

RESEARCH ARTICLE

## In-hospital and long-term mortality in Takotsubo cardiomyopathy: a community hospital experience

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**Background:** Takotsubo cardiomyopathy (TTC) is characterized by reversible left ventricular dysfunction, frequently precipitated by a stressful event. Despite the favorable course and good long-term prognosis, a variety of complications may occur in the acute phase of the disease. The aim of this study was to evaluate the in-hospital and long-term outcomes of a cohort of TTC patients.

**Methods:** Fifty-five patients (mean age  $68.1 \pm 12$  years) were prospectively followed for a mean of  $69.6 \pm 32.2$  months (64,635 days). In-hospital (death, heart failure, arrhythmias) and long-term events (death and recurrences) were recorded.

**Results:** Patients were predominantly women (87.3%) who experienced a recent stressful event (emotional or physical) and were admitted to hospital for chest pain. Eleven patients (20%) had a diagnosis of depressive disorder, and arterial hypertension was the most frequent cardiovascular risk factor. The ECG revealed ST-segment elevation in 43.6% of patients. At angiography, seven cases (12.7%) had at least one significant ( $\geq 50\%$ ) coronary artery stenosis and four patients (7.3%) had myocardial bridging of the left anterior descending artery. During hospitalization, three patients died (one from cardiac causes) and cardiovascular complications occurred in 12 patients. During follow-up, five patients died (none from cardiac causes), six patients had recurrences within the first year. Two patients had two recurrences: one after 114 days, triggered by an asthma attack as the first event, and the other after 1,850 days.

**Conclusions:** In TTC patients, in-hospital and long-term mortality is primarily due to non-cardiovascular causes. Recurrences are not infrequent and coronary artery disease is not an uncommon finding.

Keywords: *coronary artery disease; follow-up study; recurrence; Takotsubo cardiomyopathy*

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Takotsubo cardiomyopathy (TTC), also known as stress cardiomyopathy, is an acute cardiac syndrome mimicking acute myocardial infarction. It is characterized by chest pain, electrocardiographic changes and transient akinesia/dyskinesia of the left ventricle (apical and mid-ventricular segments) with wall motion abnormalities extending beyond a single vascular territory (1–5). TTC is typically triggered by an acute emotional or physical stress event and occurs mostly in postmenopausal women. Although TTC has a favorable long-term prognosis and usually resolves spontaneously within a few days to several weeks (6), there are conflicting data on in-hospital complications (ranging from 22 to 50%) (6, 7) and early mortality rates (8). Currently, TTC is

being diagnosed more frequently, likely because of heightened awareness of this syndrome with the need of a more specific approach.

The aim of this study was to evaluate the clinical and diagnostic features, the short and long-term outcomes of a cohort of TTC patients followed at a single center for 12.9 years.

### Methods

Fifty-five TTC patients admitted to the San Daniele Community Hospital (Italy) or followed as outpatients in the cardiology service from May 2003 to August 2014 were included in the study. On admission, demographics, triggering stressful events, clinical history, cardiovascular

risk factors, and presenting symptoms were collected in all patients using a uniform definition, as well as clinical data previously described (6). Cardiac catheterization was performed within 48–72 h of admission to the cath lab of the referral hospital (9).

TTC diagnosis and inclusion and exclusion criteria were based on the modified Mayo Clinic criteria (10) and the Takotsubo Italian Network (TIN) (11).

### Echocardiography

Two-dimensional echocardiography was performed in all patients on admission, and LV ejection fraction (EF) was calculated using the biplane method of disks (modified Simpson's rule). The wall motion score index (WMSI) was visually assessed on multiple views as in routine clinical practice. The left ventricle was divided into 17 segments as recommended by the American Heart Association (12). Right ventricular (RV) involvement was assessed visually (akinesia or dyskinesia of the mid or apical RV free wall segments). Mitral regurgitation was graded based on color-Doppler flow imaging in the parasternal and apical views (3, 4).

### Cardiac catheterization

Cardiac catheterization was performed within 48–72 h of hospital admission using the femoral or radial approach. Significant coronary artery disease was defined as  $\geq 50\%$  luminal diameter narrowing, by visual assessment, of at least one major epicardial artery (13). Myocardial bridging was diagnosed if the typical angiographic 'milking effect' (i.e., systolic compression and complete or partial decompression during diastole) was observed in the coronary artery (14–17). Follow-up was performed by outpatient clinic visits or telephone interview, and relapses and all-cause mortality were recorded. All patients gave written informed consent.

### Statistical analysis

Descriptive statistics for clinical characteristics are presented as means and SDs for continuous data and as counts and percentages for dichotomous and categorical data. Paired Student's *t*-test or non-parametric test was used for statistical analysis, as appropriate. A survival analysis using the Kaplan–Meier estimator was performed to determine the proportion of TTC patients who died. SYSTAT 12.0 (Systat Software Inc., San Jose, CA) was used for data analysis.

## Results

A total of 55 patients were diagnosed as having TTC (Table 1) and were followed up for 12.9 years. They were predominantly women ( $n = 48$ , 87.3%; age range: 41–87 years), more frequently of postmenopausal age; 89.5% were older than 65 years, and 10.4% were younger than 50 years. Mean follow-up was  $69.6 \pm 32.2$  months. Eleven patients (20%) were admitted with a diagnosis of anxiety

Table 1. Baseline characteristics of the study population

No. of patients	55
Age (years)	$68.2 \pm 11.4$
Female gender	48 (87.3%)
Cardiovascular risk factors	
Hypertension	36 (65.4%)
Diabetes mellitus	10 (18.1%)
Dyslipidemia	22 (40.0%)
Smoking	10 (18.1%)
History of coronary artery disease	4 (7.2%)
Menopause	45 (90%)
Presenting symptom	
Chest pain	36 (65.4%)
Dyspnea	6 (10.0%)
Chest pain + dyspnea	13 (23.6%)
Triggering factor	
Emotional stress	25 (45.4%)
Physical stress	13 (23.6%)
None	17 (30%)

or depressive disorder. According to medical history, the majority of patients had experienced a recent stressful event, either emotional or physical, and the most common clinical symptom at presentation was chest pain. Systemic arterial hypertension was the most frequent cardiovascular risk factor (Table 1). Clinical and laboratory findings are reported in Table 2. The ECG revealed ST-segment elevation in a high proportion of patients (43.6%).

### Echocardiography

In 48 patients, left ventricular ejection fraction (LVEF) was low on admission but improved at discharge ( $43.7 \pm 11.6\%$  vs.  $55.5 \pm 9.0\%$ ,  $p < 0.0001$ ). Two patients had RV involvement. Five patients (9%) had moderate to severe mitral regurgitation, and 26 (47.3%) had mild mitral regurgitation (Table 2). In 38 patients, pre-discharge echocardiography showed complete recovery of LV and RV regional wall motion abnormalities.

### Coronary angiography

Among the 55 TTC patients, coronary angiography revealed significant coronary stenosis ( $\geq 50\%$ ) in seven cases (12.7%) and a myocardial bridge within the intramural course of the left anterior descending coronary artery in four cases (7.3%). All of the seven patients with critical coronary lesions had one-vessel disease (60% occlusion of the right coronary artery in 1, complete occlusion of the posterior descending artery in 1, and left anterior descending coronary artery with hemodynamically significant lesions in 5). Five lesions showed moderate coronary stenosis (50–75%), and four lesions showed severe coronary stenosis ( $> 75\%$ ), including one chronic total occlusion of the posterior descending branch.

**Table 2.** Clinical and laboratory findings on admission and in-hospital complications and procedures

Hemodynamic data	
Systolic BP (mmHg)	142.4 ± 35
Diastolic BP (mmHg)	84.7 ± 16.8
Heart rate (bpm)	87.1 ± 21.8
Laboratory findings	
Peak troponin I (µg/ml)	3.16 ± 4.5
White blood count ( × 10 <sup>3</sup> /µl)	9.61 ± 4.82
Creatinine (mg/dl)	1.21 ± 1.26
Hemoglobin (g/dl)	12.9 ± 1.7
ECG	
ST-segment elevation	24 (43.6%)
QT interval (ms)	376.5 ± 52.4
Echocardiography	
Mitral regurgitation	
Moderate to severe	5 (9%)
Mild	26 (47.3%)
LVOT gradient	1 (1.8%)
Right ventricular involvement	2 (3.6%)
LVEF (%)	44.8 ± 11.6
Mid-apical involvement	27 (56%)
Apical involvement	20 (41.7%)
WMSI	1.66 ± 2.29
PASP (mmHg)	36.3 ± 16.5
In-hospital complications	12 (21.8%)
Cardiogenic shock	4 (7.2%)
Congestive heart failure	3 (5.4%)
Intraventricular thrombus	1 (1.8%)
Cerebral Ischemic lesion	1 (1.8%)
Pulmonary artery systolic hypertension	1 (1.8%)
Paroxysmal atrial fibrillation	2 (3.6%)
In-hospital procedures	3 (5.4%)
Stent implantation	2 (3.6%)
CABG	1 (1.8%)

BP = blood pressure; LVOT = left ventricular outflow tract; LVEF = left ventricular ejection fraction; WMSI = wall motion score index; PASP = pulmonary artery systolic pressure; CABG = coronary artery bypass grafting.

### *In-hospital management, complications, and mortality*

In the acute phase, patients received aspirin (100%), clopidogrel (67%), heparin (100%), beta-blockers (73%), statins (43.7%), nitrates (18.7%), proton pump inhibitors (100%), diuretics (12%), intravenous inotropic agents (8.3%), and antiarrhythmic drugs (5%). Complications occurred in 12 patients (21.8%), with heart failure being the most frequent one (Table 2). One patient had two stents and one patient had one stent implanted in the left anterior descending coronary artery because of a critical stenosis on coronary angiography, and another patient underwent coronary artery bypass surgery.

Three patients died during hospitalization (Table 3), two from non-cardiac causes and one from a massive cerebral hemorrhagic stroke within 12 h of hospital admission. Heart rate and cardiac troponin I levels were slightly lower and LVEF higher in survivors than in non-survivors, though without reaching statistical significance.

### *Follow-up and long-term mortality*

The 52 patients who survived were followed up, and data were 100% complete. Five additional patients died during the follow-up but none from cardiovascular causes (Table 3). Non-survivors were older than survivors, but they did not differ in cardiovascular risk factors ( $p = ns$  for systemic arterial hypertension, diabetes, serum cholesterol, and smoking). TTC did not contribute to death in those who died in hospital, and all deaths after discharge were unrelated to cardiac illness. Fatal events occurred within the first 4 years of follow-up (Fig. 1).

### *Relapse*

TTC recurrence was experienced by six patients (Table 3). Time to relapse was within the first year (mean 3 months). Consistent with a previous study from our group (7), LVEF and WMSI were less compromised, troponin I levels

**Table 3.** In-hospital and long-term mortality and relapse

In-hospital mortality		3 (5.4%)
Age (years)		65.7 ± 10.7
Time to death (days)		20 (6–45)
LVEF (%)		34.3 ± 0.6
Troponin I (ng/ml)		4.2 ± 4.0
Cause of death		
Acute bone marrow aplasia		1
Multiorgan failure		1
Cerebral hemorrhagic stroke		1
Long-term mortality		5 (9%)
Age (years)		74.6 ± 6.2
Time to death (days)		953 (477–1,415)
LVEF (%)		51 ± 8.9
Troponin I (ng/ml)		7.6 ± 12.0
Cause of death		
Femoral fracture and worsening of pre-existing disease		2
Intestinal occlusion		2
Complications of respiratory failure		1
Relapse		6 (10.9%)
Age (years)		71.2 ± 7.3
Time to relapse (days)		89.2 (8–243)
LVEF (%)		53.0 ± 15.1
Troponin I (ng/ml)		0.8 ± 2.1
Trigger event		
Asthma attack		2
No trigger event		4

LVEF = left ventricular ejection fraction.

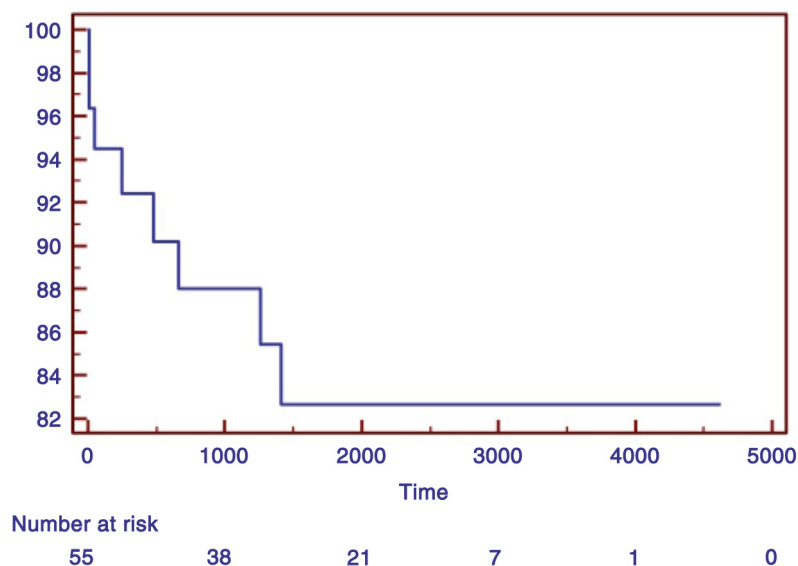


Fig. 1. Kaplan–Meier survival curve.

were lower than those observed during the first episode, and there was complete recovery of LV function with WMSI improvement. Two patients had two recurrences: after 114 days in one patient, triggered by an asthma attack as the first event, and after 1,850 days in the other, in the absence of a trigger event. In the latter, angiography was repeated but no significant coronary lesions were detected.

## Discussion

TTC is not rare and is an increasingly recognized clinical syndrome, though probably still underestimated. In the United States, in 2008, TTC was diagnosed in about 0.02% of all hospitalizations (18) and was the final diagnosis in 2% of patients with acute coronary syndrome (19). Recurrence rates were reported to range from 0 to 15% (1, 7). Results from a previous study by our group are consistent with all these data (9). Although TTC is generally considered as a benign cardiac condition with favorable long-term prognosis, complications during the acute phase of the disease have been variably reported (6, 9, 20–24). There is growing and considerable evidence suggesting that enhanced sympathetic activity plays a central role in the pathogenesis of Takotsubo cardiomyopathy: marked elevation in plasma catecholamines (compared to other types of ACS), increased heart rate variability, association with high catecholamine states (e.g., pheochromocytoma), and nuclear imaging showing increased sympathetic activity in the akinetic segments (25) have all been demonstrated in TTC.

The present series of TTC patients is among the few studies with very long-term follow-up. Clinical characteristics of the enrolled population were similar to those previously described by our group and others: most patients were postmenopausal women, the main cardiovascular risk

factor was arterial hypertension, and 20% of the patients were admitted with a diagnosis of anxiety or depression. On admission, TTC patients showed depressed LVEF that improved before discharge, wall motion abnormalities extended beyond a single epicardial vascular distribution, and 12.7% had at least one significant coronary lesion. In-hospital complications, including three deaths (5.4%) with only one death due to cardiovascular causes, occurred in 21.8% of the patients. Six patients (11.5%) experienced recurrences within the first 3 months and two patients had two episodes of TTC. Long-term mortality (9%) was due to worsening of preexisting disease.

### *Anxiety-depressive disorders*

Compared to other reports (26, 27), we found less TTC patients affected by anxiety-depressive disorders (21.8%) probably because, aside the trigger event, patients were not specifically questioned about their lifestyle or chronic psychological stress (26, 28, 29). High-anxiety trait in TTC patients is not significantly more frequent than in patients with ST-elevation myocardial infarction and seems not to be associated with a worse clinical outcome in both pathologies (28). However, in a series of 1,750 TTC patients, Templin et al. (30) reported a history of neurologic or psychiatric disorders in more than 50%, with a high incidence of psychiatric illness identified as affective disorder.

### *Myocardial bridging*

In our population, myocardial bridging was observed in 7.3% of cases. This proportion is consistent with previous findings in a large cohort (average 5%, range: 0.5–16%) (15) but is much less than the 62.5 and 76% prevalence reported in a small series by Lemaitre et al. (31) and by Migliore et al. (32), respectively, likely due to the use of cardiac computed tomography, which is far more

**Table 4.** In-hospital and long-term outcome of Takotsubo cardiomyopathy in previous studies

Author, year	Patients F/M n (F%)	Age (years)	Country	In-hospital mortality n (%)		Follow-up (months)	Recurrences n (%)	Long-term mortality (n,%)	
				CV death	Other causes			CV death	Other causes
Tsuchihashi et al. (1), 2001	88 76/12 (86)	67 ± 13	Japan	1 (1)	0	13 ± 14	2 (2.7)	1 (1.3)	0
Elesber et al. (38), 2007	100 95/5 (95)	66 ± 13	USA	2 (1)	0	26 ± 12	10 (11.4)	7 (7)	10 (10)
Burgdorf et al. (39), 2008	50 47/3 (94)	70 ± 10	Europe	0	3 (6)	35 ± 19	–	3 (6)	3 (6)
Eshtehardi et al. (40), 2009	41 35/6 (85)	65 ± 11	Europe	0	0	23 ± 10	2 (5)	0	1 (2.4)
Regnante et al. (41), 2009	70 67/3 (95)	67 ± 11	USA	1 (1.4)	0	12	2 (2.9)	0	2 (2.9)
Sharkey et al. (7), 2010	136 130/6 (96)	68 ± 13	USA	2 (1.5)	1 (0.7)	27.6 ± 24	7 (5)	0	17 (12.5)
Previtali et al. (42), 2011	132 125/7 (98)	67 ± 11	Europe	1 (0.8)	0	13	2 (1.5)	0	1 (0.8)
Parodi et al. (5), 2011	116 106/10 (91)	73 ± 10	Italy	1	1	24 ± 15	2	7 (6)	4 (3)
Eitel et al. (43), 2011	256 227/29 (89)	69 ± 12	Europe/ North America	3 (1.1)	1 (0.4)	1 to 6	–	2 (0.8)	2 (0.8)
Samardhi et al. (20), 2012	52 51/1 (98)	64 (43–89)	Australia	0	0	32.66	0	0	0
Looi et al. (44), 2012	100 95/5 (95)	65 ± 11	New Zealand	1 (1)	0	36 ± 20	7 (7)	0	4 (4)
Cacciotti et al. (45), 2012	75 73/2 (97.3)	71.9 ± 9.6	Europe	0	0	26.4 ± 24	1 (1.3)	2 (2.6)	0
Song et al. (46), 2012	137 101/36 (74)	59	Korea	0	0	68.4	0	0	9 (6.5)
Núñez-Gil et al. (23), 2012	100 89/11 (89)	68 ± 13	Spain	0	0	46	4 (4)	3 (3)	3 (3)
Buja et al. (47), 2012	54 47/7 (87)	72.1	Italy	1 (1.85)	1 (1.85)	18.5	2 (3.9)	2 (3.9)	2 (3.9)
Weihls et al. (21), 2013	179 168/11 (94)	69 ± 11	Austria	1 (0.6)	–	36.5 ± 18.9	4 (2)	3 (1.6)	10 (5.5)

Table 4 (Continued)

Author, year	Patients F/M n (F%)	Age (years)	Country	In-hospital mortality n (%)		Follow-up (months)	Recurrences n (%)	Long-term mortality (n,%)	
				CV death	Other causes			CV death	Other causes
Ribeiro et al. (22), 2014	37 35/2 (94)	63 ± 13	Portugal	0	0	16 ± 17	0	1 (2.8)	0
Vizzardì et al. (48), 2015	42 100 (100)	67 ± 11	Italy	0	0	12	0	0	0
Redfors et al. (8) 2015	302 255/47 (84%)	66 ± 12	Sweden		(4)	36	0		(12)
Templin et al. (30) 2015	1,750 1,571/179 (89.9%)	66.4 ± 13.1	Switzerland		77 (4.1%)	12	1.8% per year		5.6% per year
Gopalakrishnan et al (49) 2015	56 45/11 (80.4%)	65.8 ± 14.12	USA		5 Not specified	27.6 ± 21.6	not reported		10 Not specified
Present study	55 43/5 (89%)	68.2 ± 11.4	Italy	1	2	69.6 ± 32.2	6	0	5

CV = cardiovascular; F = female; M = male.



sensitive than angiography in identifying this congenital coronary anomaly. Notwithstanding this, Stiermaier et al. (33) found no differences in the prevalence of myocardial bridging between TTC patients and controls. Several reports have also suggested that myocardial bridging may be an underlying mechanism of apical ballooning (31, 33–35).

### Coronary atherosclerosis

In our series, 12.5% of patients had significant coronary artery stenosis which is consistent with previous findings in large series by Parodi et al. (5) and Templin et al. (30). The TIN investigators showed that the extension of myocardial dysfunction clearly exceeded the area supplied by a single epicardial vessel (5). Given that TTC affects predominantly postmenopausal women with cardiovascular risk factors, the presence of significant coronary artery disease should not be considered an unexpected finding (18, 36).

### In-hospital complications

Although TTC is considered a benign reversible condition, it poses a non-trivial risk for adverse events. In our series, complications occurred in 21.8% of the study population, with heart failure being the most frequent one. Early mortality was not negligible (5.4%) compared to the previous reports (from 1.7 to 2.8%) (6, 7, 37), and two deaths were not related to cardiovascular events. In a large TTC group evaluated by Templin et al. (30), complications occurred in 21.8% of patients, and Citro et al. (6) reported in-hospital complications up to 50% of those older than 74 years. Age, multiorgan impairment with irreversible non-cardiac conditions associated with low LVEF, and high troponin adversely affected short-term survival.

### Recurrences

Recurrences were recorded in six patients (10.9%) within the first 3 months and two patients had two episodes of TTC. Consistent with our previous experience (9), TTC recurrences were experienced by patients on  $\beta$ -blockers, but cardiac involvement was less severe than at the time of the first event. It may be hypothesized that, although  $\beta$ -blockers are not effective in preventing TTC, they might mitigate its clinical manifestations. In the literature, recurrences are reported to range from 0 to 11.4% up to 4–5 years after the first episode (1, 5, 7, 20–23, 38–48), and relapses are unpredictable. Moreover, patients with recurrences may show different LV patterns, with apical ballooning during the first episode and mid-ventricular ballooning during the second one.

### Long-term mortality

In the present study, long-term mortality was 9% and death occurred within the first 2.6 years. No death was due to cardiac causes, suggesting that mortality was independent

of TTC. In reviewing available literature on long-term follow-up of TTC, mortality rates differed considerably across studies probably because of either different follow-up lengths and sample groups or the older age of our population (Table 4) (1, 5, 7, 8, 20–23, 30, 38–50). Although in the study of Parodi et al. (5), the results of the standardized mortality ratio analysis showed that TTC patients are three times more likely to die than the general population, TTC seems to be associated with a long-term survival rate that is intermediate between the one of the general population and the one of patients with ST-elevation myocardial infarction. Comorbidities are the main predictors of mortality in TTC patients.

### Study limitations

Several limitations should be acknowledged. First, this is a single-center study, and results cannot be generalized to other ethnic groups. Second, the sample size is relatively small, even though the follow-up period is very long. Third, this is a clinical study and the diagnostic procedures applied were those used in everyday clinical practice and not addressed for answering a specific comorbidity or complication.

### Conclusions

The present study is one with the longest follow-up reported to date in TTC patients of a community hospital and takes into account a wide range of clinical and diagnostic features. Anxiety-depressive disorders were not particularly frequent in our TTC patients, and the most frequent acute complication was heart failure. Recurrences mostly occurred within the first 3 months with less severe cardiac involvement and were experienced by patients on  $\beta$ -blockers. Significant coronary artery disease was not an uncommon finding, and angiographic prevalence of myocardial bridging did not differ from that reported in other non-TTC series. Both in-hospital and long-term mortality were confined to patients with malignancies or non-cardiovascular diseases, suggesting an important role of the underlying pathology in patient outcome. TTC did not contribute to death in those who died in hospital, and all deaths after discharge were unrelated to cardiac illness.

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