Association Between Mortality and Left Ventricular Ejection Fraction in Patients With Takotsubo Syndrome Versus Acute Coronary Syndrome

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Abstract. *Background/Aim:* The association between ejection fraction (EF) and mortality in TTS patients as compared to ACS is limited. This study aims to investigate the association between EF and clinical outcomes in patients with TTS as compared to ACS. *Patients and Methods:* This study compared in-hospital, and long-term incidence of clinical outcomes for 5 years in patients with TTS and ACS. The study was composed of two groups EF $\geq$ 35% and EF<35%. *Results:* The long-term mortality of the EF $\geq$ 35% for 5 years was significantly higher in TTS patients as compared to ACS (18.1% vs. 7.7%, log-Rank; $p<0.01$). Irrespective of EF, a non-cardiovascular death was significantly higher in TTS as compared to ACS patients with EF $\geq$ 35 (6.4% vs. 2.1%; $p=0.02$) and with EF<35% (21.4% vs. 7.5%; $p=0.03$). *Conclusion:* The long-term mortality is significantly higher in TTS as compared to ACS dominated by a non-cardiovascular cause of death at 5-years-follow-up.

The Takotsubo Syndrome (TTS) is generally accepted as a malignancy (1, 2). The initial appearance of TTS resembles acute coronary syndrome (ACS), where the acute deterioration of the left ventricular (LV) systolic function can lead to severe complications, including congestive heart failure, thromboembolic events, cardiogenic shock and lethal

arrhythmias, as well as an in-hospital mortality of 2.0%-8.7% for both conditions (2-7).

A transient reduced LV ejection fraction (EF) is a known phenomenon in patients with TTS. Admittedly, the range of EF has been estimated to be lower in patients with TTS compared to ACS at time of event (2, 3). In-hospital and adverse cardiac events during long-term follow-up are higher in TTS patients with EF<35% as compared to patients with EF $\geq$ 35% (8-12). Data on in-hospital and long-term outcomes comparing EF grade between TTS and ACS patients are limited (3, 13, 14).

This study sought to compare in-hospital and long-term mortality in patients with TTS versus ACS depending on EF. Moreover, predictors of mortality were evaluated.

Patients and Methods

A total of 648 patients presenting with TTS and ACS were included in the study retrospectively. TTS was defined by the Mayo clinic criteria (15). To evaluate the diagnosis of TTS, the electrocardiograms (ECGs), echocardiograms and angiograms were inspected by two independent experienced cardiologists. Other possible differential diagnoses as valvular disease, myocarditis, coronary spasm or chemotherapy-related cardiac dysfunction were excluded. Data of patients who were suffering from ACS between 2007 and 2008 (non-ST-elevation or ST-elevation myocardial infarction or unstable angina (NSTEMI or STEMI or UA)) in the Clinic for Cardiology, University Hospital Mannheim, and afterwards underwent treatment with percutaneous coronary intervention (PCI) involving a stent implantation, were examined and assessed using the department's database. The study was composed of two groups. The first group had an EF $\geq$ 35% and consisted of 94 patients with TTS and 432 patients with ACS (241 NSTEMI, 185 STEMI, 6 UA). The second group (EF<35%) included 42 TTS and 80 ACS patients (40 NSTEMI, 32 STEMI, 2 UA). EF was measured using the Simpson method particularly from apical in TTS and ACS patients (16). Data were used for index EF from initial echocardiography when accessible. Follow-up EF was considered up to 6 months after the index event. Baseline characteristics were assessed using a chart review. Mitral regurgitation (MR) and tricuspid regurgitation (TR) were measured

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using echocardiography (17). In-hospital events: i) atrial and ventricular arrhythmias, ii) cardiac rupture, iii) thromboembolic events, iv) pulmonary congestion with use of non-invasive positive-pressure ventilation, v) intubation, vi) use of a temporary pacemaker, vii) of inotropic agents, and viii) death, as well as long-term events: i) stroke, ii) life-threatening arrhythmia as asystole or ventricular arrhythmia (VT), iii) heart failure, iv) recurrence, v) thromboembolic events, and vi) mortality, were documented. Clinical outcomes, including adverse events, were observed during follow-up. Follow-up was conducted at 30 days, and once annually for 5 years. This study was organized in compliance with the announcement of Helsinki. The study protocol was recently approved by the Ethics Committee of the University Medical Centre Mannheim.

Statistical analysis. Data of continuous variables are presented as mean±standard deviation with a normal distribution, median (interquartile range IQR) with a non-normal distribution, while categorical variables are reported as frequencies and percentages (%). The Kolmogorov-Smirnov-Test was used to test normal distribution. To compare normal or non-normal distributions of continuous variables, we used Mann-Whitney-*U*-test and Student's *t*-test, respectively. The exact Fischer test or *chi*-squared-test was used for distribution analysis of categorical variables. We applied two-tailed Fisher's exact test in tests with sample size of $n=5$ or below. The relative risk for appearance of events was calculated using Fisher's Exact Ratio test. Results are presented with 95% confidence intervals (CI). We estimated the differences in both groups using Kaplan Meier and applied Log-Rank statistics. Independent predictors of increased mortality were identified by a univariate analysis. Predictors with $p<0.10$ were analyzed using the Cox multivariate regression. Results were characterized as hazard ratios (HRs) with 95%CI. Statistical analysis was performed using IBM SPSS Statistics version 23.0. Values of $p<0.05$ were recognized as statistically significant.

Results

Patients with $EF\geq 35\%$. Four hundred and thirty-two consecutive patients were included in this study with ACS and 94 consecutive patients with TTS. As expected, more women than men were affected significantly by TTS (86.2% vs. 35.0%, $p<0.01$). The heart rate was significantly higher in TTS patients 98 ± 26 beats/min (bpm) versus 91 ± 26 bpm compared to ACS patients ($p<0.01$). Furthermore, inverted T-waves were significantly more often present in TTS patients compared to ACS patients (91.0% vs. 47.0%, $p<0.01$), similar to corrected QT Interval being longer in TTS as compared to ACS patients (478 ms vs. 444 ms, $p<0.01$). LVEF was lower in TTS as compared to ACS at index event ($44\pm 6\%$ vs. $54\pm 9\%$, $p<0.01$). Nonetheless, follow-up LVEF was similar between TTS and ACS patients ($55\pm 8\%$ vs. $54\pm 9\%$, $p=0.22$). Interestingly, mitral and tricuspid regurgitation were more often observed in TTS patients as compared to ACS patients (50.0% vs. 28.9%, $p<0.01$, and 37.2% vs. 13.7%, $p<0.01$, respectively). Drugs on admission and discharge are listed in (Table I).

Life-threatening arrhythmias (LTAs), inotropic agents, resuscitation, in-hospital death and cardiogenic shock were

demonstrated equivalent between TTS and ACS patients with $EF\geq 35\%$. However, the necessity of noninvasive positive pressure ventilation (NPPV) or mechanical ventilation was significantly higher in TTS as compared to ACS patients (51.1% vs. 5.8%, $p<0.01$) (Table II).

Patients with $EF<35\%$. Eighty consecutive patients were included in this study with ACS and 42 consecutive patients with TTS. EF was presented higher in TTS as compared to ACS patients *per event* ($27\pm 6\%$ vs. $23\pm 6\%$, $p<0.01$). The observations were sustained over 5-year-follow-up with significantly more increased EF in TTS compared to ACS (42 ± 15 vs. 23 ± 6 , $p<0.01$). However, tricuspid regurgitation was more documented in TTS patients as compared to ACS patients (45.2% vs. 12.5%, $p<0.01$). Drugs on admission were similar between ACS and TTS patients. However, TTS patients were numerically more strongly medicated with beta-blockers at discharge as compared to ACS patients (71.4% vs. 56.3%, $p=0.10$) (Table III). Additionally, TTS patients were significantly more often treated with therapeutic anticoagulants at discharge compared to ACS patients (31.0% vs. 10.0%, $p<0.01$).

In patients with $EF<35\%$, the rates of in-hospital events and treatment strategy were identical in comparison to patients with $EF\geq 35\%$ (Table II). Admittedly, the rate of resuscitation (32.5% vs. 11.9%, $p=0.01$) and device-implantation (28.7% vs. 7.1%, $p<0.01$) as well as in-hospital deaths (36.3% vs. 11.9%, $p<0.01$) were significantly higher in ACS as compared to TTS patients, respectively ($p<0.01$).

Short- and long-term mortality. The in-hospital mortality rates were comparable between TTS and ACS patients with $EF\geq 35\%$ (Table IV). However, the long-term mortality was significantly more declined in TTS patients as compared to ACS patients log-rank; $p<0.01$ (Figure 1). This difference was dominated by non-cardiovascular death (6.4% vs. 2.1%, $p=0.02$). These were chronic obstructive pulmonary diseases (COPD), anal cancer, lung cancer, and acute kidney injury.

In patients with $EF<35\%$, in-hospital mortality was significantly higher in ACS patients compared to TTS patients (36.3% vs. 11.9%, $p<0.01$), (Table V). However, the long-term mortality rate was similar in both groups long-rank; $p=0.83$, (Figure 2). In Cox univariate analysis, male gender (HR=2.41, 95%CI=1.1-5.2; $p=0.02$), malignancy (HR=2.64, 95%CI=1.2-5.8; $p=0.01$), $EF<35\%$ (HR=2.45, 95%CI=1.2-4.8; $p<0.01$), and emotional stress (HR=0.36, 95%CI=0.1-0.9; $p=0.03$) were associated with a high rate of mortality. In multivariate Cox regression analysis, male gender (HR=2.36, 95%CI=1.0-5.1, $p=0.03$), malignancy (HR=2.33, 95%CI=1.0-5.3%, $p=0.04$) and $EF<35\%$ (HR=2.00, 95%CI=1.0-4.0, $p=0.04$) were determined as independent predictors of mortality (Table VI).

Table I. Baseline characteristics of 94 Takotsubo Syndrome (TTS) patients and 432 acute coronary syndrome (ACS) patients with EF $\geq$ 35%.

Variables	TTS (n=94)	ACS (n=432)	p-Value*
Demographics			
Age, mean $\pm$ SD	67 $\pm$ 12	67 $\pm$ 14	0.60
Female (%)	81 (86.2)	151 (35.0)	<0.01
Symptoms, n (%)			
Dyspnea	35 (37.2)	102 (23.6)	<0.01
Chest pain	52 (55.3)	342 (79.2)	<0.01
Clinic parameter			
Systolic BP, mmHg	136 (62-240)	142 (0-280)	0.11
Diastolic BP, mmHg	79 (40-151)	80 (0-400)	0.82
Heart rate, bpm	98 $\pm$ 26	91 $\pm$ 26	<0.01
ECG Data, n (%)			
ST-segment elevation	30 (32.3)	182 (42.2)	0.08
Inversed T-Waves	81 (91.0)	202 (47.0)	<0.01
PQ-interval	159 $\pm$ 28	169 $\pm$ 37	0.33
QTc (ms)	478 (393-532)	444 (358-614)	<0.01
Laboratory values mean $\pm$ SD			
Troponin I (U/l) (IQR)	89.55 (0.01-2.738)	19.20 (0.02-335.2)	0.39
Creatine phosphokinase (U/L) (IQR)	612 (39-26.600)	1093 (23-1.3925)	0.53
CKMB (U/l) (IQR)	37 (1-415)	79 (0-970)	0.02
C-Reactive protein (mg/l) (IQR)	42.6 (1.3-338.4)	34.3 (0.0-594.0)	0.42
Hemoglobin (g/dl) (IQR)	12.2 $\pm$ 1.9	13.3 $\pm$ 2.0	0.01
Creatinine (mg/dl) (IQR)	1.01 (0.40-5.96)	1.17 (0.22-19.3)	0.31
Echocardiography data n (%)			
LV EF%	44 $\pm$ 6	54 $\pm$ 9	<0.01
LV EF% follow-up	55 $\pm$ 8	54 $\pm$ 9	0.22
Mitral regurgitation	47 (50.0)	125 (28.9)	<0.01
Tricuspid regurgitation	35 (37.2)	59 (13.7)	<0.01
Medical history, n (%)			
Smoking	29 (30.9)	175 (40.5)	0.08
Diabetes mellitus	21 (22.3)	132 (30.6)	0.11
BMI>25 kg/m ²	28 (35.9)	232 (53.7)	<0.01
Hypertension	59 (62.8)	299 (69.2)	0.22
COPD	21 (22.3)	23 (5.3)	<0.01
Atrial fibrillation	17 (18.1)	56 (13.0)	0.19
Coronary artery disease	19 (20.2)	392 (90.7)	<0.01
History of malignancy	8 (8.5)	24 (5.6)	0.28
Drugs on admission, n (%)			
Beta-blocker	30 (33.7)	139 (32.5)	0.82
ACE inhibitor	39 (43.8)	109 (25.3)	<0.01
Aldosterone inhibitor	1 (1.1)	2 (0.5)	0.46
ASA	24 (27.0)	120 (27.9)	0.86
Therapeutic anticoagulation	7 (8.0)	23 (5.3)	0.34
Drugs on discharge, n (%)			
Beta-blocker	71 (75.5)	368 (85.2)	0.02
ACE inhibitor	61 (64.9)	308 (71.3)	0.22
Aldosterone inhibitor	2 (2.1)	2 (0.5)	0.09
ASA	36 (38.3)	400 (92.6)	<0.01
Therapeutic anticoagulation	20 (21.3)	27 (6.3)	<0.01

*p-Values for the comparison between TTS and ACS. Significant p-Values are shown in bold. TTS: Takotsubo syndrome; ACS: acute coronary syndrome; SD: standard deviation; ECG: electrocardiogram; IQR: interquartile range; BP: blood pressure; LV: left ventricular; EF: ejection fraction; BMI: body-mass-index; COPD: chronic obstructive pulmonary disease; ACE: angiotensin-converting-enzyme; ASA: acetylsalicylic acid.

Discussion

This study analyzed and compared baseline characteristics and clinical outcomes involving the in-hospital and long-

term mortality of 5 years depending on EF between TTS and ACS patients. We revealed that: i) the short-term mortality was more declined in ACS patients as compared to TTS patients with EF<35, dominated by a

Table II. Baseline characteristics of 42 Takotsubo Syndrome (TTS) patients and 80 acute coronary syndrome (ACS) patients with EF<35%.

Variables	TTS (n=42)	ACS (n=80)	p-Value*
Demographics			
Age, mean±SD	65±10	71±12	0.63
Female (%)	34 (81.0)	28 (35.0)	<0.01
Symptoms, n (%)			
Dyspnea	19 (45.2)	31 (38.8)	0.49
Chest pain	16 (39.0)	52 (65.0)	<0.01
Clinic parameter			
Systolic BP, mmHg	130 (62-240)	125 (0-203)	0.56
Diastolic BP, mmHg	78 (50-100)	71 (0-120)	0.38
Heart rate, bpm	103±23	91±33	0.07
ECG Data, n (%)			
ST-segment elevation	9 (21.4)	37 (46.3)	<0.01
Inversed T-Waves	40 (97.6)	39 (48.8)	<0.01
PQ-interval	159±28	167±38	0.20
QTc (ms)	468 (130-700)	457 (384-540)	0.46
Laboratory values, mean±SD			
Troponin I (U/l) (IQR)	4.02 (0.01-24)	41.52 (0.03-1.704)	0.37
Creatine phosphokinase (U/l) (IQR)	542 (60-4.478)	1308 (34-10.410)	0.53
CKMB (U/L) (IQR)	32 (2-120)	77 (2-583)	0.57
C-Reactive protein (mg/l) (IQR)	60.8 (0.4-467.1)	63.2 (1.5-323.7)	0.50
Hemoglobin (g/dl) (IQR)	12.3±2.3	12.9±2.1	0.53
Creatinine (mg/dl) (IQR)	1.35 (0.52-5.56)	1.58 (0.43-7.32)	0.30
Echocardiography data, n (%)			
LV EF%	27±6	23±6	<0.01
LV EF% follow-up	45±15	23±6	<0.01
Mitral regurgitation	19 (45.2)	27 (33.8)	0.21
Tricuspid regurgitation	19 (45.2)	10 (12.5)	<0.01
Medical history, n (%)			
Smoking	12 (28.6)	22 (27.5)	0.90
Diabetes mellitus	9 (21.4)	32 (40.0)	0.04
BMI>25 kg/m ²	8 (22.2)	32 (40.0)	0.06
Hypertension	23 (54.8)	48 (60.0)	0.58
COPD	7 (16.7)	11 (13.8)	0.67
Atrial fibrillation	9 (21.4)	17 (21.3)	0.98
Coronary artery disease	7 (16.7)	74 (92.5)	<0.01
History of malignancy	8 (19.0)	5 (6.3)	0.03
Drugs on admission, n (%)			
Beta-blocker	14 (35.9)	50 (62.5)	0.97
ACE inhibitor	10 (25.6)	30 (37.5)	0.20
Aldosterone inhibitor	0 (0.0)	2 (2.5)	0.32
ASA	10 (25.6)	30 (37.5)	0.20
Therapeutic anticoagulation	4 (10.3)	13 (16.3)	0.38
Drugs on discharge, n (%)			
Beta-blocker	30 (71.4)	45 (56.3)	0.10
ACE inhibitor	19 (45.2)	34 (42.5)	0.77
Aldosterone inhibitor	0 (0.0)	4 (5.0)	0.14
ASA	17 (40.5)	48 (60.0)	0.04
Therapeutic anticoagulation	13 (31.0)	8 (10.0)	<0.01

*p-Values for the comparison between female TTS and female ACS. Significant p-Values are shown in bold. TTS: Takotsubo syndrome; ACS: acute coronary syndrome; SD: standard deviation; ECG: electrocardiogram; IQR: interquartile range; BP: blood pressure; LV: left ventricular; EF: ejection fraction; BMI: body-mass-index; COPD: chronic obstructive pulmonary disease; ACE: angiotensin-converting-enzyme; ASA: acetylsalicylic acid.

cardiovascular cause of death with a similar long-term outcome, and ii) whereas the short-term mortality rate in patients with EF≥35% was similar in both groups, the long-term mortality was significantly higher in TTS as

compared to ACS patients, dominated by a non-cardiovascular cause of death.

The rate of in-hospital mortality in TTS patients with EF≥35% was 5.3% compared to 4.7% in the ACS group.

Table III. *In-hospital events and treatment strategy in Takotsubo Syndrome and acute coronary syndrome (ACS patients) with EF $\geq$ 35% and EF<35.*

Variables	EF $\geq$ 35%			EF<35		
	TTS (n=94)	ACS (n=432)	<i>p</i> -Value*	TTS (n=42)	ACS (n=80)	<i>p</i> -Value*
Life-threatening arrhythmia	5 (5.4)	42 (9.8)	0.18	7 (16.7)	23 (28.7)	0.14
NPPV and or intubation	48 (51.1)	25 (5.8)	<0.01	31 (73.8)	26 (32.5)	<0.01
Inotropic agents	10 (10.6)	30 (7.0)	0.23	13 (31.0)	29 (36.3)	0.56
Resuscitation	4 (4.3)	29 (6.7)	0.37	5 (11.9)	26 (32.5)	0.01
Device-Implantation	1 (1.1)	25 (5.8)	0.06	3 (7.1)	23 (28.7)	<0.01
Admission to ICU length of stay (IQR)	4 (0-25)	3 (0-15)	<0.01	6 (1.52)	4 (0-31)	0.61
In-hospital death	5 (5.3)	20 (4.7)	0.78	5 (11.9)	30 (36.3)	<0.01
Thromboembolic events	10 (10.6)	9 (2.1)	<0.01	8 (19.0)	2 (2.5)	<0.01
Cardiogenic Shock	12 (13.2)	31 (7.2)	0.06	13 (31.0)	29 (36.7)	0.53

**p*-Values for the comparison between TTS and ACS. Significant *p*-Values are shown in bold. NPPV: Non-invasive positive pressure ventilation; ICU: intermediate care unit; IQR: interquartile range; EF: ejection fraction.

Table IV. *Outcome in 94 Takotsubo Syndrome (TTS) patients and 432 acute coronary syndrome (ACS) patients with EF $\geq$ 35.*

Variables	TTS (n=94)	ACS (n=432)	Relative risk (95% CI)	<i>p</i> -Value*
In-hospital mortality	5 (5.3)	20 (4.7)	1.0 (0.9-1.0)	0.78
30-day mortality	4 (4.3)	21 (4.9)	0.9 (0.3-2.5)	0.80
1-year mortality	6 (6.4)	23 (5.3)	1.2 (0.5-2.8)	0.69
5-year mortality	17 (18.1)	33 (7.7)	2.4 (1.4-4.0)	<0.01
Cardiovascular cause of death**	5 (5.3)	24 (5.6)	0.9 (0.3-2.2)	0.80
Non-cardiovascular cause of death***	6 (6.4)	9 (2.1)	3.1 (1.1-8.4)	0.02
Unknown cause of death	6 (6.4)	0 (0.0)		<0.01
30-day stroke	2 (2.1)	4 (0.9)	2.3 (0.4-12.3)	0.32
1-year stroke	2 (2.1)	6 (1.4)	1.5 (0.3-7.4)	0.60
5-year stroke	6 (6.4)	14 (3.2)	1.8 (0.7-4.6)	0.19
30-day life-threatening arrhythmia	5 (5.3)	38 (8.8)	0.6 (0.2-1.5)	0.26
1-year life-threatening arrhythmia	6 (6.4)	38 (8.8)	0.7 (0.3-1.7)	0.44
5-year life-threatening arrhythmia	6 (6.4)	41 (9.5)	0.5 (0.2-1.1)	0.40
30-day heart failure	1 (1.1)	13 (3.0)	0.4 (0.0-2.7)	0.29
1-year heart failure	2 (2.1)	24 (5.6)	0.4 (0.1-1.6)	0.16
5-year heart failure	3 (3.2)	43 (10.0)	0.3 (0.1-1.0)	0.03
30-day recurrence	0 (0.0)	7 (1.6)		0.21
1-year recurrence	1 (1.1)	22 (5.1)	0.2 (0.0-1.5)	0.08
5-year recurrence	5 (5.3)	51 (11.9)	0.5 (0.2-1.1)	0.06
30-day thromboembolic events	10 (10.6)	11 (2.6)	4.2 (1.8-9.5)	<0.01
1-year thromboembolic events	10 (10.6)	13 (3.0)	3.2 (1.4-7.2)	<0.01
5-year thromboembolic events	15 (16.0)	30 (7.0)	2.4 (1.3-4.5)	<0.01

p*-Values for the comparison between TTS and ACS patients. Significant *p*-Values are shown in bold. **Cardiovascular cause of death: cardiac decompensation, cardiac shock, asystole, sudden cardiac arrest, acute myocardial infarction, ventricular fibrillation, myocardial perforation. *Non-cardiovascular cause of death: COPD, lung cancer, acute kidney injury, metastatic anal cancer or unknown. EF: Ejection fraction.

Recently published data showed that an in-hospital mortality rate in TTS is comparable to ACS (2); however, these data were not related and divided according to EF. In addition, the rate of respiratory failure and consecutive need of respiratory support was significantly higher in TTS compared to ACS patients with EF $\geq$ 35% (51.1% vs. 5.8%).

Requiring respiratory support was more observed as compared to other published data in patients with TTS (18, 19). Of note, our clinical outcome data showed that a long-term mortality rate in TTS patients with EF $\geq$ 35% as compared to ACS patients was significantly higher (18.1% vs. 7.7%). Most patients died due to noncardiac reasons, such

Figure 1. Kaplan-Meier survival analysis in patients with EF ≥ 35%; TTS: Takotsubo syndrome; ACS: acute coronary syndrome; EF: ejection fraction; FU: follow-up.

Figure 2. Kaplan-Meier survival analysis in patients with EF < 35%; TTS: Takotsubo syndrome; ACS: acute coronary syndrome; EF: ejection fraction; FU: follow-up.

Table V. Outcome in 42 Takotsubo Syndrome (TTS) patients and 80 acute coronary syndrome (ACS) patients with EF<35%.

Variables	TTS (n=42)	ACS (n=80)	Relative risk (95% CI)	p-Value*
In-hospital mortality	5 (11.9)	29 (36.3)	0.3 (0.2-0.8)	<0.01
30-day mortality	4 (4.3)	21 (4.9)	0.9 (0.3-2.5)	0.80
1-year mortality	8 (19.0)	30 (37.5)	0.5 (0.3-1.0)	0.04
5-year mortality	18 (42.9)	34 (42.5)	1.0 (0.6-1.5)	0.83
Cardiovascular cause of death**	6 (14.3)	28 (35.0)	0.4 (0.2-0.9)	0.02
Non-cardiovascular cause of death***	9 (21.4)	6 (7.5)	2.9 (1.0-7.5)	0.03
Unknown cause of death	3 (7.14)	0 (0.0)		0.05
30-day stroke	2 (4.8)	1 (1.3)	3.8 (0.4-40.8)	0.23
1-year stroke	3 (7.1)	1 (1.3)	5.7 (0.6-53.3)	0.08
5-year stroke	3 (7.1)	3 (3.8)	1.9 (0.9-4.1)	0.41
30-day life-threatening arrhythmia	6 (14.3)	22 (27.5)	0.6 (0.3-1.4)	0.18
1-year life-threatening arrhythmia	6 (14.3)	24 (30.0)	0.6 (0.3-1.2)	0.12
5-year life-threatening arrhythmia	7 (16.7)	24 (30.0)	0.6 (0.3-1.3)	0.19
30-day heart failure	2 (4.8)	24 (30.0)	0.2 (0.0-0.6)	<0.01
1-year heart failure	2 (4.8)	27 (33.8)	0.1 (0.0-0.6)	<0.01
5-year heart failure	2 (4.8)	30 (37.5)	0.1 (0.0-0.5)	<0.01
30-day recurrence	0 (0.0)	0 (0.0)		0.21
1-year recurrence	0 (0.0)	1 (1.3)		0.47
5-year recurrence	2 (4.8)	3 (3.8)	1.9 (0.3-13.0)	0.51
30-day thromboembolic events	8 (19.0)	2 (2.5)	7.6 (1.7-34.3)	<0.01
1-year thromboembolic events	8 (19.0)	2 (2.5)	7.6 (1.7-34.3)	<0.01
5-year thromboembolic events	9 (21.4)	4 (5.0)	4.3 (1.4-13.1)	<0.01

*p-Values for the comparison between TTS and ACS patients. Significant p-Values are shown in bold. **Cardiovascular cause of death: cardiac decompensation, cardiac shock, asystole, sudden cardiac arrest, acute myocardial infarction, ventricular fibrillation, myocardial perforation. ***Non-cardiovascular of death: COPD, respiratory failure, lung cancer, acute kidney injury, breast cancer, hematological cancer, blast crisis, subarachnoid hemorrhage, hypoxic brain damage.

Table VI. Predictors of mortality, multivariate analysis.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Male	2.41	1.1-5.2	0.02	2.36	1.0-5.1	0.03
Arterial hypertension	0.84	0.4-1.6	0.60			
Smoking	0.87	0.4-1.8	0.71			
Diabetes mellitus	0.91	0.4-2.0	0.83			
Malignancy	2.64	1.2-5.8	0.01	2.33	1.0-5.3	0.04
Chronic obstructive pulmonary disease	0.84	0.3-1.8	0.64			
Apical ballooning	1.61	0.7-1.6	0.26			
Atrial fibrillation	1.72	0.8-3.6	0.16			
Ventricular arrhythmia	1.41	0.5-4.0	0.51			
EF<35%	2.45	1.2-4.8	<0.01	2.00	1.0-4.0	0.04
Physical stress	1.08	0.5-2.1	0.81			
Emotional stress	0.36	0.1-0.9	0.03	0.42	0.1-1.1	0.07

Significant p-Values are shown in bold. HR: Hazard ratio; EF: ejection fraction; CI: confidence interval.

as progressive cancer or chronic obstructive pulmonary diseases (COPD). It is, therefore, considered that some patients may require respiratory support due to COPD and not because of presentation of TTS. Looi *et al.* have

described worse long-term mortality in ACS patients as compared to TTS (19). On the other hand, Stiermaier *et al.* have reported more worse clinical outcomes in TTS patients as compared to ACS patients (20).

In addition, a malignancy rate was described to be high and may be affected the non-cardiovascular mortality in TTS patients. This finding was presented in some clinical trials and may be responsible for increasing the mortality rate in TTS patients as well as the presentation of leukemia, lymphoma, solid cancer or metastatic solid cancer, which certainly does not improve the prognosis (21-25). TTS patients might require cardiac rehabilitation to improve the poor prognosis, particularly those with $EF \geq 35\%$. It has been observed that cardiac rehabilitation may help with these patients' outcome, using exercise and weight reduction (26).

Regardless of EF, the rate of thromboembolic in-hospital events and during follow-up time is higher in TTS as compared to ACS patients. Templin *et al.* have reported a high risk for thromboembolic events as ventricular thrombi and stroke or transient ischemic attacks in TTS patients (2). The slow blood flow in the LV may be one of the reasons for the development of ventricular thrombi in TTS patients. In the course of TTS, EF increased, and the wall motion abnormalities disappeared completely. Presented thrombi could leave left chamber into the peripheral arteries which can increase the risk of an embolic event and stroke. Other explanations for thromboembolic events in TTS patients with a moderated $EF \geq 35\%$ might point towards malignancy. Our data present a higher cancer rate in TTS patients with $EF \geq 35\%$ as compared to ACS patients. Several other studies have shown an association between TTS and cancer (21, 23, 27). A high rate of breast cancer has also been observed in TTS patients following gastrointestinal and gynecological malignancies (28).

In-hospital mortality in TTS patients with $EF < 35\%$ was observed in 11.9%. Previously published data on TTS have shown that a reduced $EF < 35\%$ is more associated with a poor outcome as compared to $EF > 35\%$. Our data showed a higher rate than the reported rate in the literature (1-4.5%) (2, 14, 29, 30). This rate is significantly lower as compared to ACS patients with $EF < 35\%$ (36.3%). Consequently, a cardiopulmonary resuscitation rate was significantly higher in ACS patients as compared to TTS patients with $EF < 35\%$ (11.9% vs. 32.5%). This might be related to the higher rate of ventricular arrhythmias in ACS patients as compared to TTS patients (16.7% vs. 28.7%). Citro *et al.* have reported a higher incidence of cardiogenic shock, intra-aortic balloon pump use, and acute heart failure in TTS patients with $EF < 35\%$ as compared to $EF > 35\%$ (8). Our data present a similar cardiogenic shock rate in TTS in comparison to ACS patients with $EF < 35\%$.

There are some limitations to this study. This study is monocentric and the number of patients with TTS was relatively small compared to other studies. A bias due to unknown or unmeasured cofounders cannot be excluded due to the retrospective character of the study. However, EF measurement using the Simpson method is not always

measurable, especially in patients with obesity, COPD or under ICU management. Finally, in some patients, data are missing about cause of death.

Despite these limitations, our data show that male gender, malignancy and $EF < 35\%$ can be estimated as independent predictors of the mortality in TTS patients. A reduced EF has been proposed by numerous studies as an independent predictor of an in-hospital complication in TTS patients and ACS patients (8-10). Additional independent predictors of in-hospital complications in TTS have been previously noticed, such as an existence of physical stressor, old age, male as gender, elevated troponin level and acute neurologic or psychiatric illness (2, 8, 31).

Considering these data, it might be recommended to order a frequent in-hospital follow-up and long-term follow-up in TTS patients with an initial $EF < 35\%$ and $EF \geq 35\%$. TTS may present a catch-up phenomenon.

In conclusion, an in-hospital mortality rate in patients with $EF < 35\%$ is significantly lower in TTS compared to ACS patients dominated by cardiovascular deaths, but the long-term outcome is comparable in both groups during a 5-year follow-up. Even though the in-hospital mortality of TTS and ACS with $EF \geq 35\%$ is similar, the long-term mortality rate is significantly higher in TTS compared to ACS patients with a major impact on a non-cardiovascular cause of death at 5-years of follow-up. Respectively, TTS patients with $EF \geq 35\%$ require longer follow-up and post-rehabilitation support compared to ACS patients to reduce the long-time mortality.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

Data were gathered by MA, IE, TG and MK. MA analyzed all data. XZ and SL supported the descriptive statistics. Echocardiographic assessment was performed by IE and MB. IA and MB performed coronary angiography. IA and IE designed the study and approved the statistical analysis. MA and IA prepared the manuscript. All Authors approved the final version.

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