male patients.

Interestingly, some differences found insignificant in crude analysis became significant after propensity matching. These include a higher incidence of stroke (7.2 % vs 5.8 %, p: 0.004) and cardiac arrhythmias (55.1 % vs 49.3 %, $p < 0.001$) in males. Although females had a lower incidence of other complications (as mentioned above), they were more frequently placed on mechanical circulatory support as compared to their male counterparts (16.1 % vs 13.2 %, $p < 0.001$). Furthermore, we conducted a stratified analysis by age, dividing the population into cohorts of ≤50 and >50 years. Our results consistently showed that males with cardiogenic shock secondary to TTC had poorer outcomes, regardless of age. For patients ≤50 years, in-hospital mortality was higher for males (24.8 % vs. 16.2 %, $p = 0.004$). Similarly, for those aged >50 years, mortality remained high for males compared to females (31.5 % vs. 27.7 %, $p < 0.01$).

Crude and propensity-matched outcomes are shown in Table 2 and Fig. 2.

3.3. Gender-based differences in resource utilization for TTC-CS

In TTC-CS, males exhibit an extended length of stay (LOS), with a median length of stay of 10 days (Interquartile Range; IQR: 14 days)

Table 1
Gender-based disparities in baseline characteristics and comorbidities in patients with Takotsubo cardiomyopathy associated cardiogenic shock.

Baseline characteristics	Males	Females	p-Value
	$N = 3313$	$N = 9490$	
Age: median (IQR)	65 (19)	68 (19)	<0.001
Insurance type			
Medicare	1843 (55.7 %)	6014 (63.5 %)	<0.001
Medicaid	466 (14.1 %)	1048 (11.1 %)	
Private insurance	730 (22.1 %)	2000 (21.1 %)	
Self-pay	125 (3.8 %)	205 (2.2 %)	
Type of admission			
Non-elective	3133 (94.7 %)	8913 (94 %)	0.377
Elective	177 (5.3 %)	568 (6 %)	
Bed size of the hospital			
Small	330 (9.9 %)	1035 (10.9 %)	0.404
Medium	732 (22.1 %)	2191 (23.1 %)	
Large	2252 (68 %)	6264 (66 %)	
Control/Ownership of Hospital			
Government, nonfederal	488 (14.7 %)	976 (10.3 %)	<0.001
Private, not-profit	2638 (79.6 %)	7707 (81.2 %)	
Private, invest-own	187 (5.6 %)	807 (8.5 %)	
Teaching status of urban hospitals			
Metropolitan non-teaching	400 (12.1 %)	1462 (15.4 %)	0.001
Metropolitan teaching	2831 (85.4 %)	7679 (80.9 %)	
Non-metropolitan hospital	83 (2.5 %)	349 (3.7 %)	
Hospital urban-rural designation			
Large metropolitan areas with at least 1 million residents	2082 (62.8 %)	5561 (58.6 %)	0.003
Small metropolitan areas with <1 million residents	1149 (34.7 %)	3579 (37.7 %)	
Micropolitan areas	67 (2 %)	327 (3.4 %)	
Not Metropolitan (non-urban residual)	16 (0.5 %)	22 (0.2 %)	
Admission day of the week			
Mon–Fri	2453 (74 %)	7134 (75.2 %)	0.414
Sat–Sun	860 (26 %)	2355 (24.8 %)	
Transfer flag indicating combination of discharges involve same day events			
Not a transfer or other same-day stay	2820 (85.1 %)	8071 (85.1 %)	0.592
Transfer involving two discharges from different hospitals	248 (7.5 %)	756 (8 %)	
Same-day stay involving two discharges from different hospitals	98 (3 %)	255 (2.7 %)	
Same-day stay involving two discharges at the same hospital	89 (2.7 %)	288 (3 %)	

(continued on next page)

Table 1 (*continued*)

Baseline characteristics	Males $N = 3313$	Females $N = 9490$	p-Value
Same-day stay involving three or more discharges at the same or different hospitals	58 (1.7 %)	119 (1.3 %)	
Median household income national quartile for patient ZIP code			
0–25th percentile	902 (27.7 %)	2360 (25.2 %)	0.038
26th to 50th percentile	801 (24.6 %)	2591 (27.7 %)	
51st to 75th percentile	788 (24.2 %)	2417 (25.8 %)	
76th to 100th percentile	764 (23.5 %)	1997 (21.3 %)	
Patient state is the same as hospital state			
Non-resident	271 (8.2 %)	756 (8 %)	0.815
Resident	3042 (91.8 %)	8734 (92 %)	
A combined record involving rehabilitation transfer			
Not a combined record or a combined record not involving rehabilitation, evaluation, or other aftercare	3230 (97.5 %)	9261 (97.6 %)	0.792
Combined record involving transfer to rehabilitation, evaluation, or other aftercare	84 (2.5 %)	229 (2.4 %)	
All patient refined DRG: risk of mortality subclass			
Minor likelihood of dying	14 (0.4 %)	67 (0.7 %)	0.006
Moderate likelihood of dying	35 (1 %)	145 (1.5 %)	
Major likelihood of dying	194 (5.8 %)	789 (8.3 %)	
Extreme likelihood of dying	3070 (92.7 %)	8489 (89.5 %)	
All patient refined DRG: severity of illness subclass			
Minor loss of function (includes cases with no comorbidity or complications)	<11 (0.3 %)	27 (0.3 %)	0.002
Moderate loss of function	16 (0.5 %)	90 (0.9 %)	
Major loss of function	264 (8 %)	1051 (11.1 %)	
Extreme loss of function	3022 (91.2 %)	8322 (87.7 %)	
Comorbidities			
Diabetes	867 (26.2 %)	2351 (24.8 %)	0.340
Hyperlipidemia	1052 (31.7 %)	3514 (37 %)	<0.001
Hypertension	1255 (37.9 %)	3739 (39.4 %)	0.380
Smoker	797 (24.1 %)	2002 (21.1 %)	0.037
CKD Stage over 3	667 (20.1 %)	1545 (16.3 %)	0.003
ESRD	148 (4.5 %)	292 (3.1 %)	0.020
Prior CVA	69 (2.1 %)	160 (1.7 %)	0.379
Prior MI	239 (7.2 %)	625 (6.6 %)	0.440
Prior PCI	162 (4.9 %)	347 (3.7 %)	0.077
Prior CABG	74 (2.2 %)	123 (1.3 %)	0.023
Prior defibrillator	26 (0.8 %)	83 (0.9 %)	0.777
Prior pacemaker	77 (2.3 %)	178 (1.9 %)	0.358
OSA	196 (5.9 %)	467 (4.9 %)	0.188
Pulmonary disease	629 (19 %)	2296 (24.2 %)	<0.001
Pulmonary hypertension	195 (5.9 %)	725 (7.6 %)	0.032
Depression	323 (9.7 %)	1727 (18.2 %)	<0.001
Poverty (homelessness)	34 (1 %)	45 (0.5 %)	0.022
Substance abuse	1075 (32.4 %)	2263 (23.8 %)	<0.001
Mood disorder	395 (11.9 %)	2038 (21.5 %)	<0.001
Hypothyroidism	232 (7 %)	1588 (16.7 %)	<0.001
Anemia	168 (5.1 %)	584 (6.2 %)	0.165
Pneumonia	657 (19.8 %)	1642 (17.3 %)	0.050
Liver disease	193 (5.8 %)	387 (4.1 %)	0.019
Malnutrition	741 (22.4 %)	1944 (20.5 %)	0.163
Arrhythmias	1710 (51.6 %)	4669 (49.2 %)	0.136
COVID	111 (3.3 %)	155 (1.6 %)	<0.001
Heart failure	2209 (66.7 %)	6421 (67.7 %)	0.547

Abbreviations: CKD: chronic kidney disease; ESRD: end stage renal disease; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; OSA: obstructive sleep apnea; IQR = interquartile range (P75–P25), <11: non-reportable per HCUP.

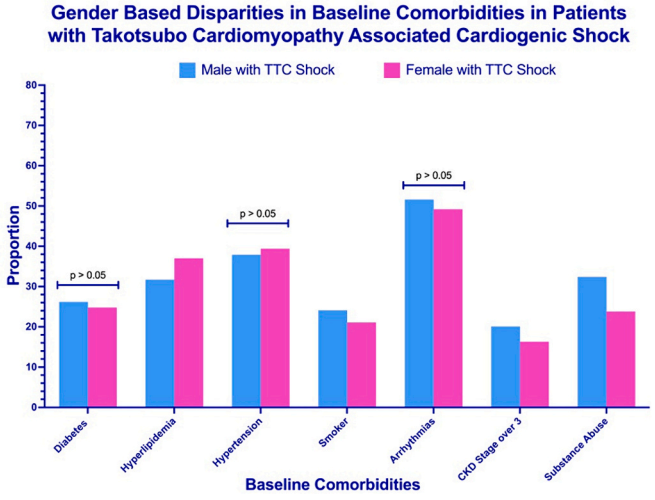

Fig. 1. Gender-based disparities in baseline characteristics and comorbidities in patients with Takotsubo cardiomyopathy associated cardiogenic shock.

compared to 9 days (IQR: 11 days) for females ($p < 0.001$). Moreover, the total cost of hospitalization was also higher in male patients, with the median total cost of USD 54,537 (IQR: $71,224) as compared to USD 42,805 (IQR: $55,327) for females, representing a 21.5 % higher cost utilization ($p < 0.001$). Gender-based differences in resource utilization for TTC-CS are shown in Table 3.

Table 2
Gender-based disparities in crude and propensity-matched in-hospital outcomes of patients with Takotsubo cardiomyopathy associated cardiogenic shock.

Outcomes	Crude outcomes			Propensity-matched outcomes		
	Males *N* = 3312	Females *N* = 9484	*p*-Value	Males N = 2609	Females N = 2609	p-Value
	N (%)	N (%)		N (%)	N (%)	
In-hospital mortality	1061 (32 %)	2490 (26.3 %)	<0.001	809 (31 %)	677 (26 %)	<0.001
SCA	472 (14.3 %)	1039 (10.9 %)	0.003	366 (14 %)	282 (10.8 %)	<0.001
MCS	498 (15 %)	1527 (16.1 %)	0.361	343 (13.2 %)	421 (16.1 %)	<0.001
CVA	229 (6.9 %)	537 (5.7 %)	0.084	187 (7.2 %)	151 (5.8 %)	0.004
Endotracheal intubation	1751 (52.8 %)	4654 (49 %)	0.013	1359 (52.1 %)	1272 (48.8 %)	0.001
Arrhythmias	1710 (51.6 %)	4669 (49.2 %)	0.136	1439 (55.1 %)	1285 (49.3 %)	<0.001
Acute liver injury	681 (20.6 %)	1527 (16.1 %)	<0.001	468 (18 %)	414 (15.9 %)	0.004
Acute kidney injury	2131 (64.3 %)	4668 (49.2 %)	<0.001	1646 (63.1 %)	1279 (49 %)	<0.001

Abbreviations: SCA: sudden cardiac arrest; MCS: mechanical circulatory support; CVA: cerebrovascular accident.

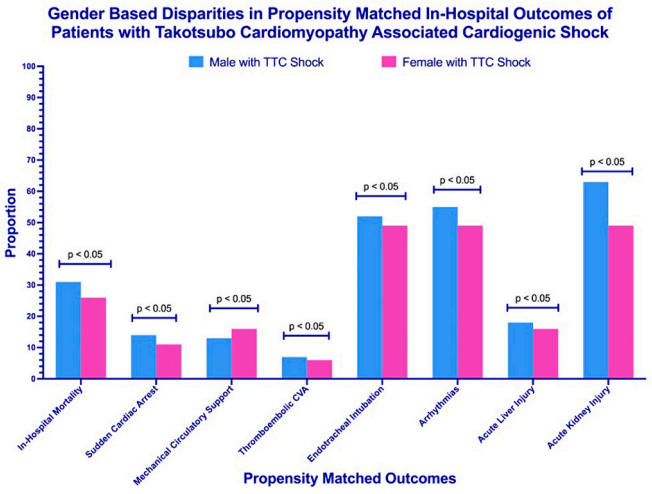

Fig. 2. Gender-based disparities in propensity-matched in-hospital outcomes of patients with Takotsubo cardiomyopathy associated cardiogenic shock.

Table 3
Gender-based disparities in resource utilization of patients with Takotsubo cardiomyopathy associated cardiogenic shock in index admission.

Resource utilization	Males	Females	p-Value
	Median (IQR)	Median (IQR)	
Index admission			
LOS (days)	10 (14)	9 (11)	<0.001
Total cost (USD $)	54,537 (71,244)	42,805 (55,327)	<0.001
Total adjusted charge (USD $)	192,620 (286,644)	165,926 (226,189)	<0.001

Abbreviations: LOS: length of stay; IQR = interquartile range (P75–P25); USD: United States dollar.

3.4. Yearly trend of gender-based differences in resource utilization for patients with TTC-CS

From 2016 to 2020, no significant change was observed in LOS of hospitalization for TTC-CS for both males and females (p-trend > 0.05). The median total cost of hospitalization has also not changed significantly in male patients across the years (p-trend >0.05). However, female patients had an up-trend in the total cost of hospitalization, increasing from $40,105 (IQR: 52,044) in 2016 to $46,610 (IQR: 56,688) in 2020, representing a 16.2 % increase in cost utilization (p-trend: 0.0008) as shown in Supplemental Table S4.

3.5. Gender-based differences in readmission rates and yearly trends of mortality, coronary angiogram and MCS use for patients with TTC-CS

No significant differences were observed between males and females for all-cause readmission rates at 30, 90 & 180-day readmissions ($p > 0.05$). Readmission rates on a propensity-matched cohort are shown in Table 4. In contrast to resource utilization in index admission, males and females with TTC-CS did not have a significant difference in resource utilization in subsequent readmissions except for a slightly higher cost of 30-day readmission in males, as shown in Supplementary Table S5.

Mortality has not changed significantly and has averaged around 27.8 % from 2016 to 2020 (p-trend >0.05). The use of coronary angiograms at index admission has decreased across the years, from 50 % in 2016 to 43 % in 2020 (p-trend: 0.02). Similarly, overall, the need for mechanical circulatory support has also trended down from 17 % to 13 % from 2016 to 2020 (p-trend: 0.029), although this change was more pronounced for females (20.2 % to 14.4 %, p-trend 0.022). Yearly trends of mortality, PCA, and MCS use for patients with TTC-CS are shown in Table 5 and Fig. 3.

4. Discussion

In the present large cohort, we found significant gender differences in the characteristics and outcomes of patients with TTC-induced CS. Thus, some of the comorbid conditions/risk factors (smoking, renal disease, previous CABG surgery, liver disease) were more common in males, while the others (hyperlipidemia, pulmonary disease, psychiatric disorders, and hypothyroidism) were more common in females. On the other hand, females had less likelihood of dying during hospitalization or developing in-hospital complications, including sudden cardiac arrest, cardiac arrhythmia, respiratory failure, acute liver injury, and Acute Kidney Injury. This translated to a lesser economic burden, notably shorter hospital stays and lower healthcare costs for the women's group (Fig. 4).

Our findings agree with previous research demonstrating better in-hospital outcomes among females with TTC than males [19–21]. Brinjikji et al. used the National Inpatient Sample database from 2008 to 2009 to evaluate the burden of TTC and its related factors. Thus, in a total cohort of 24,701 patients, male sex was found to be associated with

Table 4
Readmission rates on propensity matched cohort.

Readmission rates on propensity matched cohort			
30-day readmission	**Males**	**Females**	**p-Value**
	***N* = 2369**	**N = 2369**	
	N (%)	**N (%)**	
Readmits	187 (7.9 %)	187 (7.9 %)	1.000
90-Day readmission	**Males**	**Females**	**p-Value**
	***N* = 1940**	**N = 1940**	
	N (%)	**N (%)**	
Readmits	349 (18 %)	363 (18.7 %)	0.412
180-Day readmission	**Males**	**Females**	**p-Value**
	***N* = 1276**	**N = 1276**	
	N (%)	**N (%)**	
Readmits	317 (24.9 %)	327 (25.6 %)	0.54

Table 5
Yearly trend of in-hospital mortality, utilization of percutaneous coronary angioplasty, and mechanical circulatory support modalities for patients with Takotsubo cardiomyopathy associated cardiogenic shock.

Year	In-hospital mortality			PCA			MCS		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
2016	28.6 %	31 %	26.7 %	50 %	45.8 %	54.7 %	16.7 %	15.9 %	20.2 %
2017	28.4 %	34.2 %	26.5 %	48.9 %	48.2 %	53.9 %	17.7 %	17.7 %	18.3 %
2018	27.3 %	32.5 %	25.7 %	46.4 %	42.5 %	51.4 %	15.8 %	19.1 %	17.6 %
2019	27.1 %	32.3 %	25.9 %	48.3 %	45 %	53.2 %	16.7 %	21 %	18.2 %
2020	27.6 %	30.8 %	25.6 %	42.9 %	36 %	46.4 %	12.9 %	12.6 %	14.4 %
p-Trend	0.526	0.74	0.619	0.023	0.014	0.007	0.029	0.353	0.022

Abbreviations: PCA: percutaneous coronary angiogram; MCS: mechanical circulatory support.

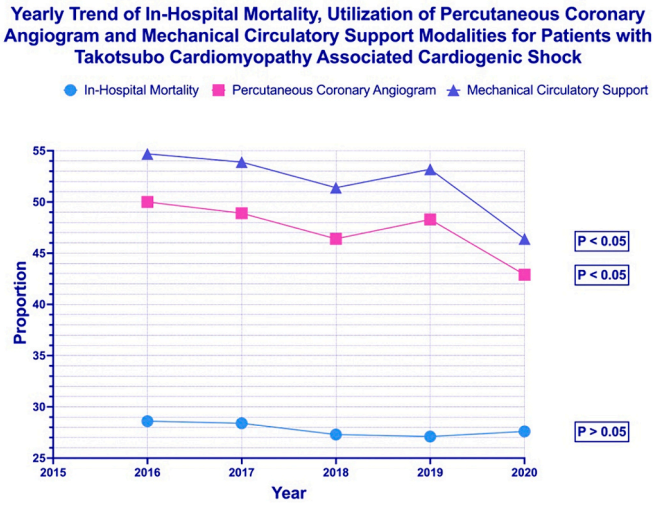

Fig. 3. Yearly trend of In-hospital mortality, utilization of percutaneous coronary angiogram, and mechanical circulatory support modalities for patients with Takotsubo cardiomyopathy associated cardiogenic shock.

increased rates of underlying critical illness and in-hospital mortality [19]. Likewise, analysis of the GEIST (German Italian Spanish Takotsubo) registry has shown that in TTC patients, men had higher rates of cardiogenic shock (16 % vs 6 %, $P < 0.05$) and mortality, both at the acute phase (8 % vs 3 %, $P < 0.05$; OR: 2.26; 95 % CI: 1.16–4.40) and long-term mortality (men 10 %, women 3.8 %; HR: 1.83; 95 % CI: 1.32–2.52) [20]. In line with this, Santoro et al. established The GEIST prognosis score to assess the risks of in-hospital complications among patients with TTC [21]. One of the key included items in this score was male gender, as the latter was shown to be a strong predictor of worse outcomes (OR, 2.46; 95 % CI, 1.61–3.75; $P < 0.001$) [21].

Classically, the effects of gender in determining different disease profiles are primarily attributed to sex hormone disparities between males and females, potentially exposing them to either worse or better clinical and therapeutic outcomes. However, since the vast majority of patients with TTC are postmenopausal females (the median age of females in our study was 68 years), factors other than female sex hormones (i.e., male sex-related factors, female non-hormonal factors, or disease-related factors) should be incriminated in explaining the influence of gender on the severity of TTC-CS.

The reversibility of LV dysfunction during TTC depends on the ability of the myocardium to recover from catecholamines-induced cardiotoxicity. Males may be more preconditioned to develop severe forms of TTC, likely due to more vulnerable cardiovascular health. Thus, male patients tend to have more comorbid conditions related to cardiovascular health (as observed in our study), which can play a significant role in the observed gender differences during TTC, favoring a worse disease course in this group. Importantly, deaths in the context of TTC are mainly driven by the underlying comorbidities rather than by the disease-related complications [19]. Males also develop TTC at younger ages, which was shown to be correlated with higher rates of cardiogenic shock (15.3 % vs. 9.1 % vs. 8.1 %; $p = 0.004$) and in-hospital mortality

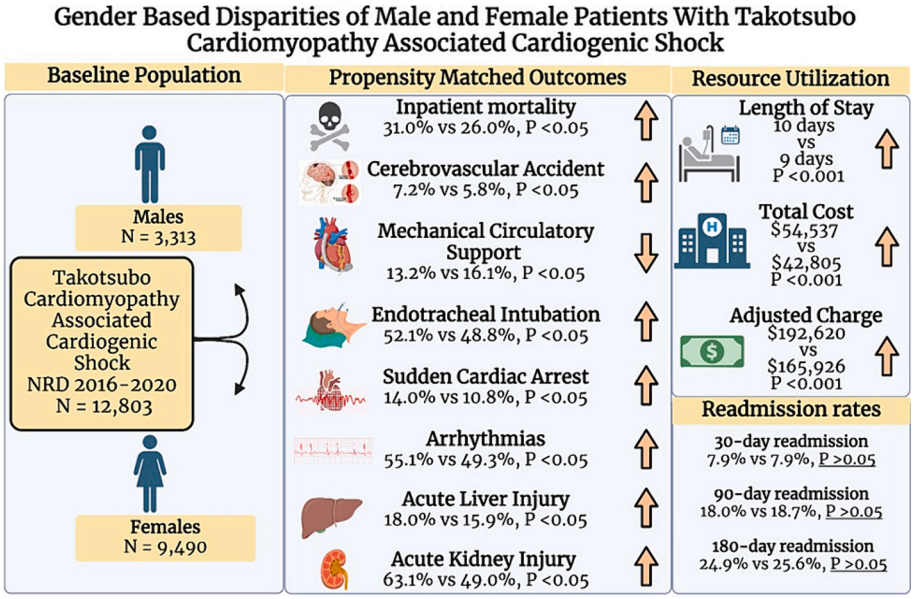

Fig. 4. Central illustration. Created with Biorender.com.

(6.6 % vs. 3.6 % vs. 5.1 %; $p = 0.07$) [22]. However, the fact that both genders in our study had cardiovascular risk factors (though more pronounced in males) suggests the role of other factors than preexisting morbidity.

In males, testosterone may favor the decompensation of TTC cardiomyopathy by mediating the secretion of molecules with deleterious circulatory action. For example, testosterone was shown to promote the release of harmful vasoconstrictors such as thromboxane A2, norepinephrine, angiotensin II, and endothelin-1 via a genomic mechanism [23]. These molecules can favor worse outcomes during acute circulatory collapse. For example, endothelin-1 was shown to exert a critical role in the transition from compensated to decompensated cardiac dysfunction [24]. Gonadectomy with hormone replacement showed that testosterone, but not estradiol, increases the soluble suppression of tumorigenicity 2 (sST2) levels in male mice with myocarditis [25]. sST2 is a member of the interleukin 1 receptor family that acts as the circulating decoy receptor for interleukin-33 (IL-33), thus preventing the cardioprotective effects of the ST2/IL-33 signaling and promoting maladaptive myocardial remodeling and cardiomyocyte apoptosis [26].

There is a body of evidence indicating that the female heart is more conditioned to tolerate acute injury. Thus, females have been shown to achieve better myocardial salvage following successful reperfusion, as compared to males [27]. In a mouse model of acute MI, female mice showed improved survival, functional recovery, and limited remodeling, suggesting better control of physiological inflammation in post-cardiac injury [28]. Another animal experiment has revealed that female cardiomyocytes have more survival capacity when challenged with oxidative stress compared to male cardiomyocytes [29]. Moreover, physiologically, the female heart structure, particularly the ventricular mass, is less affected by senescence-related changes than the male heart. Notably, the latter loses nearly 1 g of myocardium each year (accounting for the loss of approximately 64 million cells/year), a phenomenon not seen in females. Aging also leads to non-ventricular myocyte hypertrophy in males but not in females [30]. This would have particular significance in TTC cardiomyopathy, a condition that mainly affects elderly patients; therefore, the group with a less senesced cardiovascular system would be expected to recover better.

Not all TTC females are menopausal; therefore, the contribution of estrogens in disease progression can't be excluded. In the TTC model, ovariectomized rats receiving estrogen supplementation were less prone to cardiac dysfunction and blood pressure and heart rate increase than rats that didn't receive estrogen [31]. These effects were mediated by direct inhibitory action on the hypothalamo-sympatho-adrenal outflow, as well as the upregulation of cardioprotective substances, notably heat shock protein 70 and atrial natriuretic peptide. A common hypothesis is that the females' high susceptibility to TTC is in large part linked to a physiological drop in estrogen; however, an increase in estrogen at the onset of TTC could contribute to preventing complicated forms in females.

The pathophysiology of TTC is different between genders, leading to different clinical outcomes. An important notion is that TTC can be triggered by emotional stress or by physical stress, such as infections, surgery, physical activities, episodes of severe hypoxia, and neurological events. Physically triggered TSC is more common in men and has worse outcomes [20]. This could be due to the ephemeral nature of emotional triggers (e.g., familial conflict), which is contrasted by the long-lasting and potentially irreversible nature of physical triggers (e.g., acute systemic infection or neurological insult) that would eventually create different levels and burden of catecholamine-mediated cardiotoxicity [32].

5. Study strengths and limitations

We acknowledge several limitations to our study. First, due to its retrospective design, we cannot eliminate the possibility of interference from the unmeasured confounders. Second, the presented data were obtained from a National Database, which is exposed to administrative bias and information inaccuracy in a medical sense. Third, due to a lack of information, the long-term morbidity and mortality outcomes could not be explored. Furthermore, we could not assess the influence of gender on the response to different treatments, which could have generated important findings with potential interventional implications. Finally, the left ventricular ejection was not available in the database, which could be an important effect modifier.

On the other hand, our study, owing to its relatively robust and large data (including that of the male group, which represents a rare and underrepresented group), nationwide nature, and insightful findings, contributes to expanding the current knowledge regarding TTC and its characteristic patterns.

6. Conclusion

Although women are by far more commonly affected by TTC, men tend to have a worse disease course than women, particularly in TTC-induced CS. This manifests in their higher susceptibility to short-term in-hospital morbidity, mortality, and delayed recovery from TTC-induced CS. Intensive monitoring and aggressive use of effective therapies are required in male patients. The mechanisms of gender disparity during TTC are still unknown, which implies the need for further investigation.

Ethical statement

This national readmission database-guided study did not require ethical approval from the institutional review board as this is a publicly available deidentified database.

CRediT authorship contribution statement

Shafaqat Ali: Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Yehya Khlidj:** Writing – original draft. **Manoj Kumar:** Writing – original draft. **Sanjay Kumar:** Data curation. **Sanchit Duhan:** Writing – review & editing, Visualization. **Faryal Farooq:** Writing – original draft. **Bijeta Keisham:** Writing – review & editing. **Pramod Kumar Ponna:** Visualization. **Kalgi Modi:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100453.

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