

# Impact of ST-segment elevation on the outcome of Takotsubo syndrome

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Thorsten Gietzen<sup>1,2,\*</sup>  
Ibrahim El-Battrawy<sup>1,2,\*</sup>  
Siegfried Lang<sup>1,2</sup>  
Xiao-Bo Zhou<sup>1,2</sup>  
Michael Behnes<sup>1</sup>  
Uzair Ansari<sup>1</sup>  
Martin Borggrefe<sup>1,2</sup>  
Ibrahim Akin<sup>1,2</sup>

<sup>1</sup>First Department of Medicine, Faculty of Medicine, University Medical Centre Mannheim (UMM), University of Heidelberg, Mannheim, Germany; <sup>2</sup>German Center for Cardiovascular Research (DZHK), Partner Site, Heidelberg-Mannheim, Mannheim, Germany

\*These authors contributed equally to this work

**Background:** Recent studies have highlighted that Takotsubo syndrome (TTS), mimicking acute coronary syndrome (ACS), is associated with poor clinical outcome. TTS is associated with different repolarization disorders including ST-segment elevation. ST elevation myocardial infarction (STEMI) in ACS is associated with declined prognosis. However, the clinical and prognostic impact of ST-segment elevation on TTS remains lacking.

**Aim:** The aim of this study was to determine the short- and long-term prognostic impact of ST-segment elevation on TTS patients as compared with STEMI patients.

**Patients and methods:** Our institutional database constituted a consecutive cohort of 138 TTS patients and 138 ACS patients matched for age and sex. TTS patients (n=41) with ST-segment elevation were compared with ACS patients with ST-segment elevation (n=64).

**Results:** Chest pain was significantly more documented in STEMI patients as compared with TTS patients (48.8% vs 78.1%;  $P<0.01$ ). Cardiovascular risk factors such as diabetes mellitus (12.2% vs 29.7%;  $P=0.02$ ) were significantly more presented in STEMI patients. Although the initial left ventricular ejection fraction (LVEF) was more declined in TTS patients ( $39\% \pm 9\%$  vs  $45\% \pm 16\%$ ;  $P<0.01$ ), the LVEF was more declined in STEMI patients at follow-up ( $54\% \pm 10\%$  vs  $45\% \pm 16\%$ ;  $P=0.04$ ). In-hospital complications such as respiratory failure were significantly more presented in TTS patients (68.3% vs 20.3%;  $P<0.01$ ). The short-term as well as the long-term mortality was similar in both groups. In univariate analysis, male sex, ejection fraction (EF)  $<35\%$ , glomerular filtration rate (GFR)  $<60$  mL/min, cardiogenic shock, inotropic drugs, and history of cancer were predictors of 5-year mortality.

**Conclusion:** Rates of the long-term mortality in TTS patients with ST elevations are comparable with STEMI patients.

**Keywords:** Takotsubo syndrome, coronary artery syndrome, prognosis, ST elevation

## Introduction

Takotsubo syndrome (TTS) is a transient disorder of left ventricular (LV) wall dysfunction characterized by a range of wall motion abnormalities and clinically representative of an acute heart failure syndrome with substantial risk of adverse events.<sup>1-3</sup> Patients present with symptoms such as chest pain and dyspnea, mimicking acute coronary syndrome (ACS). TTS can be associated with critical complications such as heart failure, life-threatening arrhythmias, atrial fibrillation, QT prolongation, thromboembolic events, recurrence of TTS, LV outflow obstruction, mitral valve regurgitation, and cardiac rupture.<sup>6-9</sup> It has been reported that TTS is associated with cardiac fibrosis and inflammation.<sup>10</sup> Recently published data confirmed that TTS is not associated with a favorable prognosis.<sup>4</sup> However, it has been reported that the prognosis of TTS might be worse than the prognosis of ST elevation myocardial infarction (STEMI) patients.<sup>12</sup> ST elevation is known as a predictor of the prognostic impact of an ACS.<sup>13</sup> There is a lack

Correspondence: Ibrahim El-Battrawy  
First Department of Medicine,  
University Medical Centre Mannheim,  
Theodor-Kutzer-Ufer 1-3, 68167  
Mannheim, Germany  
Tel +49 621 383 1447  
Email [ibrahim.el-battrawy@medma.uni-heidelberg.de](mailto:ibrahim.el-battrawy@medma.uni-heidelberg.de)

of data describing the impact on TTS patients compared with STEMI patients. Therefore, the present study was performed to determine the prognostic impact of ST elevation on TTS patients compared with STEMI patients.

## Patients and methods

Consecutive patients with the diagnosis of TTS ( $n=138$ ) during the years 2003–2017 were included in the TTS database of our institution, of whom 41 (29.9%) presented with ST elevations. Patients were diagnosed using the Mayo Clinic criteria, which outlines the clinical features associated with TTS.<sup>14</sup>

The first criterion describes the transient wall motion abnormality in the LV mid-segments with or without apical involvement, regional wall motion abnormalities that extend beyond a single epicardial vascular distribution, and frequently, but not always in the event of a stressful trigger. The second criterion stipulates the absence of obstructive coronary disease. The third criterion outlines the appearance of new electrocardiogram (ECG) pathologies that mimic ACS or modest elevations of cardiac troponin levels. The final criterion is the absence of pheochromocytoma and myocarditis in the patient.

Furthermore, we consecutively collected the data of 532 ACS patients, who were admitted to our institution in the years 2007 and 2008. Two hundred and twenty-six of these patients were diagnosed with STEMI, and 59 out of the 226 patients were female. TTS or ACS patients ( $n=138$  per group) were matched for age and sex and assessed and divided into two groups: TTS with ST-segment elevation ( $n=41$ ) and STEMI ( $n=64$ ).

The diagnosis of ACS has been defined in accordance with the joint American Heart Association/European Society of Cardiology (ESC) definition, including elevation of cardiac troponin, significant coronary arterial stenosis, and occurrence of typical ECG pathologies such as ST-segment elevation or T inversion.

The diagnosis of STEMI has been defined in accordance with the ESC guidelines, as a new ST elevation at the J point in two contiguous leads of  $>0.1$  mV in all leads other than leads V2–V3. For leads V2–V3, the following cut points apply:  $\geq 0.2$  mV in men  $\geq 40$  years,  $\geq 0.25$  mV in men  $<40$  years, or  $\geq 0.15$  mV in women.

The angiograms, echocardiograms, and ECGs were independently reviewed by two senior cardiologists to evaluate the diagnosis of TTS. Patients were subsequently treated with percutaneous coronary intervention (PCI) and stent implantation (non-ST elevation myocardial infar-

tion [NSTEMI] or STEMI). The study was conducted in compliance with the Declaration of Helsinki with regard to investigations in human subjects, and the study protocol was approved by the ethics committee of the Medical Faculty Mannheim. All participants provided written informed consent.

Life-threatening arrhythmias (including ventricular tachycardia [VT], hemodynamically relevant nonsustained ventricular tachycardia [NSVT], and asystolia), thromboembolic events, major stroke, pulmonary congestion with the use of noninvasive, positive pressure ventilation, intubation, use of a temporary pacemaker, use of inotropic agents, cardiogenic shock, and death were assessed at index event of TTS/STEMI and during the follow-up of  $1,682\pm 1,332$  days (median 1,751 days) for TTS and  $1,181\pm 1,312$  days (median 632 days) for STEMI based on chart review. The primary end point was all-cause mortality rate as assessed by chart review and/or telephone review. Missing data on the cause of death were labeled as death due to unknown cause.

## Statistical analyses

Data are presented as mean  $\pm$  SD for continuous variables with a normal distribution, median (IQR) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normal distribution. Student's *t*-test and Mann–Whitney *U*-test were used to compare continuous variables with normal and non-normal distributions, respectively. Chi-squared test or Fisher's exact test was used to compare categorical variables. The log-rank test was used to compare the survival curves between the TTS group with ST elevation and the STEMI group. Statistical analysis was performed with SPSS statistics 23.0 (IBM Corporation, Armonk, NY, USA) in all analyses;  $P\leq 0.05$  (two-tailed) was used to indicate statistical significance.

## Results

### Baseline demographics

We studied clinical and echocardiographic data of 41 TTS patients showing ST elevation with a mean follow-up of  $1,682\pm 1,332$  days (median 1,751 days) and 64 STEMI patients with a mean follow-up of  $1,181\pm 1,312$  days (median 632 days),  $P=0.44$ . Baseline demographics with a predominance of postmenopausal females in the TTS group are presented in Table 1. Compared with the TTS group, the incidence of chest pain (48.8% vs 78.1%;  $P<0.01$ ) as well as diabetes mellitus (12.2% vs 29.7%;  $P=0.02$ ) was higher in the STEMI group. The incidence of COPD was

**Table 1** Baseline characteristics of 41 TTS patients with ST elevation and 64 STEMI patients

Variables	TTS (n=138)	Matched ACS (n=138)	TTS with ST elevation (n=41)	STEMI (n=64)	P-value <sup>a</sup>
<b>Demographics</b>					
Age, mean ± SD (years)	67±11	66±15	68±12	68±16	1.00
Female, n (%)	117 (84.8)	117 (84.8)	38 (92.7)	59 (92.2)	0.93
<b>Symptoms, n (%)</b>					
Dyspnea	54 (39.1)	44 (31.9)	13 (31.7)	17 (26.6)	0.57
Chest pain	69 (50.4)	107 (77.5)	20 (48.8)	50 (78.1)	<0.01
<b>Clinical parameter</b>					
SBP, mmHg, IQR	141 (62–240)	137 (60–240)	135 (80–220)	130 (60–210)	0.49
DBP, mmHg, IQR	79 (40–151)	76 (7–120)	81 (50–111)	74 (7–120)	0.44
Heart rate, bpm, IQR	99±26	81±19	99±20	80±18	<0.01
<b>ECG data</b>					
ST-segment elevation, n (%)	41 (29.9)	64 (46.4)	41 (100.0)	64 (100.0)	1.00
Inversed T-waves, n (%)	123 (93.2)	69 (50.0)	36 (92.3)	21 (32.8)	<0.01
PQ interval, mean ± SD	159±28	166±31	157±28	169±33	0.09
QTc (ms), mean ± SD	475 (62–604)	457 (358–614)	475 (130–604)	456 (373–614)	0.14
<b>Laboratory values, mean ± SD</b>					
Troponin I (U/L; IQR)	63.15 (0.01–2,738.00)	20.02 (0.03–233.88)	77.44 (0.06–2,631)	29.10 (0.03–233.88)	0.37
Creatine phosphokinase (U/L; IQR)	587 (39–26,600)	1,028 (35–10,250)	475 (48–939)	1,353 (53–6,260)	0.56
CKMB (U/L; IQR)	35 (1–115)	79 (0–741)	77 (4–167)	108 (0–589)	0.49
C-reactive protein (mg/L; IQR)	48.2 (0.4–467.1)	45.2 (1.0–594.0)	29.8 (1.4–467.1)	45.2 (1.0–323.7)	0.65
Hemoglobin, mean ± SD	12.2±2.0	12.8±1.9	12.4±2.4	12.8±2.2	0.32
Creatinine (mg/dL; IQR)	1.12 (0.40–5.56)	1.10 (0.43–6.44)	0.97 (0.40–1.85)	0.98 (0.43–1.87)	0.82
<b>Echocardiography data, n (%)</b>					
LVEF%, mean ± SD	39±10	49±15	39±9	45±16	0.01
LVEF% follow-up, mean ± SD	52±11	49±15	54±10	45±16	<0.01
Mitral regurgitation	66 (47.8)	39 (28.3)	19 (46.3)	14 (21.9)	<0.01
Tricuspid regurgitation	54 (39.1)	20 (14.5)	14 (34.1)	9 (14.1)	<0.01
<b>Medical history, n (%)</b>					
Smoking	41 (29.7)	45 (32.6)	10 (24.4)	19 (29.7)	0.38
Diabetes mellitus	31 (22.5)	49 (35.5)	5 (12.2)	19 (29.7)	0.02
BMI >25 kg/m <sup>2</sup>	36 (31.3)	74 (53.6)	10 (24.4)	29 (45.3)	0.11
Hypertension	82 (59.4)	98 (71.0)	25 (61.0)	39 (60.9)	0.80
COPD	28 (20.3)	12 (8.7)	9 (22.0)	4 (6.3)	0.04
Atrial fibrillation	26 (18.8)	19 (13.8)	5 (12.2)	8 (12.5)	0.96
History of malignancy	17 (12.3)	8 (5.8)	2 (5.1)	3 (4.7)	1.00
<b>Drugs on admission, n (%)</b>					
Beta-blocker	46 (35.4)	32 (23.7)	14 (35.0)	13 (20.6)	0.11
ACE inhibitor	51 (39.2)	31 (22.6)	17 (41.5)	14 (21.9)	0.03
ARB	12 (9.3)	8 (5.8)	4 (10.2)	4 (6.3)	0.49
Aldosterone inhibitor	1 (0.8)	2 (1.5)	1 (2.5)	0 (0.0)	0.39
Aspirin	36 (27.7)	31 (22.6)	14 (35.0)	11 (17.2)	0.04
Statin	26 (20.0)	17 (12.4)	10 (25.0)	10 (15.6)	0.24
OAD	6 (4.6)	11 (8.0)	1 (2.5)	5 (7.8)	0.25
Insulin	12 (9.3)	17 (12.4)	2 (5.1)	5 (7.8)	0.59
Therapeutic anticoagulation	12 (9.3)	9 (6.5)	4 (10.2)	4 (6.3)	0.47
Heparin	6 (4.6)	3 (2.2)	3 (7.7)	1 (1.6)	0.16
<b>Drugs on discharge, n (%)</b>					
Beta-blocker	103 (74.6)	110 (79.7)	32 (78.0)	48 (75.0)	0.94
ACE inhibitor	82 (59.4)	85 (61.6)	24 (58.5)	32 (50.0)	0.54
ARB	10 (7.2)	20 (14.5)	5 (12.2)	10 (15.6)	0.62
Aldosterone inhibitor	2 (1.4)	2 (1.5)	0 (0.0)	1 (1.6)	1.00
Aspirin	53 (38.4)	113 (81.9)	17 (41.5)	49 (76.6)	<0.01
Statin	48 (34.8)	110 (79.7)	17 (41.5)	46 (71.8)	<0.01
OAD	4 (2.9)	8 (5.8)	0 (0.0)	4 (6.3)	0.32

(Continued)

**Table 1** (Continued)

Variables	TTS (n=138)	Matched ACS (n=138)	TTS with ST elevation (n=41)	STEMI (n=64)	P-value <sup>a</sup>
Insulin	14 (10.1)	18 (13.0)	3 (7.7)	6 (9.4)	0.78
Therapeutic anticoagulation	33 (23.9)	10 (7.2)	10 (24.4)	5 (7.8)	<b>0.02</b>
Heparin	18 (13.0)	8 (5.8)	7 (17.1)	4 (6.3)	0.18

**Notes:** <sup>a</sup>P-values for the comparison between TTS in the presence of ST elevation as compared with STEMI. Statistically significant P-value ( $P<0.05$ ) shown in bold.

**Abbreviations:** ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CKMB, creatin kinase muscle/brain; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; OAD, oral antidiabetic drugs; STEMI, ST elevation myocardial infarction; TTS, Takotsubo syndrome.

higher in TTS patients (22.0 vs 6.3;  $P=0.04$ ). TTS patients had higher heart rates ( $99\pm 20$  vs  $80\pm 18$ ;  $P<0.01$ ) and were more frequently treated with angiotensin-converting enzyme (ACE) inhibitors (41.5% vs 21.9%;  $P<0.03$ ) and aspirin at admission (35.0% vs 17.2%;  $P=0.04$ ) compared with the STEMI group. However, STEMI patients were treated more frequently with aspirin (41.5% vs 76.6%;  $P<0.01$ ) and statins at discharge (41.5% vs 71.8%;  $P<0.01$ ), while TTS patients received more therapeutic anticoagulation (24.4% vs 7.8%;  $P=0.02$ ). Similarly, echocardiographic data showed higher prevalence of valvular heart disease in the TTS group. There was a significant difference with relation to LV ejection fraction (LVEF; TTS  $39\%\pm 9\%$  vs STEMI  $45\%\pm 16\%$ ;  $P=0.01$ ).

## In hospital events

The TTS group needed significantly more often intubation due to pulmonary congestion than the STEMI group (68.3% vs 20.3%,  $P<0.01$ ; Table 2). Furthermore, thromboembolic events were more frequently documented in TTS patients (22.0% vs 4.7%;  $P=0.02$ ).

## Short- and long-term outcome

After a slightly higher mortality rate in STEMI patients at the index event (7.3% vs 20.3%;  $P=0.10$ ), there were more events

in the TTS group during follow-up, which would lead to a higher long-term mortality (26.8% vs 21.9%) after 5 years (Table 3 and Figure 1). However, there was no significant difference in mortality between TTS patients with ST-segment elevation and STEMI patients. The causes of death in TTS and STEMI patients are listed in Table 4.

Over long-term follow-up, there was a significantly higher rate of thromboembolic events in TTS patients as compared with STEMI patients (36.6% vs 9.4%;  $P<0.01$ ). There were no significant differences in life-threatening arrhythmia, stroke, recurrence, and rehospitalization due to heart failure. In univariate analysis, male sex, ejection fraction (EF)  $<35\%$ , glomerular filtration rate (GFR)  $<60$  mL/min, cardiogenic shock, inotropic drugs, and history of cancer were predictors of 5-year mortality. ST-segment elevation in TTS patients did not impact the outcome. The univariate analysis is presented in Table 5.

## Discussion

We performed a retrospective clinical investigation in 138 consecutive TTS patients, of whom 41 showed ST-segment elevations. These patients were compared with an age- and sex-matched group of 64 STEMI patients. We demonstrated that 1) ST elevation in TTS is not uncommon; 2) those

**Table 2** Inhospital events and treatment strategy in TTS patients with ST elevation and STEMI patients

Variables	TTS (n=138)	Matched ACS (n=138)	TTS with ST elevation (n=41)	STEMI (n=64)	P-value <sup>a</sup>
Life-threatening arrhythmia	12 (8.8)	16 (11.6)	5 (12.2)	11 (17.2)	0.59
NPPV and/or intubation	80 (58.0)	16 (11.6)	28 (68.3)	13 (20.3)	<b>&lt;0.01</b>
Inotropic agents	23 (16.7)	18 (13.0)	8 (19.5)	14 (21.9)	0.77
Resuscitation	4 (12.5)	17 (12.3)	3 (7.3)	11 (17.2)	0.15
Cardiac electronic device implantation	4 (2.9)	9 (6.5)	1 (2.4)	5 (7.8)	0.25
Admission to ICU, length of stay, days (IQR)	5 (0–52)	3 (0–14)	4 (0–20)	3 (0–11)	0.43
Inhospital death	10 (7.2)	17 (12.3)	3 (7.3)	13 (20.3)	0.10
Cardiogenic shock	25 (18.5)	16 (11.6)	6 (15.4)	13 (20.3)	0.51
Thromboembolic events	18 (13.0)	3 (2.2)	9 (22.0)	3 (4.7)	<b>0.02</b>

**Notes:** <sup>a</sup>P-values for the comparison between TTS in the presence of ST elevation as compared with STEMI. Data presented as n (%). Statistically significant P-value ( $P<0.05$ ) shown in bold.

**Abbreviations:** ACS, acute coronary syndrome; ICU, intermediate care unit; NPPV, noninvasive positive pressure ventilation; STEMI, ST elevation myocardial infarction; TTS, Takotsubo syndrome.

**Table 3** Outcome in 41 TTS patients with ST elevation and 64 STEMI patients

Variables	TTS (n=138)	Matched ACS (n=138)	TTS with ST elevation (n=41)	STEMI (n=64)	RR (95% CI)	P-value <sup>a</sup>
Inhospital mortality	10 (7.2)	17 (12.3)	3 (7.3)	13 (20.3)	0.4 (0.1–1.2)	0.10
30-day mortality	10 (7.2)	17 (12.3)	4 (9.8)	13 (20.3)	0.5 (0.7–1.4)	0.18
1-year mortality	14 (10.1)	18 (13.0)	4 (9.8)	13 (20.3)	0.5 (0.7–1.4)	0.18
2-year mortality	21 (15.2)	19 (13.8)	5 (12.2)	14 (21.9)	0.6 (0.2–1.4)	0.30
3-year mortality	23 (16.7)	19 (13.8)	7 (17.1)	14 (21.9)	0.8 (0.3–1.8)	0.55
4-year mortality	29 (21.0)	19 (13.8)	8 (19.5)	14 (21.9)	0.9 (0.4–1.9)	0.77
Long-term mortality	35 (25.4)	22 (15.9)	11 (26.8)	14 (21.9)	1.2 (0.6–2.4)	0.56
Cardiovascular cause of death	11 (8.0)	17 (12.3)	6 (14.6)	11 (17.2)	0.9 (0.3–2.1)	0.73
Non-cardiovascular cause of death	15 (10.9)	5 (3.6)	2 (4.9)	3 (4.7)	1.0 (0.2–6.0)	1.00
Unknown cause of death	9 (6.5)	0 (0.0)	3 (7.3)	0 (0.0)		0.06
30-day stroke	4 (2.9)	1 (0.7)	2 (4.9)	0 (0.0)		0.15
1-year stroke	5 (3.6)	2 (1.4)	2 (4.9)	0 (0.0)		0.15
2-year stroke	7 (5.1)	2 (1.4)	3 (7.3)	0 (0.0)		0.06
3-year stroke	7 (5.1)	3 (2.2)	3 (7.3)	1 (1.6)	4.7 (0.5–43.5)	0.30
4-year stroke	8 (5.8)	4 (2.9)	3 (7.3)	1 (1.6)	4.7 (0.5–43.5)	0.30
Long-term stroke	9 (6.5)	6 (4.3)	3 (7.3)	3 (4.7)	1.6 (0.3–7.4)	0.68
30-day life-threatening arrhythmia	12 (8.7)	16 (11.6)	5 (12.2)	11 (17.2)	0.7 (0.3–1.9)	0.59
1-year life-threatening arrhythmia	13 (9.4)	16 (11.6)	5 (12.2)	11 (17.2)	0.7 (0.3–1.9)	0.59
2-year life-threatening arrhythmia	14 (10.1)	16 (11.6)	5 (12.2)	11 (17.2)	0.7 (0.3–1.9)	0.59
3-year life-threatening arrhythmia	14 (10.1)	16 (11.6)	5 (12.2)	11 (17.2)	0.7 (0.3–1.9)	0.59
4-year life-threatening arrhythmia	14 (10.1)	17 (12.3)	5 (12.2)	11 (17.2)	0.7 (0.3–1.9)	0.59
Long-term life-threatening arrhythmia	14 (10.1)	17 (12.3)	5 (12.2)	11 (17.2)	0.7 (0.3–1.9)	0.59
30-day heart failure	3 (2.2)	8 (5.8)	2 (4.9)	7 (10.9)	0.4 (0.1–1.1)	0.48
1-year heart failure	4 (2.9)	14 (10.1)	2 (4.9)	8 (12.5)	0.4 (0.1–1.7)	0.31
2-year heart failure	5 (3.6)	15 (10.9)	2 (4.9)	8 (12.5)	0.4 (0.1–1.7)	0.31
3-year heart failure	5 (3.6)	18 (13.0)	2 (4.9)	10 (15.6)	0.3 (0.1–0.7)	0.12
4-year heart failure	5 (3.6)	19 (13.8)	2 (4.9)	10 (15.6)	0.3 (0.1–0.7)	0.12
Long-term heart failure	5 (3.6)	19 (13.8)	2 (4.9)	10 (15.6)	0.3 (0.1–0.7)	0.12
30-day recurrence	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)		
1-year recurrence	1 (0.7)	7 (5.1)	1 (2.4)	2 (3.1)	0.8 (0.1–8.3)	1.00
2-year recurrence	5 (3.6)	10 (7.2)	2 (4.9)	3 (4.7)	1.0 (0.2–6.0)	1.00
3-year recurrence	7 (5.1)	11 (8.0)	3 (7.3)	3 (4.7)	1.6 (0.3–7.4)	0.68
4-year recurrence	7 (5.1)	15 (10.9)	3 (7.3)	5 (7.8)	0.9 (0.2–3.7)	1.00
Long-term recurrence	7 (5.1)	15 (10.9)	3 (7.3)	5 (7.8)	0.9 (0.2–3.7)	1.00
30-day thromboembolic events	18 (13.0)	5 (3.6)	9 (22.0)	3 (4.7)	4.2 (1.2–14.8)	<b>0.02</b>
1-year thromboembolic events	18 (13.0)	6 (4.3)	9 (22.0)	3 (4.7)	4.2 (1.2–14.8)	<b>0.02</b>
2-year thromboembolic events	19 (13.8)	6 (4.3)	9 (22.0)	3 (4.7)	4.2 (1.2–14.8)	<b>0.02</b>
3-year thromboembolic events	24 (17.4)	8 (5.8)	13 (31.7)	4 (6.3)	4.7 (1.6–13.5)	<b>&lt;0.01</b>
4-year thromboembolic events	26 (18.8)	10 (7.2)	14 (34.1)	5 (7.8)	4.1 (1.6–10.5)	<b>&lt;0.01</b>
Long-term thromboembolic events	29 (21.0)	12 (8.7)	15 (36.6)	6 (9.4)	3.6 (1.5–8.7)	<b>&lt;0.01</b>

**Notes:** <sup>a</sup>P-values for the comparison between TTS in the presence of ST elevation with compared with STEMI. Data presented as n (%) unless stated otherwise. Statistically significant P-value (P<0.05) shown in bold.

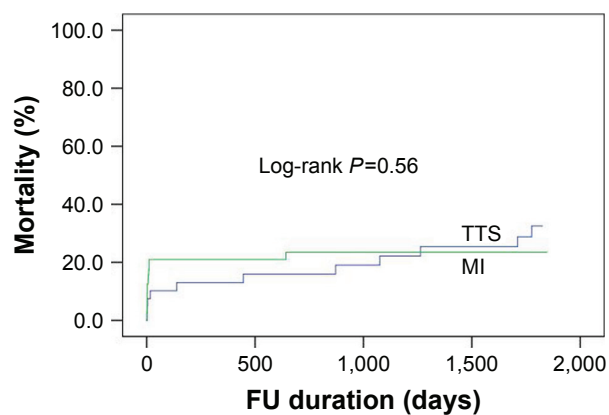
**Abbreviations:** ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; TTS, Takotsubo syndrome.

patients have similar short-term prognosis as compared with STEMI patients, and however, with a higher complication rate 3) the long-term prognosis was similar in TTS patients with ST-segment elevation as compared with STEMI patients.

Similar to other studies, the incidence of ST elevation in our TTS patient population is about one-third (29.9%).<sup>15</sup> Several studies showed that STEMI patients are suffering from a higher mortality rate as compared with NSTEMI patients. In the present study, we thought to study the impact

of ST-segment elevation in TTS patients as compared with STEMI patients. To date, TTS has been described as a benign disease with favorable prognosis. Recently, this has been disputed.<sup>11,14,16–18</sup>

Inhospital mortality rate among TTS patients ranges between 1% and 8%.<sup>5,19,20</sup> In our study, the inhospital mortality rate was 7.3% in TTS patients with ST elevation and 20.3% in STEMI patients. This did not differ significantly between both groups. The long-term mortality rate was similar in TTS as compared with STEMI patients. However,



#### Patients at risk

	TTS	MI
0	41	64
500	29	34
1,000	26	28
1,500	22	22

**Figure 1** Short- and long-term mortality rate in TTS patients with ST-segment elevation as compared with STEMI patients over mean follow-up of 5 years.

**Notes:** Expansion of FU in TTS patients: 0–3893. Expansion of FU in MI patients: 0–3934 days.

**Abbreviations:** FU, follow-up; MI, myocardial infarction; STEMI, ST elevation myocardial infarction; TTS, Takotsubo syndrome.

clinical complications such as thromboembolic events were more frequent in TTS patients during follow-up.

Studies indicated that thromboembolism is a common complication, especially in the acute phase of TTS.<sup>21,22</sup> Furthermore, it has been reported that a thromboembolic event, such as pulmonary artery embolism, is associated with ST-segment elevation. However, there are also studies estimating the prevalence of LV thrombi in TTS patients between 2% and 8%. The gold standard in diagnosing LV thrombi is the two-dimensional echocardiogram and transesophageal echocardiogram. However, there are certain limitations, as the number of echocardiograms performed per patient, time point, operator skills, and the use of contrast agents may all influence the sensitivity and specificity of this tool

**Table 4** Causes of death in TTS patients with ST elevation and STEMI patients

Variables	TTS (n=41)	STEMI (n=64)
Sudden cardiac death	2	1
Cardiac decompensation	2	1
Cardiogenic shock	2	7
Ventricular fibrillation	0	1
Septic shock	0	1
Anal carcinoma	1	0
COPD	1	0
Lung edema	0	1
Pulmonary embolism	0	1
Myocardial perforation	0	1
Unknown cause of death	3	0

**Abbreviations:** STEMI, ST elevation myocardial infarction; TTS, Takotsubo syndrome.

**Table 5** Univariate analysis for the end point in TTS patients with ST-segment elevation

	Univariate analysis		
	HR	95% CI	P-value
Male	2.2	1.0–5.0	<b>0.04</b>
Age (years)	1.0	0.9–1.0	0.45
EF <35%	2.1	1.1–4.3	<b>0.02</b>
COPD	1.1	0.4–2.4	0.85
ST-segment elevation	0.9	0.4–1.9	0.81
GFR <60 mL/min	2.4	1.2–4.9	<b>0.01</b>
Cardiogenic shock	4.6	2.2–9.3	<b>&lt;0.01</b>
Inotropic drugs	3.9	1.9–7.8	<b>&lt;0.01</b>
DM type II	1.0	0.4–2.2	0.97
Hypertension	0.7	0.3–1.5	0.41
Apical ballooning	1.8	0.7–4.3	0.18
History of cancer	2.8	1.3–6.4	<b>&lt;0.01</b>
Smoking	0.8	0.3–1.7	0.64

**Note:** Statically significant P-value ( $P < 0.05$ ) shown in bold.

**Abbreviations:** DM, diabetes mellitus; GFR, glomerular filtration rate; EF, ejection fraction; TTS, Takotsubo syndrome.

in thrombus detection. Although most thrombi occur in the LV apex, the area adjacent to the papillary muscle should be carefully examined. However, other sites may also be affected for developing a thrombus.<sup>7,23</sup> In rare cases, right ventricular involvement with concomitant thrombus formation might also be seen. Another difficulty is the differentiation of thrombus formation from a tumor, with also the possibility of overlooking smaller thrombi in echocardiography.<sup>24–26</sup> According to some study groups, patients presenting with symptoms of stroke with a supposed cardiac embolic origin should receive cardiac magnetic resonance (CMR) in addition to computer tomography (CT) to rule out an intraventricular thrombus.<sup>27,28</sup> If patients have been mechanically ventilated, the presenting signs and symptoms of an LV thrombus could be masked, which leads to underdiagnosing. Therefore, a high degree of clinical skill and interpretation is necessary in this scenario.

In our patient population, the rate of in-hospital thromboembolic events (22.0% vs 4.7%) as well as the incidence of thromboembolic events during follow-up (36.6% vs 9.4%) was significantly higher in TTS patients compared with STEMI patients.

One possible explanation may be the low blood flow in the ventricle during the initial phase of TTS, which promotes the development of ventricular thrombus.<sup>22</sup> Another study revealed that TTS patients who experience thromboembolic events have higher C-reactive protein (CRP) levels. This indicates a potential pathogenic role of inflammation in the development of thromboembolic events.<sup>29</sup>

Due to the misapprehension that TTS is thought to be benign, there is a lack of close follow-up and treatment.

This might result in underdiagnosing of several clinical complications. For example, it has been shown that there is no protective effect of a treatment with  $\beta$ -antagonists in TTS patients.<sup>4</sup>

There is evidence that ACE inhibitors and in some cases oral anticoagulation are associated with a better clinical outcome as compared with conservative wait-and-watch management.<sup>4,30–33</sup> Especially, high-risk TTS patients might benefit from anticoagulation therapy to prevent thromboembolic events.

There seems to be an association between male sex and a poor outcome. Emotional stress, depressive symptoms, and estrogen decrease may explain the sex differences, but are not clearly identified yet.<sup>34</sup> Some studies point out an association between TTS and the occurrence of malignancies, which leads to a poorer outcome.<sup>35</sup> In our study, univariate analysis showed the history of cancer as a predictor of 5-year mortality.

## Limitations

Our study has several limitations, one being it was a single-center, retrospective observational study including patients admitted over the period of 15 years. ST elevation was diagnosed based on ECG findings. Therefore, the prevalence of ST elevations may have been underestimated. In addition, we did not routinely perform magnetic resonance imaging. The impact of remnant edema and inflammation, on long-term prognosis, therefore remains undefined.

## Conclusion

ST elevation in TTS patients is not uncommon. The mortality rates in this patient population were similar as compared with those suffering from STEMI. Clinical complications such as thromboembolic events were more frequent in TTS patients with ST-segment elevation as compared with STEMI patients. Therefore, short-term as well as long-term follow-up is required in TTS patients as compared with ACS patients.

## Disclosure

The authors report no conflicts of interest in this work.

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