ESC European Society of Cardiology

European Journal of Heart Failure (2019) **21**, 781–789
doi:10.1002/ejhf.1373

RESEARCH ARTICLE

Long-term outcome in patients with Takotsubo syndrome presenting with severely reduced left ventricular ejection fraction

Rodolfo Citro[1]*, Ilaria Radano[1], Guido Parodi[2], Davide Di Vece[1,3], Concetta Zito[4], Giuseppina Novo[5], Gennaro Provenza[1], Michele Bellino[1], Costantina Prota[1], Angelo Silverio[1], Francesco Antonini-Canterin[6], Fausto Rigo[7], Olga Vriz[8], Gennaro Galasso[1], Eduardo Bossone[1], Jorge Salerno-Uriarte[9], and Federico Piscione[1]

[1]Department of Cardiology, University Hospital 'San Giovanni di Dio e Ruggi d'Aragona', Salerno, Italy; [2]Division of Interventional Cardiology, University Hospital of Sassari, Sassari, Italy; [3]Department of Cardiology, University Hospital of Zurich, Zurich, Switzerland; [4]Division of Cardiology, University of Messina, Messina, Italy; [5]Division of Cardiology, University of Palermo, Palermo, Italy; [6]Division of Rehabilitation Cardiology, Sacile Hospital, Pordenone, Italy; [7]Department of Cardiology, Dell'Angelo Hospital, Mestre, Italy; [8]Heart Centre, Hospital and Research Centre, Riyadh, Saudi Arabia; and [9]University of Insubria, Varese, Italy

Received 2 April 2018; revised 18 August 2018; accepted 2 November 2018; online publish-ahead-of-print 4 February 2019

Aim To evaluate the long-term outcome of patients with Takotsubo syndrome (TTS) and severely reduced left ventricular ejection fraction (LVEF ≤ 35%) at presentation.

Methods and results The study population included 326 patients (mean age 69.5 ± 10.7 years, 28 male) with TTS enrolled in the Takotsubo Italian Network, divided into two groups according to LVEF (≤ 35%, $n = 131$; > 35%, $n = 195$), as assessed by transthoracic echocardiography at hospital admission. In-hospital events were recorded in both groups. At long-term follow-up (median 26.5 months, interquartile range 18–33), composite major adverse cardiac events (MACE: cardiac death, acute myocardial infarction, heart failure, and TTS recurrence) and rehospitalization were investigated. Compared to patients with LVEF > 35%, patients with LVEF ≤ 35% were older (71.2 ± 10.8 vs. 68.4 ± 10.6 years; $P = 0.026$) and experienced more frequently cardiogenic shock (16% vs. 4.6%; $P < 0.001$), acute heart failure (28.2% vs. 12.8%; $P = 0.001$), and intra-aortic balloon pump support (11.5% vs. 2.6%; $P = 0.001$) in the acute phase. At long-term follow-up, higher rates of composite MACE (25.2% vs. 10.8%; $P = 0.001$) and rehospitalization for cardiac causes (26% vs. 13.3%; $P = 0.004$) were observed in these patients. LVEF ≤ 35% at admission [hazard ratio (HR) 2.184, 95% confidence interval (CI) 1.231–3.872; $P = 0.008$] and age (HR 1.041, 95% CI 1.011–1.073; $P = 0.006$) were independent predictors of MACE. Patients with LVEF ≤ 35% also had a significant lower freedom from composite MACE during long-term follow-up ($\chi^2 = 11.551$, $P = 0.001$).

Conclusion Left ventricular ejection fraction ≤ 35% at presentation is a key parameter to identify TTS patients at higher risk not only in the acute phase but also at long-term follow-up.

Keywords Takotsubo syndrome • Cardiomyopathy • Left ventricular ejection fraction • Heart failure • Cardiogenic shock

*Corresponding author. Heart Department, University Hospital 'San Giovanni di Dio e Ruggi d'Aragona', Heart Tower Room 807, Largo Città d'Ippocrate, 84131 Salerno, Italy. Tel: +39 089 673377, Email: rodolfocitro@gmail.com

Introduction

Takotsubo syndrome (TTS) is an acute and usually reversible heart failure syndrome, often resulting from a stressful emotional or physical triggering event. Presentation at admission is similar to acute coronary syndrome, but with no evidence of culprit atherosclerotic coronary artery disease at coronary angiography.[1–3] In this regard, a clinical score to early differentiate acute coronary syndromes from TTS has previously been proposed.[4] TTS aetiology is still unknown, but among the various hypotheses that have been advanced, the most accredited involves catecholamine-mediated myocardial stunning.[5] Although TTS was initially considered as a benign condition, several studies have demonstrated a substantial incidence of life-threatening complications occurring in the acute phase, with mortality ranging from 1% to 8%.[1,3,6–14] Furthermore, recent data from the InterTAK registry revealed that both short- and long-term outcomes of TTS patients are similar to those of patients with acute coronary syndrome.[11] Advanced age, hypotension at hospital admission, severe left ventricular (LV) systolic and diastolic dysfunction and significant mitral regurgitation (MR) are all conditions associated with an increased risk of early adverse events.[9,10,15] A risk stratification system based on an arbitrary LV ejection fraction (LVEF) cut-off value of ≤ 35% has been proposed by the Task Force on TTS of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) to identify patients at risk.[3] Low LVEF has been shown to have a negative impact on short-term outcome, but no data are available on follow-up. The aim of this study was to evaluate the long-term outcome of patients with TTS and severely reduced LVEF (≤ 35%) at presentation.

Methods

Study population

The study population consisted of 326 patients (mean age 69.5 ± 10.7 years, 28 male) enrolled in the Takotsubo Italian Network (TIN) according to the revised TIN diagnostic criteria (see *Appendix* for TIN Investigators), subsequently incorporated by the Task Force on TTS of the HFA of the ESC[3]:

(i) Typical transient LV wall motion abnormalities extending beyond a single epicardial vascular distribution with complete functional normalization within 6 weeks.
(ii) Absence of culprit atherosclerotic coronary artery disease (CAD), or angiographic evidence of acute plaque rupture, dissection, thrombosis, or spasm.
(iii) New and dynamic ST-segment abnormalities or T-wave inversion and new-onset transient or permanent left bundle branch block.
(iv) Mild increase in myocardial injury markers.
(v) Clinical and/or instrumental exclusion of myocarditis.

Patients with a poor acoustic window (suboptimal visualization of endocardial borders) were excluded. All participants provided informed written consent, and the study was approved by the local ethics committee.

Data collection

Clinical variables were recorded on a standardized form that included information on patient demographics (sex, age, heart rate, systolic and diastolic blood pressure), signs and symptoms at presentation, medical history, trigger events and ST-segment changes on admission electrocardiogram. Emotional or physical triggers were identified as previously described.[8] Venous blood was collected every 3 h to measure troponin I concentration in the acute phase, and collection continued until a peak value was observed. All patients underwent coronary angiography and left ventriculography within 24 h of symptom onset. In-hospital events, including acute heart failure and cardiogenic shock as previously defined, were also recorded. Patients were divided into two groups according to LVEF ≤ 35% or > 35% at first echocardiographic examination.

After hospital discharge, follow-up was performed by outpatient clinic visits or telephone interview. Occurrence of symptoms or signs of heart failure, rehospitalization, TTS recurrence, myocardial infarction, all-cause mortality, and ongoing pharmacological therapy were recorded. If medical records, treating physicians or relatives were unable to substantiate information identifying the circumstances of death, it was defined as death due to an unknown cause. Moreover, composite major adverse cardiac events (MACE: cardiac death, heart failure, acute myocardial infarction, TTS recurrence) and rehospitalization for cardiac and non-cardiac causes were investigated at long-term follow-up.

Echocardiography

All echocardiographic examinations were performed within 6 h of hospital admission, before coronary angiography, and were repeated during hospitalization. A commercially available cardiac ultrasonography system with a 2.5 to 4.5 MHz phased-array transducer with second harmonic capability was used for complete two-dimensional Doppler echocardiography. All examinations were performed by observers blinded to clinical data. LV regional wall motion abnormalities were evaluated by visual assessment of multiple apical and short-axis views, as previously described.[16] All echocardiographic images were digitally recorded and reviewed by expert readers. Three cardiac cycles from the apical 4- and 2-chamber views and the parasternal short-axis view at the level of the mitral valve and papillary muscles were stored in cine-loop format for off-line analysis. LVEF was calculated using biplane Simpson's rule from the apical 4- and 2-chamber views.[17] Right ventricular (RV) wall motion was evaluated by visual assessment for the detection of RV involvement.[18] The echo transducer was adjusted to the level of the RV chamber to achieve optimal visualization of RV size and RV endocardial borders. Tricuspid annular plane systolic excursion (TAPSE) was calculated as previously described.[19] LV diastolic function was evaluated according to the American Society of Echocardiography recommendations.[20] Early (e′) diastolic tissue Doppler velocities were measured at the septal and lateral corners of the mitral annulus, and the mean between the two values was calculated. The ratio of mitral E peak velocity and averaged e′ velocity (E/e′) was calculated. MR was quantified from colour Doppler imaging and semi-quantitatively graded as absent, minimal (within normal limits), mild, moderate, or severe, using standardized criteria.[21] Moderate MR was confirmed by vena contracta measurement (3 to 7 mm).[22] LV outflow tract obstruction (LVOTO) was detected by continuous wave Doppler. Using the modified Bernoulli equation, a cut-off value of 25 mmHg for dynamic intraventricular pressure gradient was considered to indicate significant LVOTO.[23] With continuous wave Doppler echocardiography, peak

tricuspid regurgitant velocity recorded from any view was used to determine systolic pulmonary artery pressure (sPAP) with the simplified Bernoulli equation [sPAP = 4 × (peak velocity)^2 + mean right atrial pressure]; mean right atrial pressure was estimated as previously described.[24]

Statistical analysis

Normally distributed continuous variables were reported as mean ± standard deviation, while non-normally distributed continuous variables were presented as median and interquartile range. Categorical variables were summarized as number (%) of patients. Differences between groups were assessed using Student's *t*-test or Wilcoxon–Mann–Whitney test for continuous variables, and chi-squared or Fisher's exact test for categorical variables, as appropriate.

The associations between several clinical, electrocardiographic, echocardiographic and laboratory variables with MACE were evaluated using the Cox proportional hazards model with univariate analysis. A level of significance of 0.05 was required for a variable to be included in the multivariate model, whereas 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with 95% confidence intervals (CIs) were estimated. Selected variables identified at univariate analysis (age, history of CAD, LVEF ≤ 35% at admission) were then entered into stepwise multivariate analysis to determine independent predictors of MACE.

Kaplan–Meier curves were plotted to estimate event-free survival from composite MACE.

A *P*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 20.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics

Demographic, clinical, and laboratory characteristics of the overall study population and the subgroups of patients with LVEF ≤ 35% ($n = 131$) or > 35% ($n = 195$) are summarized in *Table 1*. Patients with LVEF ≤ 35% were older than patients with LVEF > 35% (71.2 ± 10.8 vs. 68.4 ± 10.6 years, $P = 0.026$), had lower systolic blood pressure (120.5 ± 21.9 vs. 129.9 ± 23.7 mmHg; $P = 0.001$) and higher heart rate at admission (91 ± 22 vs. 84.1 ± 17.5 b.p.m.; $P = 0.002$). Moreover, they less frequently showed chest pain as presenting symptom (71.8% vs. 83.6%; $P = 0.010$), whereas they more frequently had acute onset of dyspnoea (22.9% vs. 14.4%; $P = 0.048$) and elevated peak troponin level (6.08 ± 7.94 vs. 3.60 ± 6.98; $P = 0.004$). Of note, in a greater proportion of patients with LVEF ≤ 35%, TTS was triggered by a physical event (30.5% vs. 17.9%; $P = 0.008$), whereas in patients with LVEF > 35% TTS was predominantly triggered by an emotional event (42.7% vs. 64.1%; $P < 0.001$). ST-segment elevation was more frequently observed in patients with LVEF ≤ 35% (69.7% vs. 57.3%; $P = 0.028$). Among co-morbidities, patients with LVEF ≤ 35% showed a higher prevalence of CAD (29% vs. 19%; $P = 0.035$), chronic obstructive pulmonary disease (20.6% vs. 9.2%; $P = 0.003$), and a lower prevalence of psychiatric conditions (11.5% vs. 22.6%; $P = 0.011$). There were no significant differences between groups in other cardiovascular risk factors, such as hypercholesterolaemia, hypertension, diabetes and smoking, as well as in creatinine, haemoglobin, white blood cell count, and C-reactive protein.

Echocardiographic findings at admission and at discharge

Echocardiographic features at admission are summarized in *Table 2*. In the acute phase, no significant differences in the prevalence of typical apical ballooning were detected between patients with LVEF ≤ 35% and those with LVEF > 35%.

Patients with LVEF ≤ 35% had significantly higher LV end-systolic volume index (39.7 ± 8.0 vs. 32.9 ± 8.0; $P = 0.002$) and higher wall motion score index (2.06 ± 0.23 vs. 1.81 ± 0.22; $P < 0.001$) than patients with LVEF > 35%.

Mitral inflow-derived parameters were significantly different between groups (E wave peak velocity, $P = 0.007$; A peak velocity, $P = 0.005$; E/A ratio, $P = 0.010$; E-wave deceleration time, $P < 0.001$; E/e′ ratio, $P < 0.001$). Moderate to severe MR was present in 70 patients, more often in those with LVEF ≤ 35% (29.8% vs. 15.9%; $P = 0.003$). In contrast, no significant differences between groups were reported in sPAP, TAPSE, and LVOTO.

Although all patients showed LV systolic function recovery at discharge, LVEF remained significantly lower in those with LVEF ≤ 35% at TTS onset (49.5 ± 9.8 vs. 55.9 ± 5.9; $P < 0.001$). Moreover, some diastolic indices such as E peak velocity (80.0 ± 20.6 vs. 68.2 ± 16.3; $P = 0.02$) and E-wave deceleration time (188.0 ± 37.6 vs. 220.3 ± 57.6; $P = 0.043$) were significantly different between groups. No other relevant differences about echocardiographic parameters were detected at discharge, except for a significant higher prevalence of moderate to severe MR in patients with LVEF ≤ 35% at admission (9.9% vs. 3.1%, $P = 0.010$).

In-hospital course

Overall complications during the in-hospital course are listed in *Table 3*. Acute heart failure was the most common complication, occurring in 62 patients (19%) and more frequently in the LVEF ≤ 35% group (28.2% vs. 12.8%; $P = 0.001$). Cardiogenic shock (16% vs. 4.6%; $P < 0.001$) and intra-aortic balloon pump use (11.5% vs. 2.6%; $P = 0.001$) were recorded more frequently in patients with LVEF ≤ 35%. Moreover, a greater proportion of patients with LVEF ≤ 35% had atrial fibrillation, though without reaching statistical significance (9.2% vs. 4.1%, $P = 0.062$).

Clinical events and pharmacological therapy at long-term follow-up

At long-term follow-up (median 26.5 months, interquartile range 18–33), more patients in the LVEF ≤ 35% group experienced acute heart failure (16% vs. 5.1%; $P = 0.001$), rehospitalization from any cause (29.8% vs. 15.9%; $P = 0.003$), cardiac rehospitalization (26% vs. 13.3%; $P = 0.004$), and composite MACE (25.2% vs. 10.8%; $P = 0.001$).

A total of 24 deaths (7.4%) occurred during the follow-up. Overall mortality was significantly higher in patients with LVEF ≤ 35%

Table 1 Demographic, anamnestic, clinical, and laboratory data at admission in patients with Takotsubo syndrome

Variables	Overall population ($n = 326$)	Patients with LVEF ≤ 35% ($n = 131$; 40.1%)	Patients with LVEF > 35% ($n = 195$; 59.9%)	*P*-value
Demographic and clinical variables				
Age, years	69.5 ± 10.7	71.2 ± 10.8	68.4 ± 10.6	0.026
Male sex	28 (8.6)	9 (6.9)	19 (9.7)	0.364
BSA, m^2	1.68 ± 0.16	1.74 ± 0.18	1.66 ± 0.15	0.019
SBP, mmHg	126.1 ± 23.4	120.5 ± 21.9	129.9 ± 23.7	0.001
DBP, mmHg	74.1 ± 13.9	71.8 ± 14.6	75.7 ± 13.2	0.017
HR, b.p.m.	86.9 ± 19.7	91.0 ± 22.0	84.1 ± 17.5	0.002
Identifiable TE	257 (78.8)	97 (74.0)	160 (82.1)	0.083
Emotional TE (primary TTS)	181 (55.5)	56 (42.7)	125 (64.1)	< 0.001
Physical TE (secondary TTS)	75 (23.0)	40 (30.5)	35 (17.9)	0.008
Chest pain	257 (78.8)	94 (71.8)	163 (83.6)	0.010
Dyspnoea	58 (17.8)	30 (22.9)	28 (14.4)	0.048
ST-segment elevation	203 (62.3)	91 (69.7)	112 (57.3)	0.028
Cardiovascular risk factors and co-morbidities				
Hypertension	208 (63.8)	78 (59.5)	130 (66.7)	0.189
Diabetes	35 (10.7)	18 (13.7)	17 (8.7)	0.151
Hypercholesterolaemia	132 (40.5)	46 (35.1)	86 (44.1)	0.105
Smoking	63 (19.3)	24 (18.3)	39 (20.0)	0.707
Menopause	279 (93.6)	114 (93.4)	165 (93.8)	0.915
CAD	75 (23.0)	38 (29.0)	37 (19.0)	0.035
COPD	45 (13.8)	27 (20.6)	18 (9.2)	0.003
Cancer	36 (11.0)	14 (10.7)	22 (11.2)	0.867
Psychiatric disorder	59 (18.1)	15 (11.5)	44 (22.6)	0.011
Laboratory data				
Troponin peak, μg/L	4.58 ± 7.46	6.08 ± 7.94	3.60 ± 6.98	0.004
Creatinine, mg/dL	0.88 ± 0.29	0.86 ± 0.27	0.89 ± 0.29	0.499
Hb, g/dL	13.0 ± 1.5	13.0 ± 1.6	13.0 ± 1.4	0.767
WBC count ($\times 10^3$)	9.2 ± 3.6	9.6 ± 4.3	9.0 ± 3.1	0.186
CRP, mg/L	8.0 ± 18.4	11.0 ± 24.8	6.4 ± 14.2	0.169

Values are given as mean ± standard deviation, or *n* (%).
BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; Hb, haemoglobin; HR, heart rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TE, trigger event; TTS, Takotsubo syndrome; WBC, white blood cell.

($n = 14$, 10.7% vs. $n = 10$, 5.1%; $P = 0.049$), while no significant differences were observed between groups in cardiac and non-cardiac mortality, as well as in TTS recurrence and acute myocardial infarction. Pharmacological therapy at follow-up did not differ between patients with LVEF ≤ 35% and those with LVEF > 35% (*Table 4*).

TTS patients on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) therapy at discharge had lower rates of cardiac death at long-term follow-up (46.7% vs. 70.7%; $P = 0.048$), but overall mortality did not differ between groups (7.0% vs. 8.1%; $P = 0.743$).

Predictors of composite MACE at follow-up at univariate and multivariate Cox regression analysis are reported in *Table 5*. LVEF ≤ 35% at admission (HR 2.184, 95% CI 1.231–3.872; $P = 0.008$) and age (HR 1.041, 95% CI 1.011–1.073; $P = 0.006$) were independent predictors of MACE at follow-up. At Kaplan–Meier survival analysis, patients with LVEF ≤ 35% had a significant lower freedom from composite MACE during long-term follow-up ($\chi^2 = 11.551$, $P = 0.001$) (*Figure 1*). Among patients with LVEF ≤ 35%, those on beta-blockers at discharge had a lower incidence of MACE at long-term follow-up compared with those not receiving beta-blockers ($\chi^2 = 9.490$, $P = 0.004$). A favourable trend in patients with LVEF > 35% taking beta-blockers was also appreciated, although no significant difference was detected compared with those not receiving beta-blockers ($\chi^2 = 3.491$, $P = 0.062$). No differences were observed among patients with and without ACEi/ARB, both in the LVEF > 35% group ($P = 0.735$) and the LVEF ≤ 35% group ($P = 0.264$).

Discussion

The main findings of our study are that (i) severe LV systolic dysfunction (LVEF ≤ 35%) is observed in 41.5% of TTS patients at admission; (ii) in-hospital complications and mortality are significantly higher in TTS patients with severely reduced LVEF; and (iii) despite substantial myocardial function recovery, patients with LVEF ≤ 35% at TTS onset experience more frequently adverse

Table 2 Echocardiographic features at admission

Variables	Overall population ($n = 326$)	Patients with LVEF ≤ 35% ($n = 131$; 40.1%)	Patients with LVEF > 35% ($n = 195$; 59.9%)	*P*-value
LVEF, %	36.8 ± 7.4	29.3 ± 5.4	41.9 ± 3.1	< 0.001
LVEDVI, mL/m^2	56.4 ± 12.4	57.8 ± 11.3	55.9 ± 12.9	0.560
LVESVI, mL/m^2	34.9 ± 8.5	39.7 ± 8.0	32.9 ± 8.0	0.002
WMSI	1.88 ± 0.25	2.06 ± 0.23	1.81 ± 0.22	< 0.001
E wave velocity, cm/s	75.6 ± 20.0	82.6 ± 22.0	72.6 ± 18.4	0.007
A wave velocity, cm/s	76.6 ± 21.6	68.7 ± 19.4	80.0 ± 21.7	0.005
E/A ratio	1.11 ± 0.62	1.32 ± 0.57	1.02 ± 0.62	0.010
E wave DT, ms	192.5 ± 55.2	159.8 ± 44.3	205.4 ± 54.0	< 0.001
E/e′ ratio	11.1 ± 4.2	15.0 ± 3.3	9.4 ± 3.4	< 0.001
sPAP, mmHg	40.0 ± 11.3	42.7 ± 10.9	38.8 ± 11.3	0.065
TAPSE, mm	19.8 ± 4.1	19.9 ± 3.8	19.8 ± 4.3	0.945
Moderate to severe MR	70 (21.5)	39 (29.8)	31 (15.9)	0.003
Apical form	275 (84.4)	109 (83.2)	166 (85.1)	0.640
LVOTO	25 (7.7)	11 (8.4)	14 (7.2)	0.685

Values are given as mean ± standard deviation, or *n* (%).
DT, deceleration time; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score index.

Table 3 In-hospital course

Variables	Overall population ($n = 326$)	Patients with LVEF ≤ 35% ($n = 131$; 40.1%)	Patients with LVEF > 35% ($n = 195$; 59.9%)	*P*-value
Inotropic agents	10 (3.1)	6 (4.6)	4 (2.1)	0.194
IABP	20 (6.1)	15 (11.5)	5 (2.6)	0.001
Acute heart failure	62 (19)	37 (28.2)	25 (12.8)	0.001
Cardiogenic shock	30 (9.2)	21 (16.0)	9 (4.6)	< 0.001
VT/VF	7 (2.1)	3 (2.3)	4 (2.1)	0.884
Atrial fibrillation	20 (6.1)	12 (9.2)	8 (4.1)	0.062

Values are given as number (%).
IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

cardiac events during long-term follow-up compared with patients with LVEF > 35%.

Reduced LVEF is a common finding in patients with TTS, with even lower values than in acute myocardial infarction.[11,16] In our study, the high prevalence of LV systolic dysfunction seems to be related to the greater extension of myocardial damage, as demonstrated by elevated troponin level and high wall motion score index.

Patients with LVEF ≤ 35% were older than those with LVEF > 35%, confirming previous data on the association between advanced age and LV systolic dysfunction in TTS patients.[1,11–13] According to the pathophysiological hypothesis of catecholaminergic myocardial stunning, the localization of myocardial impairment is determined by the distribution and expression of beta-adrenergic receptors.[25] The impairment of myocardial function in older patients should be related to reduced $beta_1$-adrenergic subtype receptor density in advanced age. Moreover, the high levels of circulating catecholamines induce a 'desensitization process' due to increase in Gi (inhibitory) protein expression.[25,26] Owing to the higher rates of acute heart failure and cardiogenic shock in patients with LVEF < 35%, this parameter should be added to other already used variables (such as ST-segment changes) in a prognostic score helpful in stratifying outcome and guiding therapeutic approach.[10]

Myocardial injury induces not only pump failure, but also increased collagen deposition along with a loss of elastic tissue, ultimately leading to diastolic dysfunction, myocardial wall stiffness, and increased LV filling pressure.[27] High E/e′ ratio, a surrogate index of increased LV diastolic pressure, has been proven to be an independent predictor of adverse outcome in TTS patients during hospitalization.[10,28] E/e′ ratio was found to be significantly higher in patients with LVEF ≤ 35%, accounting for the rapid increase in post-capillary pulmonary hypertension, leading in turn to acute heart failure, which occurred more frequently in this subgroup.

Table 4 Clinical events and pharmacological therapy at long-term follow-up

Variables	Overall population ($n = 326$)	Patients with LVEF ≤ 35% ($n = 131$; 40.1%)	Patients with LVEF > 35% ($n = 195$; 59.9%)	*P*-value
Clinical events				
TTS recurrence	9 (2.8)	3 (2.3)	6 (3.1)	0.671
AMI	6 (1.8)	4 (3.1)	2 (1.0)	0.182
Acute heart failure	31 (9.5)	21 (16.0)	10 (5.1)	0.001
All-cause rehospitalization	70 (21.5)	39 (29.8)	31 (15.9)	0.003
Cardiac rehospitalization	60 (18.4)	34 (26.0)	26 (13.3)	0.004
Overall mortality	24 (7.4)	14 (10.7)	10 (5.1)	0.049
Cardiac death	15 (4.6)	9 (6.9)	6 (3.1)	0.092
Non-cardiac death	9 (2.8)	5 (3.8)	4 (2.1)	0.268
Composite MACE[a]	54 (16.6)	33 (25.2)	21 (10.8)	0.001
Pharmacological therapy				
ASA[b]	217 (77.5)	85 (75.9)	132 (78.6)	0.599
$P2Y_{12}$ RA[c]	37 (26.4)	21 (29.6)	16 (23.2)	0.391
BB	224 (68.7)	89 (67.9)	135 (69.2)	0.805
ACEi/ARB	227 (69.6)	92 (70.2)	135 (69.2)	0.848
No BB or ACEi/ARB	31 (9.5)	13 (9.9)	18 (8.2)	0.834
Statins	159 (48.8)	62 (47.3)	97 (49.7)	0.669

Values are given as *n* (%).
ACEi, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BB, beta-blocker; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; RA, receptor antagonist; TTS, Takotsubo syndrome.
[a]Cardiac death, heart failure, AMI, TTS recurrence.
[b]Data available for 280 patients ($n = 112$ with LVEF ≤ 35%, $n = 168$ with LVEF > 35%).
[c]Data available for 140 patients ($n = 71$ with LVEF ≤ 35%, $n = 69$ with LVEF > 35%).

Table 5 Predictors of composite major adverse cardiac events at follow-up at univariate and multivariate Cox regression analysis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.042 (1.012–1.073)	0.006	1.041 (1.011–1.073)	0.006
History of CAD	1.800 (1.028–3.152)	0.040		
LVEF ≤ 35% at admission	2.493 (1.442–4.311)	0.001	2.184 (1.231–3.872)	0.008

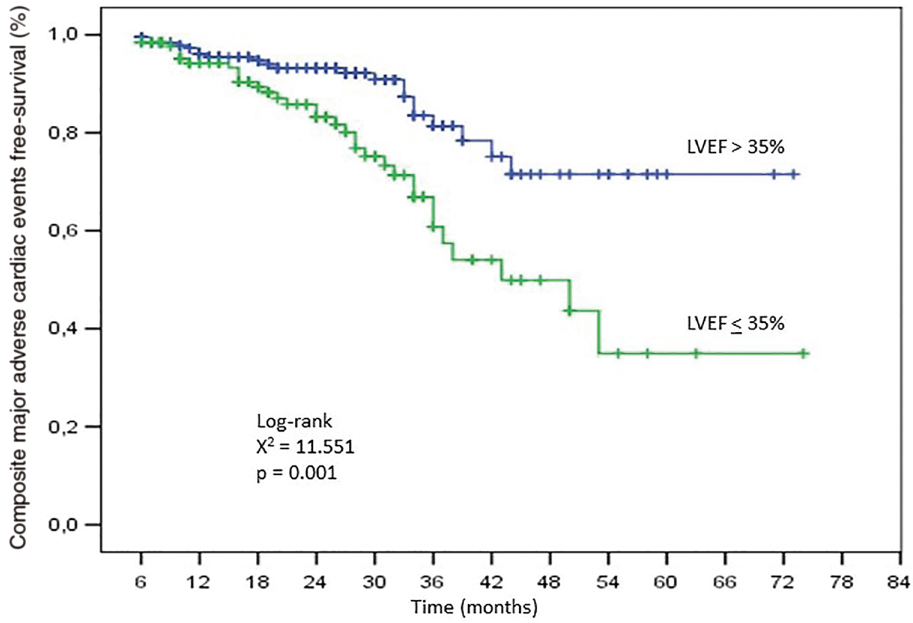
CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Additionally, extensive myocardial injury involving the mitral valve apparatus could explain the higher incidence of reversible, functional, moderate-to-severe MR observed in patients with LVEF ≤ 35%. Significant MR results in increased LV end-diastolic pressure, accounting for either dyspnoea as main symptom at admission, or for the higher prevalence of acute heart failure in these patients. Moreover, MR results in low cardiac output, higher heart rate and decreased systolic blood pressure, with subsequent haemodynamic instability, leading to cardiogenic shock, especially in patients with LVEF ≤ 35%.

Although an in-hospital adverse outcome is expected in patients with severe LV systolic dysfunction at presentation, the novelty of our study is the finding that these patients had a poor prognosis also at long term, as evidenced by higher mortality and all-cause and cardiac rehospitalization rates at long-term follow-up despite myocardial function recovery. A considerable burden of cardiovascular risk factors and co-morbidities has been associated with TTS.[29] In our series, patients with severe LV systolic dysfunction at hospital admission showed a higher prevalence of co-morbidities, including CAD and chronic obstructive pulmonary disease. CAD is a relatively common finding in patients with TTS and can contribute to abnormal myocardial contraction and relaxation due to hypoxia.[30]

Despite a substantial recovery in systolic function, the subgroup of patients with LVEF ≤ 35% had a significantly lower LVEF and more compromised diastolic function at discharge.

Myocardial function and architecture after TTS has been extensively assessed using speckle tracking echocardiography (LV strain and twist) and cardiac magnetic resonance. Regardless of apparent normalization of LVEF, persistence of subtle LV systolic and



Overall population	326	310	254	208	160	105	51	35	21	12	4	3	2
Events	3	11	7	7	7	11	4	2	2	0	0	0	0
LVEF ≤ 35%	131	126	101	81	59	40	18	13	8	4	2	1	1
Events	2	5	5	5	5	6	2	1	2	0	0	0	0
LVEF > 35%	195	184	153	127	101	65	33	22	13	8	2	2	1
Events	1	6	2	2	2	5	2	1	0	0	0	0	0

Figure 1 Kaplan–Meier survival curves for freedom from composite major adverse cardiac events in patients with Takotsubo syndrome. LVEF, left ventricular ejection fraction.

diastolic abnormalities along with the development of microscopic fibrosis after myocardial oedema resolution have been demonstrated at follow-up in TTS patients.[31] Also anatomic and metabolic changes are more frequently detected in patients with history of TTS compared to controls.[32] Of note, diastolic dysfunction, regardless of LVEF recovery, was found to have a negative impact on long-term prognosis in TTS patients.[33] It is conceivable that patients with more severe acute myocardial dysfunction also had a higher grade of persistent structural and metabolic impairment after discharge. This might explain why patients with LVEF ≤35% experienced worse outcomes not only at short-term, but also at long-term follow-up. In addition, although previous studies could not demonstrate a beneficial effect of beta-blockers at long-term follow-up, we observed a lower incidence of MACE in TTS patients with LVEF ≤35% on beta-blocker treatment after discharge. This suggests that such medications might be useful in patients with more impaired cardiac function during the acute phase. However, this aspect needs further investigation in future studies.

Therefore, the cohort of patients with LVEF ≤35% seems to represent a peculiar clinical phenotype in which genetic factors, age and co-morbidities make subjects not only more susceptible to severe myocardial impairment in the acute phase, but also predisposed to persistent structural and functional damage leading to worse outcome.

Conclusions

Our findings not only confirm that a LVEF cut-off of 35% is a key parameter to identify TTS patients at high risk for in-hospital adverse events, but also provide new and unique information about its prognostic power at follow-up. Despite apparent myocardial functional recovery, patients with TTS presenting with severe LV systolic dysfunction remain at high risk during long-term follow-up, showing increased rehospitalization, acute heart failure, and mortality rates. This patient subset requires closer monitoring and more appropriate preventive therapy to improve outcome.

Conflict of interest: none declared.

Appendix

Takotsubo Italian Network (TIN) Investigators

Corinna Armentano, MD, Ospedale Guglielmo da Saliceto, Piacenza, Italy; Costantino Astarita, MD, and Antonino Coppola, MD, Ospedale S. Maria della Misericordia, Sorrento, Naples,

Italy; Amelia Ravera MD, and Pompea Bottiglieri, MD, Azienda Ospedaliera Universitaria "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy; Daniella Bovelli, MD, and Marco Mariano Patella, MD, Ospedale S. Maria, Terni, Italy; Marco Fabio Costantino, MD, Ospedale San Carlo, Potenza, Italy; Giovanni Gregorio, MD, and Michele Santoro, MD, Ospedale San Luca, Vallo della Lucania, Salerno, Italy; Fiore Manganelli, MD, and Francesco Rotondi, MD, Azienda Ospedaliera San Giuseppe Moscati, Avellino, Italy; Benedetta Bellandi, Stefano Del Pace, Fernando Scudiero, Careggi Hospital, Florence, Italy; Marco Pascotto, MD, Ospedale Fatebenefratelli, Naples, Italy; Elisabetta Grolla, MD, Ospedale Umberto I, Mestre, Venice, Italy; Ercole Tagliamonte, MD, Ospedale Umberto I, Nocera Inferiore, Salerno, Italy; Alfredo Bianchi, MD, Giovanni Marinosci, MD, Michele Pappalettera, MD, and Andrea Pozzi MD, Ospedale di Circolo and Fondazione Macchi, Università dell'Insubria, Varese, Italy; Federico Nardi, MD, Ospedale Castelli, Verbania, Italy; Giuseppina Novo, MD, University of Palermo, Palermo, Italy; Francesco Antonini-Canterin, MD, S. Maria degli Angeli Hospital, Pordenone, Italy; Francesco Bovenzi, U.O. Cardiologia, Ospedale Campo di Marte, Lucca.

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