Outcomes of catecholamine and/or mechanical support in Takotsubo syndrome

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ABSTRACT

Objective This study aimed to reveal the clinical characteristics of patients with severe Takotsubo syndrome (TTS) who needed catecholamine support (CS) or mechanical support (MS) and to identify factors associated with serious illness and in-hospital mortality.

Methods This was a nationwide retrospective study that used claims data from the JROAD-DPC registry, from April 2012 to March 2016. The TTS patients were divided into severe TTS and mild TTS groups. The severe group was defined as patients who needed CS and/or MS.

Results Among 6,169 TTS patients, 1,148 (18.6%) had severe TTS. No significant difference in age was found between the two groups, but the number of female patients was significantly lower in the severe group than in the mild group. Among 130 patients who underwent MS, 22 and 108 patients required MS alone and both MS and CS, respectively. The 30-day mortality rate was significantly higher in the severe group than in the mild group (11.4% vs. 2.6%, $P<0.01$) and increased with age. Of the patients with severe TTS, 65.6% died within 7 days. Multivariable analysis showed that male sex (odds ratio [OR]: 1.22, $P=0.03$), higher Charlson scores (OR: 1.11, $P<0.01$), comorbid pneumonia (OR: 1.68, $P<0.01$), comorbid sepsis (OR: 6.02, $P<0.01$), and ambulance use

(OR: 2.01, P<0.01) were associated with severe TTS.

Conclusions The rate of severe TTS was 18.6% among 6,169 patients registered in the Japanese nationwide database, and the 30-day mortality was higher in patients with severe TTS than in those with mild TTS (11.4% vs. 2.6%).

Keywords: Takotsubo syndrome; catecholamine support; mechanical support; mortality.

Key questions

What is already known about this subject?

Takotsubo syndrome (TTS) is usually a reversible heart failure syndrome, and many reports have suggested that cardiac function often returns within days to several weeks. Recent observational studies have found that in-hospital mortality for TTS is low, ranging from 2.4% to 8.4%. However, there have been very few reports of severe TTS requiring catecholamine support (CS) or mechanical support (MS).

What does this study add?

Although TTS is a relatively rare disease, our study analysed 6,169 TTS cases using a large Japanese clams database to evaluate the clinical features of severe TTS requiring CS and/or MS. The prognosis of severe TTS was poor (30-day in-hospital mortality rate: 11.4%), and the rate of acute deaths within 7 days was high (percentage of deaths within

7 days / within 30 days: 65.6%). The rate of patients with severe TTS was as high as 18.6%.

How might this impact on clinical practice?

Although TTS is usually a reversible heart failure syndrome, severe TTS requiring CS and/or MS had high mortality in this study. Although MS seems to have some benefit in severe TTS, the questions of which patients with TTS need MS and how CS affects TTS remain unresolved. The results of this study may provide some insights into these clinical issues.

INTRODUCTION

Takotsubo syndrome (TTS) is a cardiac syndrome characterised by acute reversible ventricular dysfunction that is generally triggered by extreme stress in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture. Recent observational studies have found that in-hospital mortality for TTS ranges from 2.4% to 8.4%.[1-4]

The pathophysiological mechanisms of TTS are unclear, but there is considerable evidence that sympathetic stimulation is central to its pathogenesis.[5] Previous reports have suggested that TTS causing cardiogenic shock accounts for 6% to 20% of all

cases.[6-8] However, there have been very few reports of severe TTS requiring catecholamine support (CS) or mechanical support (MS).[9,10] Thus, the clinical characteristics of severe TTS remain unknown owing to the small number of cases.

This study aimed to determine the clinical characteristics of patients with severe TTS who needed CS and/or MS and to identify factors associated with serious illness and in-hospital mortality using a nationwide cardiovascular hospital database.

METHODS

Database

This was a nationwide retrospective descriptive study using the Japanese registry of all cardiac and vascular diseases and the diagnosis procedure combination (JROAD-DPC) database from April 2012 through March 2016.

JROAD is a nationwide institutional database.[11,12] Data were collected from all training hospitals with cardiovascular beds, and the response rate was 100% each year. The JROAD-DPC includes patient data, such as age, sex, medical diagnoses (main diagnosis and comorbidities), prescriptions, diagnostic and therapeutic procedures, length of hospital stay, and patient outcomes.

Study population and outcomes

We extracted TTS patient data from the JROAD-DPC database using the Japanese ICD-10 coding system based on the 2013 version of the ICD-10 (code I518) (http://www.iryohoken.go.jp/shinryohoshu/downloadMenu/ [in Japanese]). The accuracy of the ICD-10 code (code I518) has been proven as valid with a sensitivity and specificity of diagnosis of 0.83 and 1.0, respectively, with a positive predictive value of 1.0.[13] Comorbidities were also extracted from the JROAD-DPC database using ICD-10 codes. The inclusion criterion was the main diagnosis code, admission-precipitating diagnosis code, or most resource-consuming diagnosis code for TTS. The exclusion criteria were as follows: patients who underwent percutaneous coronary intervention, were diagnosed with pheochromocytoma (D350) according to the Mayo Clinic diagnostic criteria, aged < 20 years, or had missing data on study variables. Patients were divided into a mild TTS group and a severe TTS group. Patients who underwent CS or MS within 7 days of hospitalisation were defined as those with severe TTS. The remaining patients were defined as those with mild TTS. MS was defined as intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) use. Mechanical supports other than IABP and ECMO were not used for the study population during this period. First, the baseline characteristics of all patients with TTS were analysed and compared between the two groups. The primary outcome was the 30-day in-hospital mortality. Second, we

analysed the factors associated with severe conditions and 30-day in-hospital mortality using univariate and multivariable mixed-effect logistic regressions. In previous reports, age, male sex, physical triggers, acute neurologic or psychiatric diseases, and cancer have been reported as prognostic factors. We included those factors that could be extracted from the DPC data (such as age, sex, stroke, and cancer) in the model.[1,14,15] Covariates with $P<0.05$ or clinically informative parameters were included in the multivariable model. Third, TTS is thought to be associated with catecholamine excess. To determine the characteristics and outcomes for patients who underwent MS without catecholamine, patients were divided into four groups according to the use of CS and MS. Then, the clinical characteristics and 30-day in-hospital mortality of each group were compared. Given that the DPC database only includes in-hospital data, patient follow-up data covered the period from admission to discharge.

Sensitivity analyses

We defined severe TTS as patients who underwent CS and/or MS. However, those patients may have included any type of shock (septic or haemorrhagic). Therefore, we performed a sensitivity analysis by excluding patients with ICD-10 codes for septic or haemorrhagic shock (online supplemental tables S1-S4).

Statistical analysis

Data are presented as mean±standard deviation (SD) for normally distributed data or median (interquartile range) for non-normally distributed data, or as the number (percentage) for categorical data. The baseline characteristics were compared using the t-test or Mann–Whitney test for continuous variables or the χ^2 test for categorical variables (table 1). The factors associated with severe conditions and 30-day in-hospital mortality were analysed using univariate and multivariable mixed-effect logistic regression that allowed for inter-facility variability (tables 2, 3). The data among the four groups were compared using the Kruskal–Wallis test for continuous variables or the χ^2 test for categorical variables. Subsequently, Bonferroni multiple comparisons were performed and those that showed a significant difference have been marked with an asterisk next to the P-values (table 4). The Kaplan–Meier method was used to provide survival estimates, which were compared using the log-rank test (figure 4). The STATA software package (version 15, Stata Corp., College Station, TX, USA) was used for all statistical analyses. All statistical tests were two-sided, and P-values < 0.05 were considered significant.

Ethics statement

The study protocol was approved by the ethical committee of Nara Medical University, Nara, Japan (registration number: 1899). The requirement for individual informed consent was waived because no identifying information on individual patients was

included. Data anonymisation of the patient identifiers was performed using the originally provided DPC data.

Patient and public involvement

Patients or the public were not involved in the study design.

RESULTS

Clinical characteristics of TTS

Between April 2012 and March 2016, a total of 10,782 patients were diagnosed with TTS using the ICD-10 code I518, and 6,363 patients met the inclusion criterion. We excluded 151 patients who underwent percutaneous coronary intervention, 24 patients with pheochromocytoma, four patients aged <20 years, and 15 patients with missing data on variables, and finally analysed 6,169 patients with TTS in 775 hospitals (figure 1).

The mean age (±SD) of the 6,169 patients with TTS was 75 (±11) years, and 4,998 (81.0%) patients were female (table 1). The Charlson score, a summed score comprising severity-weighted points for a select number of medical disorders,[16] was calculated from ICD-10 codes.[17] The median interquartile range of the Charlson score was 1 (1−2). On admission, 2,591 (42.0%) patients with TTS had hypertension, and 111 (1.8%) had sepsis. Ambulances were used in 3,470 (56.2%) patients. Of all TTS patients, catecholamines were administered to 1,126 (18.3%) patients during hospitalisation. MS

was performed in 130 (2.1%) patients, and 125 (2.0%) and 20 (0.3%) patients underwent IABP and ECMO, respectively. The overall 30-day in-hospital mortality rate was 4.2%.

Table 1. Clinical characteristics of TTS

n, (%)	Total 6,169	Mild TTS 5,021 (81.4%)	Severe TTS 1,148 (18.6%)	P- value
Age (years), mean±SD	75±11	75±12	76±11	0.9<
Male, n (%)	1,171 (19.0)	921 (18.3)	250 (21.8)	< 0.01
Charlson score, median (IQR)	1 (1–2)	1 (0–2)	1 (1–2)	< 0.01
Comorbidities at admission, n (%)				
Hypertension	2,591 (42.0)	2,203 (43.9)	388 (33.8)	< 0.01
Diabetes mellitus	867 (14.1)	699 (13.9)	168 (14.6)	0.53
Dyslipidaemia	1,307 (21.2)	1,123 (22.4)	184 (16.0)	< 0.01
Chronic kidney disease	156 (2.5)	129 (2.6)	27 (2.4)	0.67
Malignancy	390 (6.3)	304 (6.1)	86 (7.5)	0.07
Psychiatric disorders	291 (4.7)	236 (4.7)	55 (4.8)	0.9<
Pneumonia	372 (6.0)	263 (5.2)	109 (9.5)	< 0.01
Urinary tract infection	151 (2.5)	119 (2.4)	32 (2.8)	0.41
Stroke	277 (4.5)	214 (4.3)	63 (5.5)	0.07
Sepsis	111 (1.8)	53 (1.1)	58 (5.1)	< 0.01
Ambulance use, n (%)	3,470 (56.2)	2,682 (55.4)	788 (68.7)	< 0.01
CAG, n (%)	4,842 (78.5)	3,888 (77.4)	954 (83.1)	< 0.01

Medications during hospitalization, n (%)				
ACEi/ARBs	2,133 (34.6)	1,740 (34.7)	393 (34.2)	0.79
Beta-blockers	1,915 (31.0)	1,533 (30.5)	382 (33.3)	0.07
Calcium channel blockers	1,672 (27.1)	1,392 (27.7)	280 (24.4)	0.02
Loop diuretics	1,912 (31.0)	1,342 (26.7)	570 (49.7)	< 0.01
Spironolactone	785 (12.7)	558 (11.1)	227 (19.8)	< 0.01
Statins	1,417 (23.0)	1,185 (23.6)	232 (20.2)	0.01
Oral antidiabetic drugs	491 (8.0)	392 (7.81)	99 (8.6)	0.36
Catecholamine	1,126 (18.3)	0 (0)	1,126 (98.1)	< 0.01
Noradrenaline	759 (12.3)	0 (0)	759 (66.1)	< 0.01
Dopamine	439 (7.1)	0 (0)	439 (38.2)	< 0.01
Dobutamine	266 (4.3)	0 (0)	266 (23.2)	< 0.01
Mechanical support	130 (2.1)	0 (0)	130 (11.3)	< 0.01
IABP	125 (2.0)	0 (0)	125 (10.9)	< 0.01
ECMO	20 (0.3)	0 (0)	20 (1.7)	< 0.01
Hospital length of stay (days), median (IQR)	11 (7–18)	11 (7–17)	16 (10–25)	< 0.01
Death within 7 days, n (%)	146 (2.4)	60 (1.2)	86 (7.5)	< 0.01
Death within 30 days, n (%)	261 (4.2)	130 (2.6)	131 (11.4)	< 0.01
Percentage of deaths within 7 days, %	55.9	46.2	65.6	

TTS, Takotsubo syndrome; IQR, interquartile range; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; IABP, intra-aortic balloon pumping; ECMO, extracorporeal membrane oxygenation; CAG, coronary angiography, SD, standard deviation.

Percentage of deaths within 7 days = number of deaths within 7 days / number of deaths within 30 days.

Comparison between the mild and severe TTS groups

All patients were divided into mild (n=5,021, 81.4%) and severe TTS groups (n=1,148, 18.6%), as shown in table 1. Patients in the severe TTS group were older than those in the mild TTS group (severe TTS, 75±12 years vs. mild TTS, 76±11 years, P<0.01). The proportion of female patients was lower in the severe TTS group than in the mild TTS group (mild TTS, 81.7% vs. severe TTS, 78.2%, P<0.01). The Charlson score was higher in the severe TTS group (P<0.01), which had a lower rate of hypertension and dyslipidaemia and a higher rate of pneumonia, and sepsis. No significant difference was noted in the use of ACEi/ARBs or beta-blockers between the two groups. The hospital stay was significantly longer in the severe TTS group. The 7-day and 30-day mortality rates in the severe TTS group were significantly higher than those in the mild TTS group (30-day mortality: mild TTS, 2.6% vs. severe TTS, 11.4%, P<0.01). Among patients who died in the hospital within 30 days, 55.9% died within 7 days. In the severe TTS group, 65.6% of the patients died within 7 days.

Figure 2 shows the age distribution of the patients. The percentage of patients with severe TTS was approximately 20% for all ages; the 30-day in-hospital mortality rate was higher in older patients.

Predictors of severe TTS and 30-day in-hospital mortality

Table 2 shows the predictors of severe TTS using univariate and multivariable mixed-effect logistic regressions. Univariate analysis showed that male sex, higher Charlson score, comorbidities of pneumonia and sepsis, and ambulance use were predictors of severe TTS. Multivariable analysis showed that male sex (odds ratio [OR]: 1.22, 95% confidence interval [CI]: 1.02–1.47, P=0.03), higher Charlson scores (OR: 1.11, 95% CI: 1.04–1.18, P<0.01), comorbidities of pneumonia (OR: 1.68, 95% CI: 1.28–2.21, P<0.01), comorbidities of sepsis (OR: 6.02, 95% CI: 3.88–9.35, P<0.01), and ambulance use (OR: 2.01, 95% CI: 1.72–2.36, P<0.01) were associated with severe TTS.

Table 2. Predictors of severe TTS

	Univariate analysis			Multivariable analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (per 1 year)	1.01	0.99–1.01	0.08	1.00	0.99–1.01	0.90
Male	1.24	1.06–1.45	< 0.01	1.22	1.02–1.47	0.03
Charlson score	1.12	1.07–1.17	< 0.01	1.11	1.04–1.18	< 0.01
Diabetes mellitus	1.06	0.88–1.27	0.53			
Chronic kidney disease	0.91	0.60–1.39	0.67			
Malignancy	1.26	0.98–1.61	0.07	1.11	0.80–1.56	0.52
Psychiatric disorders	1.02	0.76–1.38	0.90			

Pneumonia	1.90	1.50–2.40	< 0.01	1.68	1.28–2.21	< 0.01
Urinary tract infection	1.18	0.80–1.75	0.41			
Stroke	1.30	0.98–1.74	0.07	1.18	0.85–1.65	0.33
Sepsis	4.99	3.42–7.28	< 0.01	6.02	3.88–9.35	< 0.01
Ambulance use	1.91	1.67–2.19	< 0.01	2.01	1.72–2.36	< 0.01
ACEi/ARBs	0.98	0.86–1.12	0.79			
Beta-blockers	1.13	0.99–1.30	0.07	1.16	0.99–1.36	0.07

TTS, Takotsubo syndrome; CI, confidence interval; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker.

Table 3 shows the predictors of 30-day in-hospital mortality. Univariate analysis showed that older age, male sex, higher Charlson score, comorbidities of malignancy, pneumonia, stroke, and sepsis, and ambulance use were predictors of 30-day in-hospital mortality. CS and MS were also associated with a higher 30-day in-hospital mortality rate. The use of ACEi/ARBs and beta-blockers was associated with a lower 30-day in-hospital mortality rate. Multivariable analysis showed that older age (OR: 1.06, 95% CI: 1.05–1.08, P<0.01), male sex (OR: 1.53, 95% CI: 1.13–2.07, P<0.01), comorbidities of malignancy (OR: 3.30, 95% CI: 2.08–5.24, P<0.01), comorbidities of pneumonia (OR:

2.11, 95% CI: 1.45–3.07, P<0.01), comorbidities of stroke (OR: 2.18, 95% CI: 1.33–3.55, P<0.01), ambulance use (OR: 1.46, 95% CI: 1.09–1.95, P=0.01), CS (OR: 3.91, 95% CI: 2.93–5.21, P<0.01), and MS (OR: 4.53, 95% CI: 2.70–7.58, P<0.01) were associated with a higher 30-day mortality. Use of ACEi/ARBs (OR: 0.21, 95% CI: 0.14–0.31, P<0.01), and use of beta-blockers (OR: 0.66, 95% CI: 0.48–0.92, P=0.01) were associated with a lower 30-day in-hospital mortality rate.

Table 3. Predictors of 30-day in-hospital mortality in TTS

	Univariate analysis			Multivariable analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (per 1 year)	1.05	1.04–1.07	<0.01	1.06	1.05–1.08	<0.01
Male	1.84	1.40–2.42	<0.01	1.53	1.13–2.07	<0.01
Charlson score	1.22	1.14–1.32	<0.01	1.04	0.93–1.15	0.51
Diabetes mellitus	1.01	0.71–1.45	0.96			
Chronic kidney disease	0.90	0.40–2.06	0.81			
Malignancy	3.36	2.39–4.72	<0.01	3.30	2.08–5.24	<0.01
Psychiatric disorders	0.71	0.36–1.40	0.33			
Pneumonia	3.56	2.53–5.00	<0.01	2.11	1.45–3.07	<0.01
Urinary tract infection	1.27	0.62–2.63	0.51			
Stroke	2.15	1.38–3.36	<0.01	2.18	1.33–3.55	<0.01

Sepsis	4.00	2.32–6.89	< 0.01	1.59	0.85–2.99	0.14
Ambulance use	1.91	1.45–2.50	< 0.01	1.46	1.09–1.95	0.01
ACEi/ARBs	0.23	0.15–0.33	< 0.01	0.21	0.14–0.31	< 0.01
Beta-blockers	0.55	0.41–0.75	< 0.01	0.66	0.48–0.92	0.01
Catecholamine	4.73	3.68–6.09	< 0.01	3.91	2.93–5.21	< 0.01
Mechanical support	7.54	4.91–11.58	< 0.01	4.53	2.70–7.58	< 0.01

TTS, Takotsubo syndrome; CI, confidence interval; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker.

Clinical characteristics of TTS in the CS and MS groups

Table 4 shows the clinical characteristics of TTS patients who received CS and/or MS. Of all TTS patients, 5,021 (81.4%) received neither CS nor MS [CS (-) MS (-) group], 1,018 (16.5%) received CS only [CS (+) MS (-) group], 22 (0.4%) received MS only [CS (-) MS (+) group], and 108 (1.8%) received both CS and MS [CS (+) MS (+) group]. The CS (+) MS (+) group was significantly younger than the other groups. The proportion of patients taking beta-blockers was significantly higher in the CS (-) MS (+) group than in the other groups. The CS (-) MS (+) group had a lower 30-day in-hospital mortality rate than the CS (+) MS (+) group (table 4 and figure 3). Figure 4 shows the cumulative

incidence function of 30-day in-hospital mortality among the four groups. The percentages of deaths within 7 days were high in all four groups (table 4). In the CS (-) MS (-) group, 46.5% of the patients died within 7 days. In the CS (+) MS (+) group, the percentage of deaths within 7 days was 74.1%, which was the highest among the four groups.

Table 4. Clinical characteristics of the four groups based on the use of CS and MS

	CS (-) MS (-)	CS (+) MS (-)	CS (-) MS (+)	CS (+) MS (+)	P-value
n (%)	5,021 (81.4)	1,018 (16.5)	22 (0.4)	108 (1.8)	
Age (years), mean±SD	77±12	76±11	75±12	71±12	<0.01*
Male, n (%)	921 (18.3)	217 (21.3)	3 (13.6)	30 (22.8)	0.01
Charlson score, median (IQR)	1 (0–2)	1 (1–2)	1 (1–2)	1 (1–2)	<0.01*
CAG, n (%)	3,888 (77.4)	866 (85.0)	14 (63.6)	74 (68.5)	<0.01*
Medications during hospitalization, n (%)					
ACEi/ARBs	1,740 (34.7)	352 (34.6)	7 (31.8)	34 (31.5)	0.91
Calcium channel blockers	1,392 (27.7)	253 (24.9)	3 (13.6)	24 (22.2)	0.08
Beta-blockers	1,533 (30.5)	326 (32.0)	13 (59.1)	43 (39.8)	<0.01*
Loop diuretics	1,342 (26.7)	485 (47.6)	15 (68.2)	70 (64.8)	<0.01*
Spironolactone	558 (11.1)	203 (19.9)	3 (13.6)	21 (19.4)	<0.01*
Statin	1,185 (23.6)	211 (20.7)	4 (18.2)	17 (15.7)	0.06

Hospital length of stay (days), median (IQR)	11 (7–17)	15 (10–24)	16 (13–29)	18.5 (9–36.5)	< 0.01*
Death within 7 days, n (%)	60 (1.2)	65 (6.4)	1 (4.6)	20 (18.5)	< 0.01*
Death within 30 days, n (%)	130 (2.6)	101 (9.9)	3 (13.6)	27 (25.0)	< 0.01*
Percentage of deaths within 7 days, %	46.2	64.4	33.3	74.1	

CS, catecholamine support; MS, mechanical support; IQR, interquartile range; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; CAG, coronary angiography, SD, standard deviation.
Percentage of deaths within 7 days = number of deaths within 7 days / number of deaths within 30 days.

Sensitivity analysis

There were 139, 79, and 37 patients with cardiogenic, septic, and haemorrhagic shocks, respectively, in total TTS. We excluded patients with septic or haemorrhagic shock in the sensitivity analysis. The 30-day in-hospital mortality was higher in the severe TTS group: 2.5% in mild TTS and 10.1% in severe TTS. Multivariable analyses of factors associated with severe TTS and 30-day mortality were consistent with the original analyses (tables S2 and S3, respectively). The clinical characteristics of the four groups based on the use of CS and MS were also consistent with those of the original analysis (online supplemental table S4).

DISCUSSION

In this study, we investigated the clinical characteristics of severe TTS with CS and/or MS. We identified factors associated with serious illness and in-hospital mortality using a nationwide cardiovascular hospital database. The findings of this study are as follows. The percentage of patients with severe TTS who received CS and/or MS was 18.6%. The 30-day mortality rate was significantly higher in the severe TTS group than in the mild TTS group (11.4% vs. 2.6%, $P<0.01$) and increased with age. Of the severe TTS patients who died within 30 days, 65.6% died within 7 days. Multivariable analysis showed that male sex, a higher Charlson score, comorbidities of pneumonia and sepsis, and ambulance use were associated with severe TTS. In terms of CS and MS, the 30-day in-hospital mortality rate was the highest in the CS (+) MS (+) group (25.0%). Although TTS is thought to have a relatively good prognosis, recent reports have suggested that the mortality rate is the same as that of acute coronary syndrome.[18] In the present study, the 30-day in-hospital mortality was 4.2%, which is consistent with existing reports (2.4%–8.4%).[1-4] Severe TTS was observed in 18.6% of all patients with TTS, and the 30-day in-hospital mortality rate of severe TTS was 11.4%. The rate of cardiogenic shock was 9.5% in reports regarding the Inter-TAK Registry and 11.4% regarding the RETAKO Registry.[7,8] In the present study, the frequency of severe TTS was slightly higher than in the previous reports. This may be partly because the cause of severe TTS includes any

kind of shock other than cardiogenic shock. The sensitivity analysis excluding patients with septic and haemorrhagic shock revealed a severe TTS rate of 18.0% and a 30-day mortality rate in severe TTS of 10.4%, which were comparable to the results including these patients.

In the multivariable analysis, male sex, a high Charlson score, pneumonia, sepsis, and ambulance use were associated with severe TTS. Older age, male sex, malignancy, pneumonia, stroke, ambulance use, CS, and MS were poor prognostic factors for TTS, while use of ACEi/ARBs and beta-blocker during hospitalisation were better prognostic factors. Although TTS in younger patients has been reported to be associated with cardiogenic shock,[15] in the present study, no significant correlation was found between age and severe TTS. Males were a significant predictor of severe TTS. Of all TTS patients, 30-day mortality was higher in males (3.7% in females and 6.6% in males), which was consistent with previous findings.[19] TTS in males was also a significant poor prognostic factor in the multivariable analysis. The Charlson score is an indicator of the degree of comorbidity at the time of admission. A study reported that TTS due to physical stress was associated with a higher Charlson score.[20] We showed that the Charlson score might be useful in predicting TTS severity. The Charlson score was not significant in the multivariable analysis of 30-day mortality, which was presumably because of the large

weight of cancer comorbidity in the Charlson score. Recently, TTS has become increasingly recognized among patients with cancer.[21] In the present study, cancer was also strongly associated with 30-day mortality as were pneumonia and stroke. Regarding the favourable outcome of patients with ACEi/ARB and beta-blockers during hospitalisation, this was a retrospective observational study; thus, further prospective studies are needed to evaluate the effects of these medications accurately.

Although TTS is usually a reversible heart failure syndrome and many reports have suggested that cardiac function often returns within days to several weeks, management of severe TTS with cardiogenic shock is a challenging clinical problem.[22] CS and/or MS in the acute phase may be useful for the management of severe TTS. However, few studies have examined the efficiency of CS and/or MS in TTS patients.[9,10] The present study included 1,126 cases of CS and 130 cases of MS, making it one of the largest consecutive retrospective studies. The use of catecholamines, however, may not be recommended for several reasons, including the possibility that catecholamine overstimulation may be a cause of TTS.[23] Catecholamines might also be avoided because they may contribute to the onset or exacerbation of left ventricular outflow tract obstruction, which has been reported in 20% of TTS cases and is a risk factor for cardiogenic shock.[7,24] This study showed that there were patients who received MS

without CS, and the 30-day in-hospital mortality rate of the group was 13.6%. This rate was higher than that for patients with CS (+) MS (-), but better than that for patients with CS (+) MS (+) as shown in table 4. Given that over activation of adrenergic system would be involved in the development of TTS, clinical usefulness of CS and/or MS is inconclusive from the present analyses. Further studies are needed to evaluate the effects of catecholamine use and mechanical support in severe TTS.

LIMITATIONS

This study has several limitations. First, this was a retrospective observational study. Although the accuracy of the TTS diagnosis was well validated, the accuracy of the initial diagnoses and procedures in the DPC database was unclear. Second, the JROAD-DPC did not include detailed patient characteristics, such as laboratory and physiological data, including some important confounding factors. As we did not account for unmeasured confounders, this has limited any conclusions regarding causal inferences. Third, because the JROAD-DPC, a claims database, did not include prehospitalization data, it was difficult to examine the triggers of TTS by comparing mental and physical triggers. Fourth, this study defines severe TTS as patients who have received CS and/or MS, and it could not be completely excluded the possibility that CS and MS were used for diseases other

than TTS. On the other hand, cardiogenic shock according to ICD-10 codes accounted for 2.3% of all TTS (online supplemental figure S1), a very low rate compared with previous reports of 9.5% to 11.4% [7, 8], suggesting that it is insufficient to define cardiogenic shock by ICD-10 codes alone. One reason for the discrepancy between our definition and the ICD-10 definition might be the underestimation of cardiogenic shock as a complication of TTS, probably because the diagnosis based on ICD-10 was extracted from the list of associated diseases by each physician on-site. A sensitivity analysis was performed to confirm the robustness of the results, but further validation studies are needed to confirm the accuracy of diagnosis more precisely. Finally, the causes of in-hospital deaths remain unclear in our study.

CONCLUSIONS

This study demonstrated that 18.6% of patients with severe TTS needed CS or MS, and their 30-day mortality rate was 11.4%, much worse than those who did not receive either CS or MS. Further studies seeking more effective treatment strategies for severe TTS patients are needed.

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FOOTNOTES

Contributors: YS, KK, and ST conceived the study. All authors contributed to the planning of the study and the manuscript.

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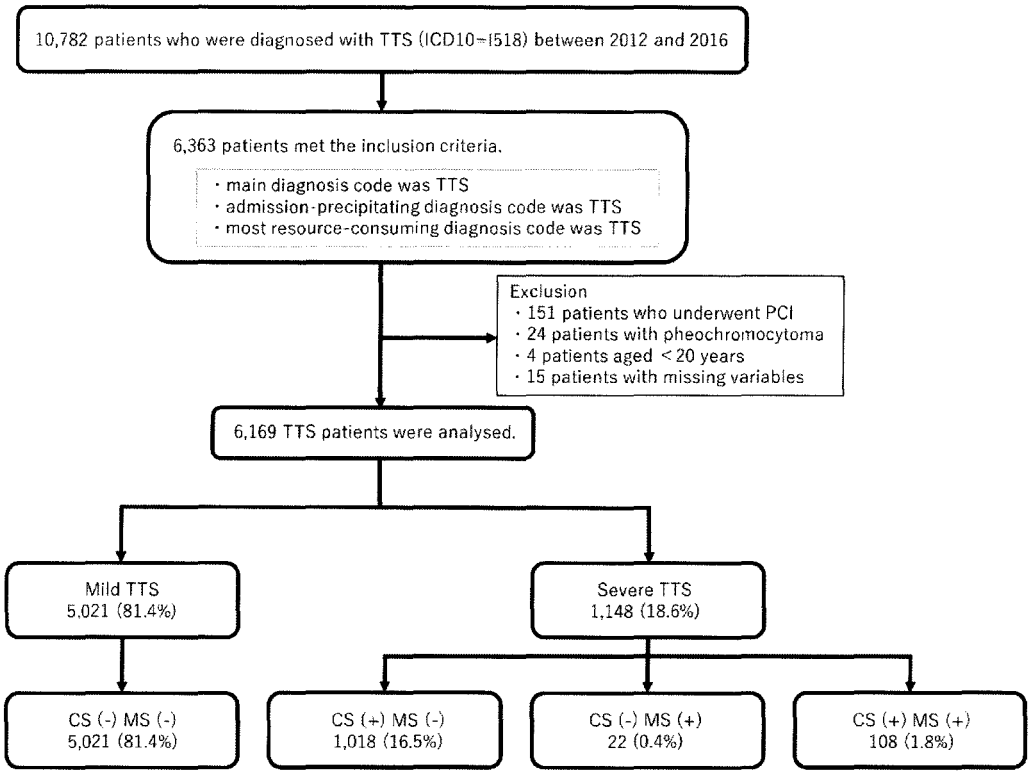

Figure 1 Study flow chart. In total, 6,169 patients with TTS were analysed.

CS, catecholamine support; MS, mechanical support; PCI, percutaneous coronary intervention; TTS, Takotsubo syndrome.

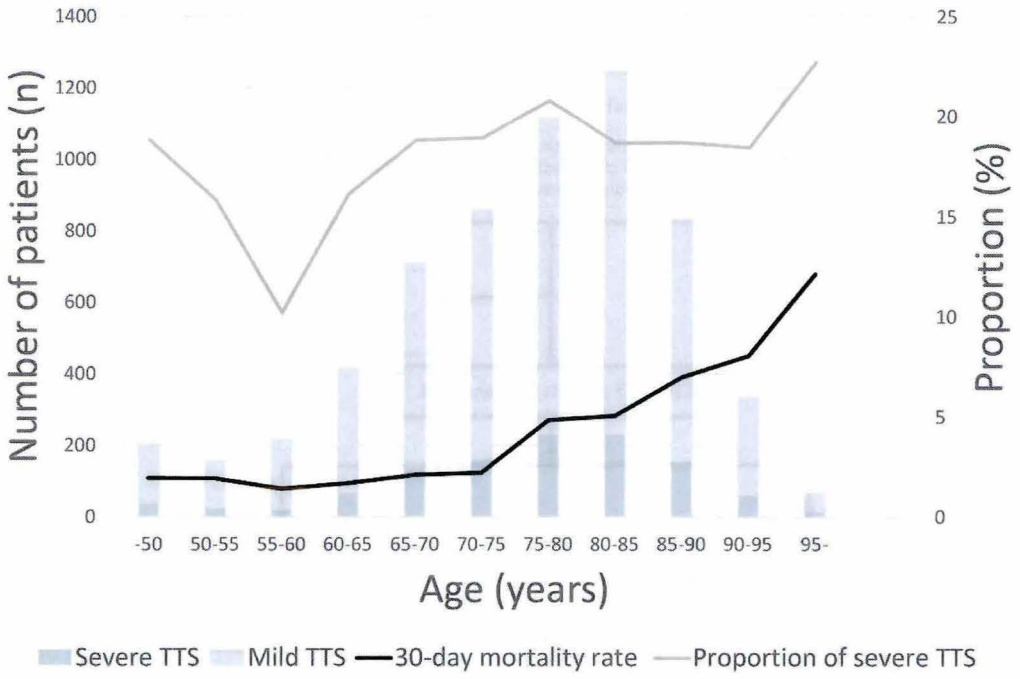

Figure 2 Age distribution of TTS according to the 30-day in-hospital mortality and the proportion of severe TTS.

TTS, Takotsubo syndrome.

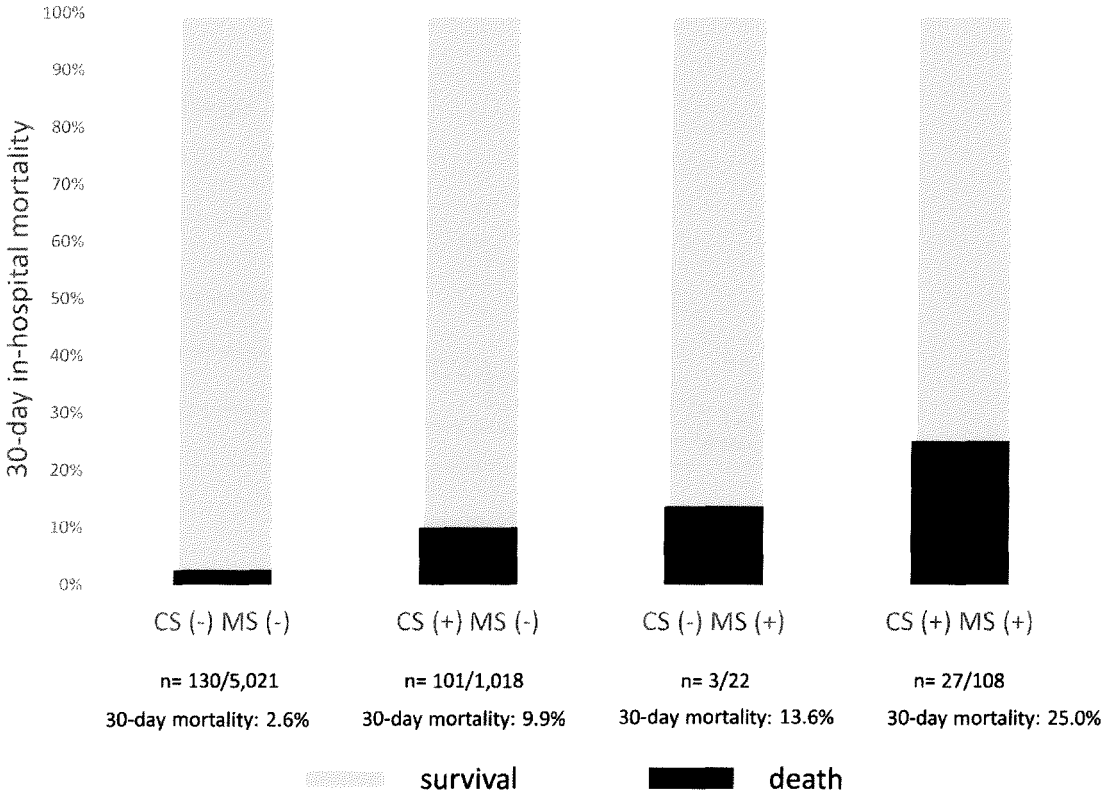

Figure 3 The 30-day in-hospital mortality rate of TTS patients by CS and MS.

CS, catecholamine support; MS, mechanical support; TTS, Takotsubo syndrome.

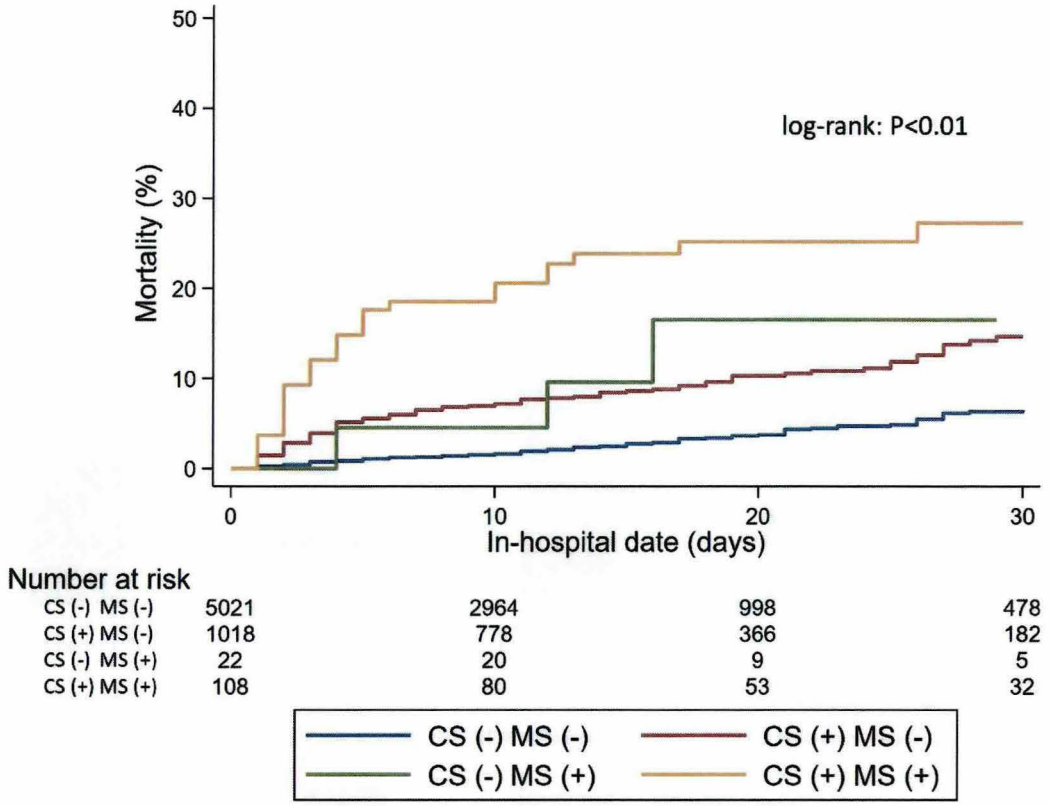

Figure 4 Cumulative incidence function curves of 30-day in-hospital mortality compared among the four groups based on the use of CS and MS.

CS, catecholamine support; MS, mechanical support.

Supplemental Material

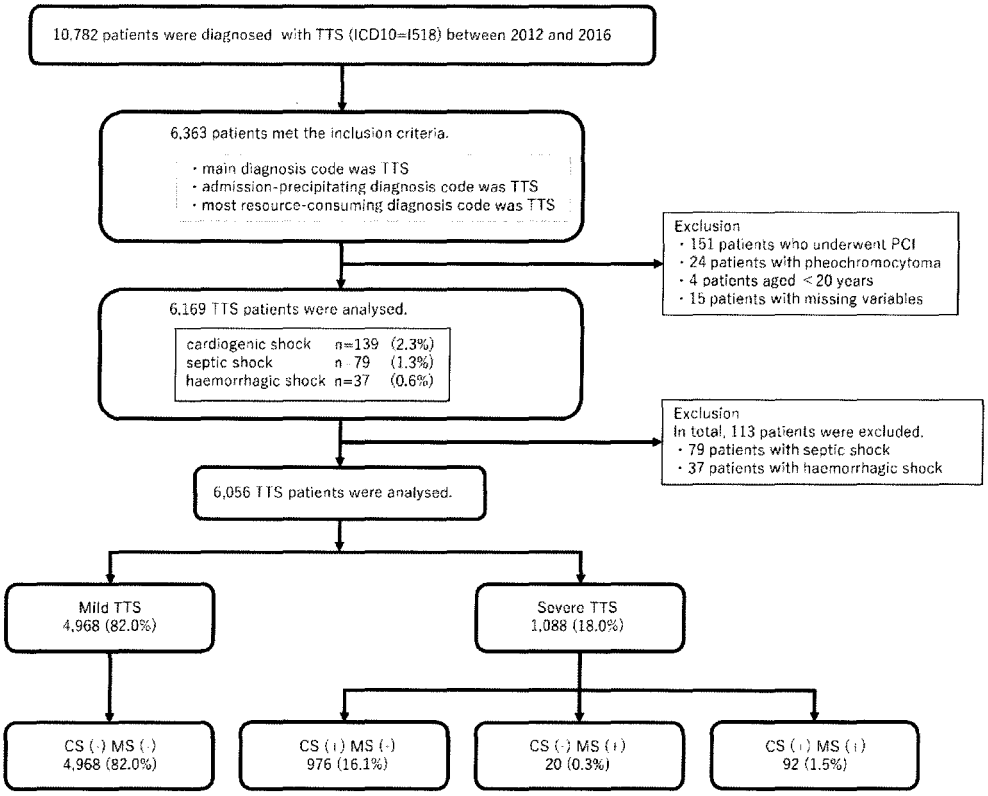

Figure legends

Figure S1 Study flow chart of the sensitivity analysis.

CS, catecholamine support; MS, mechanical support; PCI, percutaneous coronary intervention; TTS, Takotsubo syndrome.

Table S1. Clinical characteristics of TTS

n, (%)	Total 6,056	Mild TTS 4,968 (82.0%)	Severe TTS 1,088 (18.0%)	P-value
Age (years), mean±SD	75±12	75±12	75±11	0.07
Male, n (%)	1,138 (18.8)	905 (18.2)	233 (21.4)	0.01
Charlson score, median (IQR)	1(1–2)	1 (0–2)	1 (1–2)	<0.01
Comorbidities at admission, n (%)				
Hypertension	2,570 (42.4)	2,189 (44.1)	381 (35.0)	<0
Diabetes mellitus	856 (14.1)	693 (14.0)	163 (15.0)	0.38
Dyslipidaemia	1,301 (21.5)	1,121 (22.6)	180 (16.5)	<0.01
Chronic kidney disease	152 (2.5)	126 (2.5)	26 (2.4)	0.78
Malignancy	380 (6.3)	298 (6.0)	82 (7.5)	0.06
Psychiatric disorders	286 (4.7)	233 (4.7)	53 (4.9)	0.80
Pneumonia	359 (5.9)	259 (5.2)	100 (9.2)	<0.01
Urinary tract infection	140 (2.3)	112 (2.3)	28 (2.6)	0.93
Stroke	270 (4.5)	211 (4.3)	59 (5.4)	0.09
Sepsis	32 (0.5)	17 (0.3)	15 (1.4)	<0.01
Ambulance use, n (%)	3,385 (55.9)	2,641 (53.2)	744 (68.5)	<0.01
CAG, n (%)	4,772 (78.8)	3,859 (77.7)	913 (83.9)	<0.01
Medications during hospitalization, n(%)				
ACEi/ARBs	2,104 (34.7)	1,725 (34.7)	379 (34.8)	0.94
Beta-blockers	1,882 (31.1)	1,518 (30.6)	364 (33.5)	0.06
Calcium channel blockers	1,649 (27.2)	1,381 (27.8)	268 (24.6)	0.03
Loop diuretics	1,839 (30.4)	1,307 (26.3)	532 (48.9)	<0.01

Spironolactone	756 (12.5)	541 (10.9)	215 (19.8)	< 0.01
Statins	1,401 (23.1)	1,180 (23.7)	221 (20.3)	0.02
Oral antidiabetic drugs	483 (8.0)	388 (7.8)	95 (8.7)	0.31
Catecholamine	1,068 (17.6)	0 (0)	1,068 (98.2)	< 0.01
Noradrenaline	712 (11.8)	0 (0)	712 (65.4)	< 0.01
Dopamine	416 (6.9)	0 (0)	416 (38.2)	< 0.01
Dobutamine	245 (4.1)	0 (0)	245 (22.5)	< 0.01
Mechanical support	112 (1.9)	0 (0)	112 (10.3)	< 0.01
IABP	118 (1.8)	0 (0)	118 (9.9)	< 0.01
ECMO	15 (0.3)	0 (0)	15 (1.4)	< 0.01
Hospital length of stay, median (IQR)	12 (8–19)	11 (7–17)	16 (10–25)	< 0.01
Death within 7 days, n (%)	126 (2.1)	56 (1.1)	70 (6.4)	< 0.01
Death within 30 days, n (%)	236 (3.9)	126 (2.5)	110 (10.1)	< 0.01
Percentage of deaths within 7 days, %	53.4	44.4	63.6	

TTS, Takotsubo syndrome; IQR, interquartile range; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; IABP, intra-aortic balloon pumping; ECMO, extracorporeal membrane oxygenation; CAG, coronary angiography; SD, standard deviation. Percentage of deaths within 7 days = number of deaths within 7 days / number of deaths within 30 days.

Table S2. Predictors of severe TTS

	Univariate analysis			Multivariable analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (per 1 year)	1.01	1.00–1.01	0.07	1.00	0.99–1.01	0.63
Male	1.22	1.04–1.44	0.02	1.23	1.02–1.48	0.03
Charlson score	1.13	1.07–1.18	<0.01	1.11	1.03–1.18	<0.01
Diabetes mellitus	1.09	0.90–1.31	0.38			
Chronic kidney disease	0.94	0.61–1.44	0.78			
Malignancy	1.28	0.99–1.65	0.06	1.14	0.81–1.60	0.4
Psychiatric disorders	1.04	0.77–1.41	0.80			
Pneumonia	1.84	1.45–2.34	<0.01	1.64	1.24–2.18	<0.01
Urinary tract infection	1.15	0.75–1.74	0.53			
Stroke	1.29	0.96–1.74	0.09	1.15	0.82–1.63	0.41
Sepsis	4.07	2.03–8.17	<0.01	5.28	2.36–11.84	<0.01
Ambulance use	1.91	1.66–2.20	<0.01	2.07	1.76–2.44	<0.01
ACEi/ARBs	1.00	0.88–1.15	0.94			
Beta-blockers	1.14	0.99–1.31	0.06	1.15	0.97–1.35	0.10

TTS, Takotsubo syndrome; CI, confidence interval; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker.

Table S3. Predictors of 30-day in-hospital mortality for TTS

	Univariate analysis			Multivariable analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (per 1 year)	1.06	1.04–1.07	<0.01	1.06	1.05–1.08	<0.01
Male	1.80	1.35–2.40	<0.01	1.44	1.05–1.98	0.02
Charlson score	1.25	1.16–1.35	<0.01	1.05	0.94–1.17	0.40
Diabetes mellitus	1.02	0.71–1.48	0.90			
Chronic kidney disease	0.84	0.34–2.06	0.70			
Malignancy	3.51	2.47–4.99	<0.01	3.25	2.02–5.22	<0.01
Psychiatric disorders	0.79	0.40–1.56	0.50			
Pneumonia	3.88	2.74–5.50	<0.01	2.42	1.66–3.55	<0.01
Urinary tract infection	0.91	0.37–2.25	0.84			
Stroke	2.19	1.37–3.48	<0.01	2.12	1.28–3.53	0.01
Sepsis	2.57	0.78–8.50	0.12			
Ambulance use	1.88	1.41–2.49	<0.01	1.46	1.08–1.97	0.02
ACEi/ARBs	0.25	0.17–0.37	<0.01	0.23	0.15–0.34	<0.01
Beta-blockers	0.59	0.43–0.80	<0.01	0.70	0.50–0.98	0.04
Catecholamine	4.19	3.21–5.47	<0.01	3.58	2.66–4.83	<0.01
Mechanical support	6.55	4.03–10.64	<0.01	4.15	2.36–7.33	<0.01

TTS; Takotsubo syndrome; CI, confidence interval; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker.

Table S4. Clinical characteristics of the four groups based on the use of CS and MS

	CS (-) MS (-)	CS (+) MS (-)	CS (-) MS (+)	CS (+) MS (+)	P-value
n, (%)	4,968 (82.0)	976 (16.1)	20 (0.3)	92 (1.5)	
Age (years), mean±SD	75±12	76±11	75±13	72±12	< 0.01*
Male, n (%)	905 (18.2)	204 (20.9)	3 (15.0)	26 (28.3)	0.02
Charlson score, median (IQR)	1 (0–2)	1 (1–2)	1.5 (1–2)	1 (1–2)	< 0.01*
CAG, n (%)	3,859 (77.7)	837 (85.8)	12 (60.0)	64 (69.6)	< 0.01*
Medications during hospitalization, n (%)					
ACEi/ARBs	1,725 (34.7)	342 (35.0)	6 (30.0)	31 (33.7)	0.96
Calcium channel blockers	1,381 (27.8)	244 (25.0)	3 (15.0)	21 (22.8)	0.13
Beta-blockers	1,512 (30.5)	312 (32.1)	12 (57.1)	39 (39.4)	0.01
Loop diuretics	1,307 (26.3)	461 (47.2)	13 (65.0)	58 (63.0)	< 0.01*
Spironolactone	541 (10.9)	193 (19.7)	3 (15.0)	19 (20.7)	< 0.01*
Statin	1,180 (23.8)	202 (20.7)	3 (15.0)	16 (17.4)	0.08
Hospital length of stay, median (IQR)	11 (7–17)	15 (10–24)	16 (13–26)	20 (11–40)	< 0.01*

Death within 7 days, (%)	56 (1.1)	55 (5.6)	1 (5.0)	14 (15.2)	< 0.01*
Death within 30 days, (%)	126 (2.5)	88 (9.0)	3 (15.0)	19 (20.7)	< 0.01*
Percentage of deaths within 7 days, %	44.4	62.5	33.3	73.7	

CS, catecholamine support; MS, mechanical support; IQR, interquartile range; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; CAG, coronary angiography; SD, standard deviation.
Percentage of deaths within 7 days = number of deaths within 7 days / number of deaths within 30 days.