Journal of the American Heart Association

ORIGINAL RESEARCH

Cardiogenic Shock Complicating Takotsubo Syndrome: Sex-Related Differences

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BACKGROUND: Sex-related differences in Takotsubo syndrome have been described, but no information is available in patients who develop cardiogenic shock.

METHODS AND RESULTS: Of 412 patients with Takotsubo syndrome with cardiogenic shock, 71 (17.2%) were men. Male patients were older (71.1±12.2 versus 65.3±17.1 years, *P*<0.001), more frequently smokers (47 [66.2%] versus 66 [19.4%], *P*<0.01), with higher prevalence of neoplasms (6 [8.5%] versus 8 [2.3%], *P*=0.01), lower left ventricular ejection fraction (31% versus 37%, *P*<0.001), more frequent invasive mechanical ventilation (30 [42.3%] versus 90 [26.4%], *P*=<0.01), higher rate of infections (43 [60.6%] versus 148 [43.4%], *P*=<0.01), and longer in-hospital stay (19±20 days versus 13±15 days, *P*=0.02). A total of 55 patients (13.3%) died during hospital admission, and 90 patients (21.8%) died at the end of the 5-year follow-up. Male sex was not significantly associated with the in-hospital (odds ratio, 1.31 [95% CI, 0.64–2.68]) or 5-year mortality rate (hazard ratio, 1.66 [95% CI, 0.93–2.94]). In the matched cohort, no significant differences in the short- and long-term mortality rate were found either.

CONCLUSIONS: Cardiogenic shock due to Takotsubo syndrome has high short- and long-term mortality rates that are similar in men and women.

Key Words: cardiogenic shock ■ heart failure ■ prognosis ■ sex ■ Takotsubo

Takotsubo syndrome (TTS) was first described in 1990.[1] It is characterized by acute transient left ventricular systolic dysfunction typically triggered by severe emotional or physical stress, in the absence of significant or complicated coronary artery disease. Although several pathophysiologic theories have been proposed,[2] the classic one suggests that TTS is caused by a massive sympathetic nervous system activation and subsequent catecholamine-induced myocardial injury.[2,3]

Even though TTS is about 10 times more frequent in women than in men, previous studies have shown that TTS in men entails a higher-risk phenotype with particular clinical features, such as a higher prevalence of comorbid conditions and physical triggers, and higher rates of ventricular arrhythmias, cardiogenic shock, in-hospital death, and long-term death.[4–9]

Cardiogenic shock (CS) is defined by end-organ hypoperfusion and tissue hypoxia due to deficient cardiac output. Several observational studies have investigated the impact of sex in clinical presentation and outcomes of CS, obtaining contrasting results. Recent observational data showed worse survival outcomes in women with CS of multiple pathogeneses.[10–13] In contrast, a

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This manuscript was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036800

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This is the first study to analyze sex-related differences in patients with cardiogenic shock and Takotsubo syndrome.

What Are the Clinical Implications?

- Sex does not affect the prognosis once cardiogenic shock is established in patients with cardiogenic shock due to Takotsubo syndrome.
- Management and treatment of cardiogenic shock due to Takotsubo syndrome should be similar for both sexes, though further studies are needed to explore sex-specific factors.

Nonstandard Abbreviations and Acronyms

CS	cardiogenic shock
CS-TTS	cardiogenic shock due to Takotsubo syndrome
CULPRIT-SHOCK	Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock
DOREMI	Dobutamine Compared With Milrinone
IABP-SHOCK II	Intra-aortic Balloon Pump in Cardiogenic Shock II
RETAKO	Registry of Takotsubo Syndrome
SCAI	Society for Cardiovascular Angiography and Interventions
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
TTS	Takotsubo syndrome

substudy of the IABP-SHOCK II (Intra-aortic Balloon Pump in Cardiogenic Shock II) trial did not show significant sex-related differences in short- and long-term outcomes of patients with CS complicating acute myocardial infarction.[14] Also, a Spanish monocentric study did not observe significant outcome differences between sexes in patients with CS.[15] Moreover, a post hoc analysis of the randomized DOREMI (Dobutamine Compared With Milrinone) trial showed no significant sex differences in outcomes of patients with CS.[16]

According to several series, CS complicates 5% to 20% cases of TTS, and it has been clearly associated with a higher morbidity burden and worse short- and long-term outcomes.[17–19] However, whether CS due to Takotsubo syndrome (CS-TTS) presents with significant clinical differences in male and female sex, and if, as demonstrated in patients with general TTS, male sex also implies a higher risk profile in patients with CS-TTS has not yet been analyzed.

The aim of our study was to investigate potential sex-related differences in clinical characteristics at admission, during hospitalization, and follow-up of patients with CS-TTS included in a large multicenter registry.[20]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

All data were collected from the Spanish multicenter RETAKO (Registry of Takotsubo Syndrome). It is a voluntary observational study that enrolled patients from 23 centers in Spain. Its rationale and design have been previously described.[21] Baseline patient characteristics, triggering factors, in-hospital course, procedures, and therapies performed at the discretion of the attending physician, and short- and long-term outcomes were captured through a dedicated electronic case report form. The admission value of all vital signs, clinical measurements, and laboratory

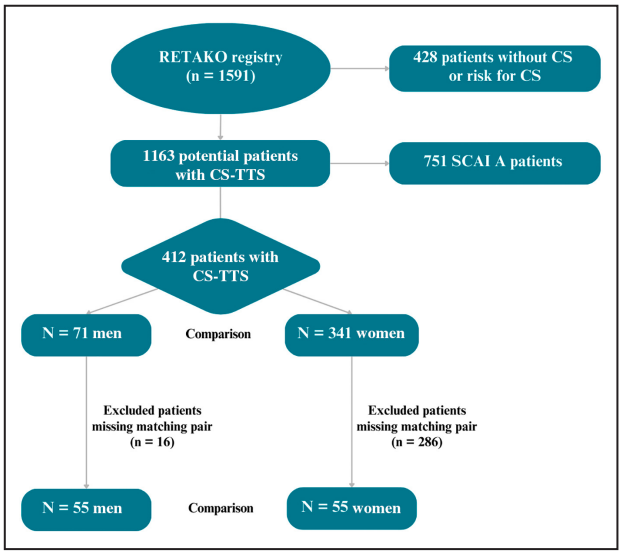

Figure 1. Algorithm of the study design.
The study consisted of an analysis of the Spanish multicenter RETAKO registry. The diagram depicts the study design, for which comparisons were carried out between male and female patients with TTS both in the overall and matched cohorts. CS indicates cardiogenic shock; CS-TTS, cardiogenic shock complicating Takotsubo syndrome; RETAKO, Registry of Takotsubo syndrome; and SCAI, Society for Cardiovascular Angiography and Interventions.

values was defined as either the first value recorded after hospital admission or the value recorded closest to hospital admission. All participants were treated in compliance with the principles of the Declaration of Helsinki and provided signed informed consent for the use of personal data for research purposes. The study was approved by the institutional ethics committee.

Study Population

We analyzed a database of consecutive unique adult patients aged >18 years admitted to the hospital with a diagnosis of TTS between January 1, 2003, and December 31, 2022. The inclusion in the RETAKO registry required a TTS diagnosis according to the Modified Mayo Clinic Criteria (Data S1).[22] Patients who had CS-TTS before December 31, 2016, whose characteristics and outcomes have been previously reported,[23] have also been included in the present study. CS was clinically diagnosed at each hospital, and for the purposes of this study it was defined by 1 of the following criteria: systolic blood pressure <90 mm Hg for at least 30 minutes, use of vasoactive agents or mechanical support to maintain systolic blood pressure >90 mm Hg, cardiac index <2.2 L/min per m^2 in the absence of hypovolemia, each determined to be secondary to cardiac dysfunction. In Data S2 and S3, the definitions of the analyzed variables and the primary and secondaries objectives of the study are described.

Patients without CS at admission and not considered at risk for developing CS were excluded. To better select and stratify patients with CS, investigators at each center retrospectively evaluated patients assigned to the CS group and classified according to the Society for Cardiovascular Angiography and Interventions (SCAI) staging system for CS severity, which provides stepwise mortality risk stratification in TTS.[24] Patients who persisted in SCAI stage A

Table 1. Baseline Characteristics of Patients

	Overall cohort (n=412)		Propensity-matched cohort (n=110)	
	Men, n=71	Women, n=341	Men, n=55	Women, n=55
Age, y	71±12	65±17	66±16	69±13
Comorbidities				
Hypertension	40/71 (56)	214/341 (63)	33/55 (60)	31/61 (56)
Diabetes	15/71 (21)	66/341 (19)	12/55 (22)	13/55 (24)
Smoking	47/71 (66)	66/341 (20)	32/55 (58)	33/55 (60)
Pulmonary disease	24/71 (34)	83/341 (24)	18/55 (33)	18/55 (33)
Malignancies	6/71 (8)	8/341 (2)	2/55 (4)	4/55 (7)
Coronary artery disease	1/71 (1)	13/341 (4)	1/55 (2)	2/55 (4)
Charlson comorbidity index	4.16±2.7	4.08±2.0	4.04±2.5	4.17±3.5
Clinical presentation				
Chest pain	28/71 (39)	200/341 (59)	26/55 (47)	24/55 (44)
Dyspnea	29/71 (41)	134/341 (30)	22/55 (40)	22/55 (40)
Stressful trigger				
None	15/71 (27)	91/341 (31)	15/55 (39)	13/55 (34)
Emotional	9/71 (13)	101/341 (30)	8/55 (15)	10/55 (18)
Physical	47/71 (66)	149/341 (44)	32/55 (58)	32/55 (58)
Echocardiogram				
TTS pattern				
Apical	60/71 (86)	299/341 (88)	47/55 (85)	50/55 (91)
Midventricular	7/71 (10)	27/341 (8)	6/55 (11)	4/55 (7)
Basal	2/71 (3)	6/341 (2)	0	1/55 (2)
Focal	2/71 (3)	9/341 (3)	2/55 (4)	0
LVEF at admission, %	31±12	37±12	32±12	34±12
Right ventricular failure	2/71 (3)	23/341 (7)	1/55 (2)	3/55 (6)
LVOTO	9/71 (13)	61/341 (18)	8/55 (15)	7/55 (13)
Severe MR-SAM	5/71 (3)	18/341 (1)	2/55 (4)	3/55 (5)

Values are mean±SD, or n/N (%). LVEF indicates left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR-SAM, mitral regurgitation due to systolic anterior movement of the mitral leaflets; and TTS, Takotsubo syndrome.

(at risk for CS) after 24 hours from admission were excluded.

Statistical Analysis

Categorical variables were compared using a χ^2 analysis or Fisher exact test. Continuous variables are presented as mean±SD and were compared with the Student's *t* test for independent samples or the Mann–Whitney *U* test. Univariable and multivariable logistic regression analyses were used to calculate estimated odds ratios (ORs) and 95% CIs for factors associated with male sex and in-hospital death. Univariate Cox regression analyses were conducted to examine the association of baseline covariates with 5-year mortality rate. Subsequently, a backward stepwise Cox regression analysis (inclusion criteria, $P<0.05$; exclusion criteria, $P<0.1$) was performed to identify potential confounding variables and predictive factors for 5-year mortality rate. Missing data were <10% for most covariates (Table S1). Propensity score 1:1 matching analysis was used to define subgroups of male and female patients, providing a comparison between clinical characteristics and outcomes in both sexes, both in the overall cohort and in the matched cohort. Propensity score matching included age, smoking status, history of neoplasm, and physical trigger; match tolerance was set at <10% of the standard deviation of the propensity score values. Kaplan–Meier curves and log-rank tests were used to assess survival function at 30 days and at 5 years of follow-up. Data were analyzed with Stata software version 17.0 (StataCorp, College Station, TX).

RESULTS

Clinical Characteristics

Of the 1591 patients included in RETAKO registry, 428 were excluded for not presenting with CS during the admission and not being at risk for CS. Of the remaining 1163 potential patients with CS-TTS, 751 were excluded for persisting in SCAI stage A (Figure 1). Overall, 26% of the patients with TTS presented with CS (25% of women and 33% of men, $P<0.01$). These 412 patients in SCAI stages B through E constituted the overall cohort.

Baseline characteristics stratified by sex of the overall and matched cohorts are reported in Table 1 and Table S2. Seventy-one (17%) of 412 patients with CS-TTS were men. Male patients were significantly older, with higher prevalence of smoking habits and neoplasms. Other comorbidities were distributed in the 2 sexes without significant differences: The prevalence of arterial hypertension was 62%; diabetes, 20%; pulmonary disease, 26%; and coronary artery disease, 3%. Chest pain was a symptom in 39% of male patients and in 59% of female patients ($P=<0.01$), whereas dyspnea was accused by 41% and 30%, respectively ($P=0.81$). A physical trigger was present in the majority of the patients, with higher prevalence in

Table 2. Vital Signs, Illness Severity Scores, Laboratory Data, and Therapies

	Men, n=71	Women, n=341	*P* value
Vital signs and illness severity scores			
Systolic blood pressure, mm Hg	94±28	95±23	0.84
Mean blood pressure, mm Hg	70±19	69±16	0.77
Heart rate, beats/min	104±28	93±23	<0.01
Shock index	1.17±0.4	1.07±0.7	0.23
Glasgow Coma Scale	12.9±3.6	13.1±3.0	0.87
Prehospital cardiac arrest	2/71 (3)	13/341 (4)	0.68
SCAI B	27/71 (38)	159/341 (47)	0.19
SCAI C	32/71 (45)	109/341 (32)	0.03
SCAI D	4/71 (6)	37/341 (11)	0.20
SCAI E	8/71 (11)	36/341 (11)	0.92
Laboratory data			
Hemoglobin, g/L	133±2	129±2	0.15
Platelets, 10^3 g/L	236±92	252±118	0.31
Creatinine, mg/dL	1.3±0.9	1.1±1.1	0.25
BUN, mg/dL	42±31	45±41	0.50
Peak troponin T, ng/mL*	1780±3276	1210±2175	0.09
Peak NT-proBNP, ng/L	10 184±14 467	9929±14 489	0.91
pH	7.34±0.1	7.35±0.1	0.52
Peak lactate, mmol/L	3.8±3	3.6±4	0.72
Therapies and procedures			
Number of vasoactive and inotropic drugs in the first 24 h	1.0±1	0.8±1	0.15
Vasoactive Inotropic Score first 24 h	31±48	26±46	0.47
Noninvasive mechanical ventilation	17/71 (24)	66/341 (19)	0.38
Invasive mechanical ventilation	30/71 (42)	90/341 (26)	0.01
Orotracheal intubation, d	3.7±5	4.5±9	0.57
Renal replacement therapy	4/71 (6)	17/341 (5)	0.82
Intra-aortic balloon pump	3/71 (4)	21/341 (6)	0.53
Impella	0/71	3/341 (1)	0.43
Extracorporeal membrane oxygenation	2/71 (3)	6/341 (2)	0.56
Days of mechanical support	1.7±2	2.7±3	0.38

Values are mean±SD, or n/N (%). NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; and SCAI, Society for Cardiovascular Angiography and Interventions stage.

*In 18 of 23 centers, high-sensitivity troponin T was used, while in 5 of 23 centers, high-sensitivity troponin I was used. Values before the year 2010 were not included in this analysis as they were obtained using conventional troponin assays.

men. Men had a lower left ventricular ejection fraction (Table S3), whereas no significant differences between the 2 sexes were found regarding echocardiogram pattern, with a preponderance of the apical ballooning pattern (87%), or on the incidence of left ventricular outflow tract obstruction (17%) or severe mitral regurgitation due to systolic anterior movement of the mitral leaflets (5.6%).

Vital signs, illness severity scores, laboratory data, and therapies performed are reported in Table 2. At admission, the mean blood pressure was 69±17 mm Hg, and the peak lactate was 3.6±3.4 mmol/L, without differences between sexes. SCAI shock stage was B in 38% and 47% (P=0.19), C in 45% and 32% (P=0.03), D in 6% and 11% (P=0.20) of male and female patients, respectively, and E in 11% of both sexes (P=0.92). Four percent of patients had out-of-hospital cardiac arrest, and the vasoactive inotropic score in the first 24 hours was 27±46 points, without differences between men and women.

Concerning therapies and procedures used, 8% of the patients required mechanical circulatory support: 24 intra-aortic balloon pump, 3 intravascular microaxial blood pump (Impella, Abiomed), and 8 venoarterial extracorporeal membrane oxygenation. Furthermore, noninvasive mechanical ventilation was used in 20% of the patients; invasive mechanical ventilation was used in 30% of patients and during 4.3±8.5 days; renal replacement therapy was required in 5% of the patients. Therapies and procedures used did not significantly differ between sexes, except for more frequent use of invasive mechanical ventilation in male patients.

After multivariate analysis, current smoking status (OR, 9.2 [95% CI, 4.9–17.4]) and the presence of a physical trigger (OR, 3.1 [95% CI, 1.6–5.9]) remained variables associated with male sex (Table 3). We performed 1:1 propensity score matching for age, current smoking status, history of neoplasm, and physical trigger; the SD of the propensity scores was 0.17, and a match caliper of 0.01 was used. We identified 55 paired couples of patients whose baseline characteristics did not significantly differ between men and women. In the matched cohort, male and female patients had similar age, current smoking status, history of neoplasm, and physical trigger prevalence.

Table 4. Complication and In-Hospital Course

	Men, n=71	Women, n=341	*P* value
In-hospital death	12/71 (17)	43/341 (13)	0.34
Cardiovascular cause	7/71 (10)	23/341 (7)	0.36
Other causes	5/71 (7)	20/341 (6)	0.71
Atrial fibrillation	13/71 (18)	52/341 (15)	0.52
Ventricular arrhythmias	10/71 (14)	28/341 (8)	0.12
Major bleeding	6/71 (8)	24/341 (7)	0.68
Stroke	1/71 (1)	13/341 (4)	0.31
Infection	43/71 (61)	148/341 (43)	0.01
Acute renal injury	24/71 (33)	85/341 (25)	0.12
In-hospital stay, d	19±20	13±15	0.02

Values are mean±SD, or n/N (%).

Outcome

Complications during the hospital course stratified by sex in the overall cohort are exposed in Table 4. No significant sex differences were found regarding development of atrial fibrillation (16%), ventricular arrhythmias (9%), intraventricular thrombus (4%), systemic embolic events (3%), cerebrovascular accident (3%), worsening of renal function (26%), and major bleeding (7%), whereas infections were significantly more frequent in male patients. No significant sex difference regarding the mentioned complications were found in the matched cohort.

The in-hospital stay of male patients was longer, whereas in-hospital death did not significantly differ between sexes. After propensity score matching, in-hospital stay was 18±20 days in men versus 17±22 days

Table 3. Univariable and Multivariable Analysis for Factors Associated With Male Sex

	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, per 5-y increase*	0.85 (0.77–0.93)	0.001	0.91 (0.81–1.01)	0.08
Hypertension	0.77 (0.46–1.29)	0.31	…	…
Diabetes	1.12 (0.59–2.10)	0.73	…	…
Smoking*	8.16 (4.66–14.29)	<0.001	9.19 (4.86–17.4)	<0.01
Pulmonary disease	1.59 (0.92–2.75)	0.10	…	…
Malignancies*	3.84 (1.29–11.4)	0.02	1.69 (0.43–6.63)	0.46
Physical trigger*	2.52 (1.48–4.31)	0.001	3.05 (1.59–5.85)	<0.01
LVEF (per 5-point increase)	0.82 (0.73–0.92)	0.001	0.88 (0.77–1.00)	0.05
Apical ballooning	0.77 (0.37–1.57)	0.47	…	…

LVEF indicates left ventricular ejection fraction; and OR, odds ratio.
*Variables used for propensity score matching. Caliper 0.01. Propensity score SD: 0.17.

in women (*P*=0.81), and in-hospital death was 18% in men and 11% in women (*P*=0.28). Within 30 days from admission, the short-term mortality rate in men and women was 11% and 9%, respectively (*P*=0.57), in the overall cohort, and 9% and 13% in the matched cohort (*P*=0.54). The mortality rate from 30 days to 5-year follow-up was 6.3% in men and 3.5% in women (*P*=0.30) in the overall cohort, and 4.0% and 6.3%, respectively, in the matched cohort (*P*=0.62). Kaplan–Meier curves with landmark analysis at 30 days in the overall and the matched cohorts are displayed in Figure 2. The mortality curves of the whole cohort of patients with TTS from the RETAKO registry, stratified by sex, are shown in Figures S1 and S2.

On multivariable analysis (Table 5), age (OR per 5-year increase,1.16 [95% CI, 1.01–1.34]), diabetes (OR, 2.18 [95% CI, 1.08–4.38]), and malignancies (OR, 5.79 [95% CI, 1.62–20.7]) remained independently associated with higher in-hospital death in the overall population, whereas male sex did not (OR, 1.31 [95% CI, 0.64–2.68]). Similarly, age (HR per 5-year increase,1.28 [95% CI, 1.14–1.45]), diabetes (HR, 1.86 [95% CI, 1.05–3.30]), pulmonary disease (HR, 2.08 [95% CI, 1.23–3.54]), and malignancies (HR, 4.23 [95% CI, 1.23–14.5]) were independent predictors of the long-term mortality rate.

DISCUSSION

The main findings of this study are (1) approximately one-sixth of patients with CS-TTS are men; (2) compared with women, men with CS-TTS are older and have a higher prevalence of comorbid conditions and physical triggers; (3) CS-TTS entails substantial in-hospital complications and significant short- and long-term mortality rates; and (4) sex is not associated with the prognosis in CS-TTS.

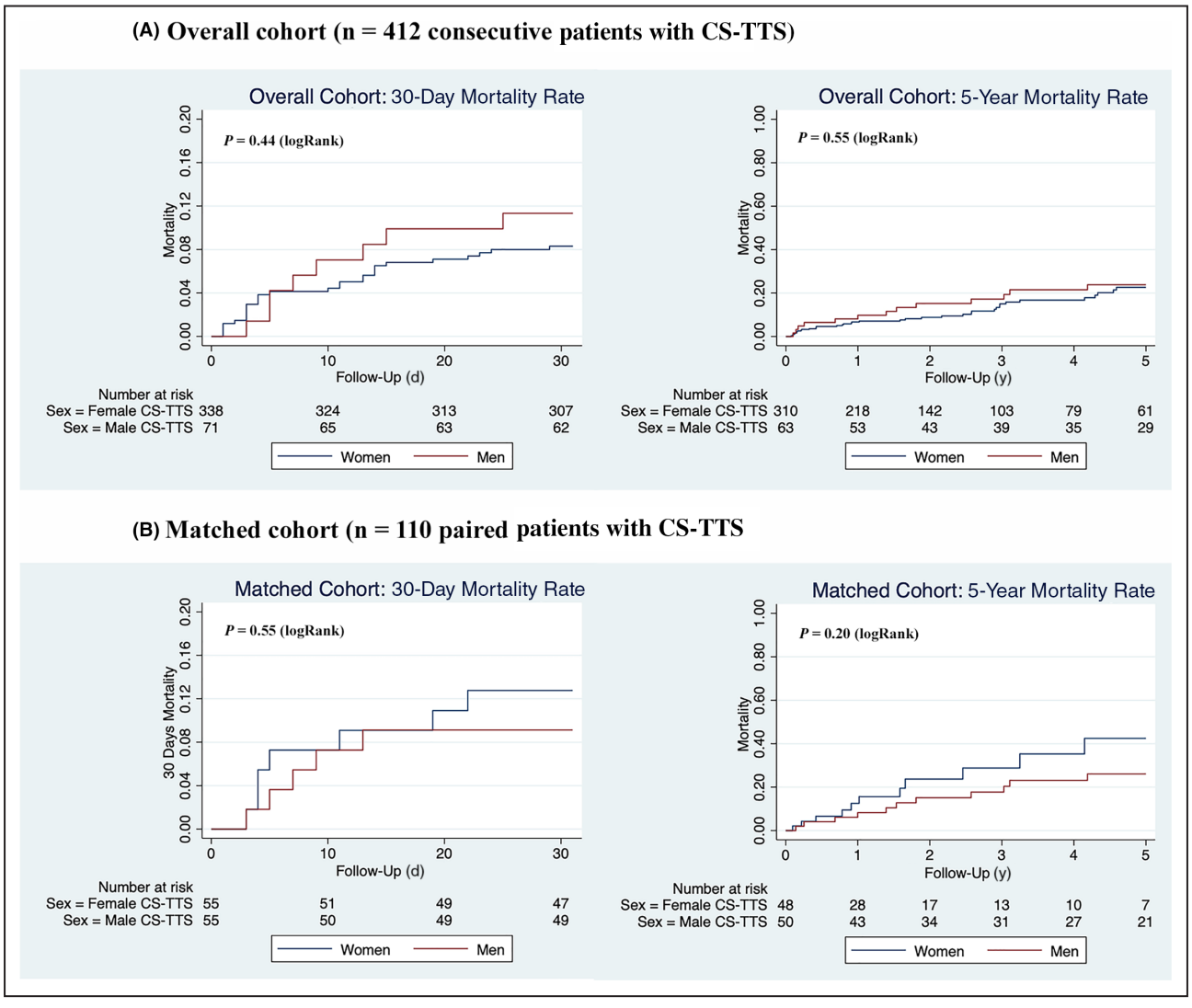

Figure 2. Short- and long-term outcomes-based sex.
A, Overall cohort (n=412 consecutive CS-TTS patients). **B**, Matched cohort (n=110 paired CS-TTS patients). CS-TTS indicates cardiogenic shock complicating Takotsubo syndrome.

Table 5. Univariable and Multivariable Analysis for Factors Associated With In-Hospital and 5-Year Mortality Rates

	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
In-hospital death				
Age, per 5-y increase	1.16 (1.02–1.31)	0.027	1.16 (1.01–1.34)	0.04
Male sex	1.31 (0.64–2.68)	0.468	…	…
Hypertension	1.13 (0.62–2.06)	0.689	…	…
Diabetes	2.18 (1.15–4.12)	0.017	2.18 (1.08–4.38)	0.03
Smoking	1.43 (0.77–2.64)	0.255	…	…
Pulmonary disease	1.72 (0.93–3.17)	0.081	NS	NS
Malignancies	5.60 (1.86–16.9)	0.002	5.79 (1.62–20.70)	0.01
Physical trigger	1.81 (1.01–3.26)	0.048	NS	NS
LVEF, per 5-point increase	0.86 (0.75–0.98)	0.029	0.87 (0.76–1.00)	0.06
Apical ballooning	1.18 (0.48–2.91)	0.719	…	…
5-y mortality rate				
Age, per 5-y increase	1.28 (1.14–1.43)	<0.001	1.28 (1.14–1.45)	<0.01
Male sex	1.66 (0.93–2.94)	0.085	NS	NS
Hypertension	1.60 (0.97–2.65)	0.067	…	…
Diabetes	1.97 (1.15–3.39)	0.014	1.86 (1.05–3.30)	0.03
Smoking	1.26 (0.76–2.10)	0.376	…	…
Pulmonary disease	2.51 (1.53–4.13)	<0.001	2.08 (1.23–3.54)	0.01
Malignancies	5.14 (1.73–15.22)	0.003	4.23 (1.23–14.53)	0.02
Physical trigger	1.51 (0.94–2.41)	0.087	NS	NS
LVEF, per 5-point increase	0.93 (0.84–1.03)	0.192	…	…
Apical ballooning	1.23 (0.59–2.56)	0.575	…	…

HR indicates hazard ratio; LVEF, left ventricular ejection fraction; and NS, nonsignificant.

A notably high prevalence of postmenopausal women has been consistently reported in all series of TTS. It has been postulated that due to underlying neurohormonal characteristics of this population, such as increased resting sympathetic tone and abnormal vasomotor function, a lower adrenergic drive is needed to trigger TTS. Conversely, in less susceptible male patients, the stronger adrenergic drive required to initiate TTS may produce larger myocardial involvement, causing higher rates of pump failure and death.[3,4,25,26]

In contrast with the majority of CS series described in the literature, in which a clear male predominance is present, ranging from 65% to 80%,[10,13,27] it is relevant to notice that in our cohort of CS-TTS, female sex is largely prevalent. Nevertheless, male sex prevalence is higher (17%) than in the general TTS population, consistent with previous observations that showed a higher risk of CS in male patients with TTS. Interestingly, while in multiple-pathogenesis CS cohorts, female patients are older and have a higher comorbidity burden,[14,28] the opposite happens in our CS-TTS cohort, which is consistent with previous findings of older age and higher prevalence of comorbid conditions in men with TTS.[4]

Importantly, the presence of a physical trigger in TTS, which is thought to unleash a massive adrenergic activation capable of initiating the syndrome, has been previously associated with worse outcomes and CS-TTS development, especially in men.[4,29] In contrast, the present study suggests that once CS-TTS is instituted, its outcomes are not significantly affected by the nature of the trigger, with similar mortality rates for emotional and physical triggers.

Moreover, left ventricular outflow tract obstruction and severe mitral regurgitation due to systolic anterior movement of the mitral leaflets, physiopathological conditions that, together with the sudden loss of regional left ventricular contraction, are known to potentially cause profound acute heart failure in TTS are distributed similarly in both sexes in our study.[30,31]

Conflicting data exist regarding sex-related differences in the management, in-hospital course, and outcomes of CS. In our study, the in-hospital course of CS-TTS was similar in both sexes, with the only significant differences being a higher rate of infections and a longer hospital stay for male patients in the overall cohort, with no significant differences in the matched one. Consistent with previous knowledge,[32] the CS-TTS mortality rate in our cohort is

lower compared with that described in patients with CS complicating acute myocardial infarction and CS of multiple pathogeneses, and this applies to both short- and long-term mortality rates. This may have been influenced by the fact that our cohort selected patients with SCAI stage B, which has a better prognosis than deeper stages of shock, while previous studies selected patients with stricter definitions of shock, currently considered stages C, D, and E of the SCAI classification.[24]

When assessing the sex impact on acute phase and long-term mortality rates of CS-TTS, no significant differences were found in either the overall or the matched cohort. This important finding is consistent with several previous trials that did not show significant sex differences in outcomes of patients with CS complicating acute myocardial infarction, such as the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial[33] and the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial for the 30-day mortality rate,[27] and the IABP-SHOCK trial for the 1-year mortality rate.[14] The long-term mortality rate in TTS, mainly driven by noncardiovascular complications, has been reported to be higher in male patients, probably due to their higher comorbidity burden.[4,34,35] In the present study, this sex difference did not emerge; possible explanations for this are the smaller size of the cohort, a shorter follow-up period, and relatively lower mortality rates after surviving the acute phase. Of note, despite having fewer comorbidities, female patients with CS-TTS exhibited a similar prognosis to their male counterparts. This finding raises the possibility that women with CS-TTS may actually experience worse outcomes than men, aligning with recent research on CS complicating acute myocardial infarction and other causes of CS.[36] On the other hand, when comparing the outcomes of the overall cohort from the registry, male sex was associated with a better prognosis.

Altogether, despite men with TTS having higher rates of CS and having a higher mortality rate, data from our study suggest that once CS-TTS has begun, there is not any significant sex difference regarding outcomes.

Study Limitations

Our study has certain inherent limitations due to its retrospective nature that should be considered when interpreting the results, including possible missing data and selection bias limiting its generalizability. CS was clinically diagnosed at the discretion of each of the 23 centers, creating the possibility of nonuniform reporting. The lack of available invasive hemodynamic data may have limited the correct diagnosis of CS, potentially leading to misclassification of other types of noncardiogenic shock as CS. Because the diagnosis of CS did not require evidence of impaired tissue perfusion, the incidence of CS-TTS may have been overestimated, and its severity might have been underestimated. Due to its observational nature, unmeasured confounding variables may have influenced the results. To address this limitation, we performed a multivariable analysis adjusting for many variables considered as possible confounders and a propensity score analysis. The relatively small number of men reduces the statistical power of the study; however, this is the first multicenter work focused on sex differences in patients with TTS and CS.

CONCLUSIONS

The male-to-female ratio in patients with CS-TTS is 1:5. Men with CS-TTS are older and experience more comorbidities. The 30-day and 5-year mortality rates for CS-TTS are 9.5% and 21.8%, respectively. Sex does not influence short- or long-term outcomes in CS-TTS.

ARTICLE INFORMATION

Received August 9, 2024; accepted October 25, 2024.

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Acknowledgments

The authors acknowledge all the researchers of the RETAKO team.

Sources of Funding

The RETAKO webpage is maintained thanks to the support of a nonconditional Fundación Interhospitalaria para la Investigación Cardiovascular scholarship.

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S3
Figures S1–S2

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