

Left ventricular outflow tract obstruction and myocardial edema burden in Takotsubo syndrome: acute and long-term outcomes—insights from the EVOLUTION registry

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ARTICLE INFO

Keywords:

Takotsubo syndrome
Cardiovascular magnetic resonance
LVOTO
Myocardial edema
Prognosis

ABSTRACT

Objective: To evaluate the clinical and CMR characteristics and the in-hospital and long-term outcomes of patients with Takotsubo syndrome (TTS) and left ventricular outflow tract obstruction (LVOTO).

Material and method: This sub-analysis of the multicenter retrospective EVOLUTION registry included patients with TTS enrolled between November 21, 2007, and December 22, 2024, who underwent CMR within 5 days of echocardiographic assessment. Patients were stratified according to the presence or absence of LVOTO.

Results: A total of 249 patients were included (226 women [90.8%]; mean age 70.6 ± 10.9 years), of whom 26 (10.4%) had LVOTO. Patients with LVOTO exhibited higher left ventricular mass, greater basal septal wall thickness, and more extensive T2-STIR involvement. Among CMR parameters, the number of T2-STIR-positive segments was independently associated with the presence of LVOTO (OR = 1.38, 95% CI: 1.17–1.63, $p = 0.001$). In-hospital complications, including pulmonary edema and cardiogenic shock, were more frequent among patients with LVOTO (34.6% vs. 15.8%; $p = 0.018$), and LVOTO remained independently associated with in-hospital complications on exploratory multivariable analysis (OR = 3.16, 95% CI: 1.08–9.26, $p = 0.035$). No

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<https://doi.org/10.1016/j.ijcard.2026.134777>

Received 25 June 2026; Received in revised form 7 September 2026; Accepted 9 September 2026

Available online 10 September 2026

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significant association was observed between LVOTO and long-term MACE (HR 1.523, 95% CI 0.641–3.620; $p = 0.340$).

Conclusion: LVOTO in patients with TTS, is independently associated with the extent of myocardial edema, and is more frequently observed in patients who experience in-hospital complications. No significant association with long-term MACE was found, though the limited number of events and wide confidence interval warrant cautious interpretation.

1. Introduction

Takotsubo syndrome (TTS) is an acute and reversible form of heart failure, typically triggered by emotional or physical stress and characterized by transient left ventricular (LV) systolic dysfunction [1–6]. Although traditionally considered a benign condition due to the recovery of myocardial function, growing evidence indicates that the rate of acute complications in TTS is comparable to that observed in acute coronary syndromes [3]. The in-hospital course may be complicated by severe conditions, including heart failure, cardiogenic shock, and mechanical complications [7].

Among these, left ventricular outflow tract obstruction (LVOTO) represents a clinically relevant but underrecognized entity, occurring in a proportion of patients and potentially leading to hemodynamic instability. LVOTO in TTS is a dynamic phenomenon, typically related to hypercontractility of the basal segments in combination with septal thickening or transient “pseudohypertrophy” due to myocardial edema [7].

Cardiovascular magnetic resonance (CMR) is the reference standard for the non-invasive assessment of cardiac morphology, function, and tissue characterization in TTS [4,8–14]. While CMR has provided important insights into myocardial tissue abnormalities in this condition [10,15,16], the tissue characterization features associated with LVOTO, and their clinical implications remain poorly defined. In particular, the relationship between CMR findings and LVOTO, as well as the prognostic impact of LVOTO on both in-hospital and long-term outcomes, has not been systematically investigated.

Therefore, in this multicenter international study based, one of the largest CMR cohorts of patients with TTS to date, we aimed to evaluate the clinical and CMR correlates of LVOTO, as well as its prognostic significance for both in-hospital and long-term outcomes in patients with TTS.

2. Methods

2.1. Study population

The rationale and design of the EVOLUTION Registry have been previously described in detail [17]. Briefly, EVOLUTION is a multicenter registry of patients with a diagnosis of TTS who fulfilled the criteria outlined in the Position Statement of the Heart Failure Association of the European Society of Cardiology [18] and were referred for clinically indicated CMR imaging. Diagnostic criteria comprise regional wall motion abnormalities extending beyond a single epicardial vascular territory, typically preceded by a stressful trigger, in the absence of culprit atherosclerotic disease as assessed by invasive coronary angiography. Additional criteria include new electrocardiographic abnormalities, elevated serum natriuretic peptides with an increase in cardiac troponin levels, and recovery of LV dysfunction at follow-up.

Patients were considered ineligible for registry entry if they met any of the following criteria: age < 18 years, pre-existing cardiomyopathy, prior myocardial infarction, suspected or known irreversible myocardial damage, or significant valvular heart disease.

For the present sub-analysis, the EVOLUTION Registry was queried for consecutive patients enrolled between November 21, 2007, and December 22, 2024, who underwent CMR examination within 5 days of the echocardiographic assessment, yielding a total of 249 patients with

TTS (Fig. 1). Details on the echocardiographic acquisition protocol and assessment of LVOTO are reported in the Supplementary Material.

2.2. CMR examinations and image post-processing

CMR examinations were performed at participating centers using locally approved imaging protocols based on clinical indications [19,20]. Protocols were required to include short- and long-axis cine sequences, short- and long-axis T2-weighted STIR sequences, and short- and long-axis LGE sequences. **Supplemental Table 1.**

Studies with non-diagnostic CMR image quality due to artifacts or incomplete anatomical coverage were excluded from the analysis ($n = 9$).

CMR data were anonymized before analysis and transferred to commercially available software for analysis (CVI42, version 6.2; Circle Cardiovascular Imaging Inc., Calgary, Canada). Images were analyzed at a central core laboratory by an experienced observer with more than 10 years of expertise in cardiovascular imaging, who was blinded to all clinical data. Endocardial and epicardial borders of both ventricles were manually contoured on short-axis cine images at end-diastole and end-systole. Papillary muscles and trabeculae were included in the ventricular cavity and excluded from myocardial mass calculations. Right ventricle (RV) dysfunction was defined as an RV ejection fraction below sex-specific reference values (<44% in men and < 47% in women) as assessed by CMR, according to current normal reference ranges [21]. LV dysfunction was defined as an LV ejection fraction below 50% as assessed by CMR [22].

Focal areas of regional high signal intensity with a non-ischemic distribution were visually assessed on T2-weighted short-tau inversion recovery (T2-STIR) and late gadolinium enhancement (LGE) images. Short-axis ECG-gated steady-state free-precession cine images were used as anatomical reference, and findings were confirmed in two perpendicular views.

A positive T2-STIR signal, indicative of myocardial edema, required fulfillment of both criteria, which were consistently applied across all participating centers: (i) a signal intensity ≥ 2 standard deviations above the mean signal intensity of remote myocardium, and (ii) a myocardium-to-skeletal-muscle T2 signal intensity ratio ≥ 1.9 [23].

For quantitative LGE assessment, the endocardial and epicardial contours were manually delineated on each short-axis slice. A reference region of interest (ROI) was placed in visually normal myocardium without enhancement, and LGE-positive areas were defined as regions with signal intensity exceeding 2 standard deviations (SD) above the mean signal of the reference myocardium. The extent of LGE was expressed as a percentage of total LV mass [15].

All CMR data, were analyzed in a dedicated core laboratory in accordance with recommendations from the Society for Cardiovascular Magnetic Resonance (SCMR) and the European Association of Cardiovascular Imaging [19,20]. Intra-observer variability was evaluated by having the same observer re-analyze a random subset of 20 TTS patients after a minimum interval of six weeks. Inter-observer variability was assessed by a second blinded observer, with four years of experience in cardiovascular imaging, who independently performed post-processing analysis on the same subset without access to the initial results.

2.3. Variable and outcome definition

LVOTO was defined as a resting peak instantaneous gradient >25 mmHg, measured by echocardiography in the absence of inotropic support.

TTS patients were stratified into two groups according to the presence of LVOTO.

All patients underwent follow-up through clinical visits after CMR examination, and hospital records were systematically reviewed to identify clinical events. Time origin was defined as the index hospitalization for TTS. Patients without a documented event were censored at the date of their last available clinical follow-up. For patients experiencing more than one event during follow-up, only the first event was considered for the time-to-event analysis; recurrent events were not separately modeled.

The primary endpoint was a composite of in-hospital adverse events, including death, pulmonary edema, cardiogenic shock, and arrhythmias.

Secondary endpoints included a composite of all-cause mortality and major cardiovascular or cerebrovascular events occurring after hospital discharge (MACE), including heart failure hospitalization, arrhythmias, TTS recurrence, transient ischemic attack, and ischemic stroke.

Pulmonary edema was defined as the presence of respiratory distress and pulmonary rales due to congestion, confirmed by chest radiography, along with evidence of respiratory failure (hypoxemia and/or hypercapnia), tachypnea (>25 breaths/min), and increased work of breathing [24].

Cardiogenic shock was defined as a sustained systolic blood pressure < 90 mmHg for at least 30 min, or the need for vasopressors, inotropes, or mechanical circulatory support to maintain systolic blood pressure ≥ 90 mmHg, in the presence of pulmonary congestion and signs of end-organ hypoperfusion. The latter was defined by at least one of the following: (1) altered mental status; (2) cold, clammy skin or extremities; (3) oliguria (urine output ≤ 30 mL/h); or (4) arterial lactate ≥ 2 mmol/L (≥ 18 mg/dL) [25].

Recurrence of TTS was defined as the development of new regional wall motion abnormalities, in the absence of obstructive coronary artery disease, after complete recovery from the index event [26].

Stroke was defined as an ischemic cerebral infarction due to embolic

or thrombotic occlusion of a major intracranial artery [27], while transient ischemic attack was defined as the sudden onset of focal neurological symptoms resolving within 24 h [28].

2.4. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), as appropriate. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Comparisons between groups for continuous variables were performed using the independent-samples *t*-test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data.

Categorical variables are expressed as counts and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate.

Univariable logistic regression analyses were conducted to identify factors associated with the presence of LVOTO. Variables showing statistically significant associations in univariable analysis and those considered biologically relevant based on their potential association with LVOTO were considered for inclusion in the multivariable logistic regression model.

Event-free survival was assessed using Kaplan–Meier estimates, with differences between groups evaluated by the log-rank test. Univariable Cox proportional hazards regression analysis was performed to identify predictors of the secondary endpoint.

The proportional hazards assumption was verified using Schoenfeld residuals. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). Variables with more than 10% missing data were excluded from the analysis. In-hospital complications were analyzed separately using univariable and multivariable logistic regression models, and results are reported as odds ratios (ORs) with 95% confidence intervals. Intra- and inter-observer reproducibility were assessed using the intra-class correlation coefficient (ICC).

All tests were two-tailed, and a *P* value <0.05 was considered statistically significant. Statistical analyses were performed using JASP software.

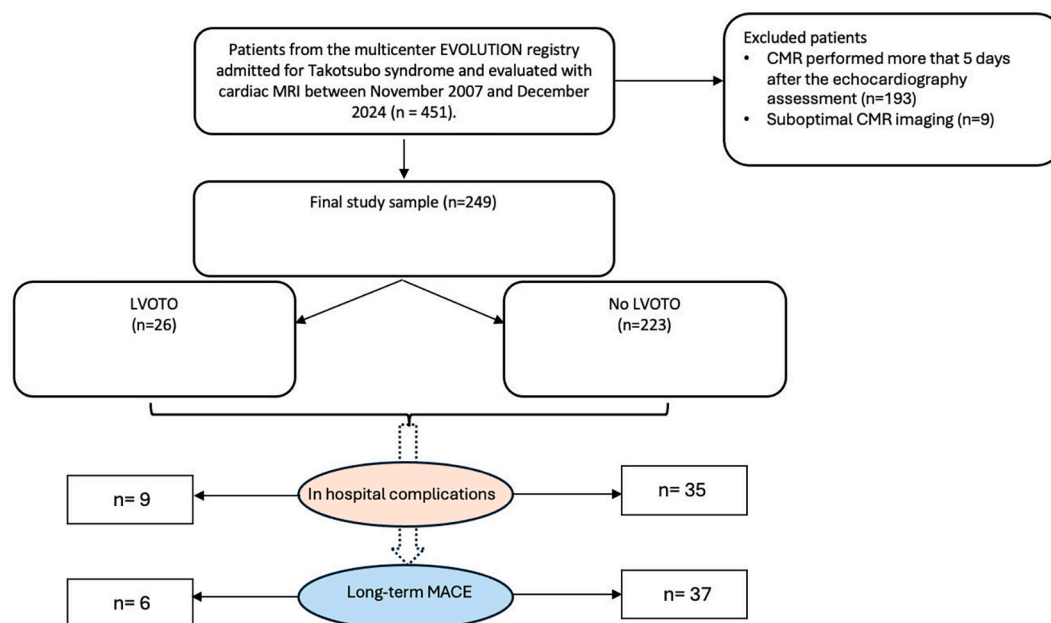


Fig. 1. Flowchart of patients enrolled.

Abbreviations: CMR, cardiovascular magnetic resonance; LVOTO, left ventricular outflow tract obstruction.

3. Results

3.1. Baseline characteristics

A total of 249 patients with TTS were included in the analysis, including 226 females (90.8%) and 23 males (9.2%), with a mean age of 70.6 ± 10.9 years. Patients were categorized into two groups: those with LVOTO ($n = 26$; 10.4%) and those without LVOTO ($n = 223$; 89.6%). Among LVOTO patients, the mean intraventricular pressure gradient was available in 15 patients (15/26, 57%), with a mean value of 44.8 ± 23.3 mmHg. CMR was performed at a median of 3.0 days after symptom onset (interquartile range: 2.0–5.0 days). Mitral regurgitation was observed in 195 patients (78.3%) overall and was more frequent among patients with LVOTO compared with those without (96.2% vs. 76.2%, $p = 0.020$). Systolic anterior motion of the mitral valve was identified in 17 patients (6.8%) overall and was markedly more prevalent in the LVOTO group compared with the non-LVOTO group (53.8% vs. 1.3%, $p = 0.001$).

Baseline demographic and clinical characteristics were largely comparable between groups, with no significant differences in age, sex, cardiovascular risk factors, or comorbidities. There were no differences in term of triggering stressor between groups. Regarding clinical presentation, patients with LVOTO more frequently presented with dyspnea (50% vs. 29.7%, $p = 0.044$), whereas rates of typical chest pain, incidence of pericardial and pleural effusion, as well as triggering factors were similar.

When evaluating the association between TTS patterns and the occurrence of LVOTO, no patients with basal ballooning exhibited LVOTO. Apical ballooning was the most frequent pattern in both groups, observed in 159 patients (71.6%) without LVOTO and 22 patients (84.6%) with LVOTO.

Baseline and clinical characteristics are summarized in Table 1.

3.2. CMR findings

LVEF was similarly reduced in both groups ($44.4 \pm 10.8\%$ in patients without LVOTO vs. $42.5 \pm 12.7\%$ in those with LVOTO, $p = 0.267$). No significant differences were observed in LV volumes.

Right ventricular function and volumes did not differ significantly between groups, with similar right ventricular ejection fraction (RVEF), end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume.

Patients with LVOTO exhibited greater LV basal septum wall thickness and higher LV mass ($p = 0.021$ and $p = 0.001$, respectively).

T2-STIR positivity was observed in the majority of patients in both groups (96.2% vs. 86.9%, $p = 0.219$); however, the extent of myocardial edema was significantly greater in the LVOTO group, as reflected by a higher number of involved segments (6.9 ± 2.9 vs. 4.7 ± 2.8 , $p = 0.001$). T2-STIR assessment, both as a dichotomous variable (presence/absence of myocardial edema) and as a continuous variable (number of involved segments), demonstrated good intra- and inter-observer agreement, as shown in Supplemental Table 2.

The distribution of myocardial edema predominantly involved the apical (69.5%) and mid-ventricular segments (47.4%), with less frequent basal involvement (3.6%), and did not significantly differ according to the presence of LVOTO ($p = 0.954$, $p = 0.055$, and $p = 0.087$, respectively). Fig. 2.

Late gadolinium enhancement (LGE) was present in 34.6% of patients with LVOTO and 21.6% of those without LVOTO ($p = 0.138$), with no significant difference in the number of involved segments ($p = 0.074$).

CMR findings are summarized in Table 1.

3.3. LVOTO and its determinants in TTS patients

The univariable and multivariable associations with LVOTO are

Table 1

Baseline and CMR characteristics of patients with Takotsubo syndrome with and without LVOTO.

Variables	Overall (n = 249)	No LVOTO (n = 223)	LVOTO (n = 26)	P-value
Age, mean (SD)	70.6 $\pm$ 10.9	70.4 $\pm$ 11.3	71.8 $\pm$ 6.4	0.927
Sex (female), n (%)	226 (90.8)	201 (90.5)	25 (96.2)	0.343
Hypertension, n (%)	161 (64.6)	142 (63.7)	19 (73.1)	0.381
Dyslipidemia, n (%)	135 (54.2)	119 (53.4)	16 (61.5)	0.460
Obesity, n (%)	36 (14.5)	31 (13.9)	5 (19.2)	0.390
Smoke, n (%)	46 (18.5)	39 (17.5)	7 (26.9)	0.384
Diabetes, n (%)	38 (15.3)	33 (14.8)	5 (19.2)	0.582
CAD, n (%)	31 (12.4)	27 (12.1)	4 (15.4)	0.667
COPD, n (%)	18 (7.2)	16 (7.2)	2 (7.7)	0.951
Malignancies, n (%)	51 (20.5)	49 (22)	2 (7.7)	0.080
Neurological disease, n (%)	30 (12)	29 (13.1)	1 (3.8)	0.167
Psychiatric disease, n (%)	33 (13.3)	28 (12.6)	5 (19.2)	0.376
Typical chest Pain, n (%)	160 (64.2)	139 (62.6)	21 (80.7)	0.107
Dyspnea, n (%)	79 (31.7)	66 (29.7)	13 (50)	0.044
Emotional Trigger, n (%)	92 (36.9)	86 (38.7)	6 (23.1)	0.144
Physical Trigger, n (%)	74 (29.7)	69 (31.1)	5 (19.2)	0.285
Duration of hospitalization, median (IQR)	7 (5–10)	7 (5–10)	7 (5–10)	0.257
In Hospital complications, n (%)	44 (17.7)	35 (15.8)	9 (34.6)	0.018
In Hospital pulmonary edema, n (%)	20 (8)	15 (6.8)	5 (19.2)	0.027
In Hospital cardiogenic shock, n (%)	9 (3.6)	5 (2.3)	4 (15.4)	0.001
In Hospital arrhythmia, n (%)	20 (8)	16 (7.2)	4 (15.4)	0.149
In Hospital death, n (%)	0	0	0	/
Long-term MACE, n (%)	43 (17.2)	37 (16.7)	6 (23.1)	0.416
Apical ballooning, n (%)	181 (72.7)	159 (71.6)	22 (84.6)	0.250
Midventricular ballooning, n (%)	41 (16.5)	39 (15.6)	2 (7.7)	0.155
Basal ballooning, n (%)	7 (2.8)	7	0	/
Focal Ballooning, n (%)	20 (8)	19 (8.6)	1 (3.8)	0.442
Mitral regurgitation, n (%)	195 (78.3)	170 (76.2)	25 (96.2)	0.020
Systolic anterior motion, n (%)	17 (6.8)	3 (1.3)	14 (53.8)	0.001
LVEF, mean (SD)	44.2 $\pm$ 11	44.4 $\pm$ 10.8	42.5 $\pm$ 12.7	0.267
EDV/BSA LV, mean (SD)	62.9 $\pm$ 28.3	77.8 $\pm$ 28.5	81.4 $\pm$ 24.1	0.431
ESV/BSA LV, mean (SD)	43 $\pm$ 22.1	42.1 $\pm$ 21.7	44.3 $\pm$ 20.6	0.289
SV/BSA LV, mean (SD)	35.5 $\pm$ 12.8	35.6 $\pm$ 12.9	34.6 $\pm$ 12.7	0.853
RVEF, mean (SD)	52.9 $\pm$ 9	53 $\pm$ 9.1	52.2 $\pm$ 8.8	0.406
EDV/BSA RV, mean (SD)	62.1 $\pm$ 22.6	61.7 $\pm$ 23.6	62.3 $\pm$ 17.1	0.609
ESV/BSA RV, mean (SD)	29.5 $\pm$ 14.1	28.9 $\pm$ 14.5	31.5 $\pm$ 12.3	0.271
SV/BSA RV, mean (SD)	33.9 $\pm$ 12.3	34.3 $\pm$ 12.9	30.7 $\pm$ 7.6	0.311
LV Thickness, mean (SD)	10.5 $\pm$ 1.9	10.4 $\pm$ 1.8	11.4 $\pm$ 2.1	0.021
LV mass/BSA, mean (SD)	46.5 $\pm$ 29.6	43.6 $\pm$ 30.7	59 $\pm$ 18.8	0.001
Time CMR, median (IQR)	3 (2–5)	3 (2–5)	3.5 (2–5)	0.840
T2 STIR, n (%)	219 (87.9)	193 (86.9)	25 (96.2)	0.219
T2 STIR (segments involvement), mean (SD)	4.9 $\pm$ 2.9	4.7 $\pm$ 2.8	6.9 $\pm$ 2.9	0.001
LGE, n (%)	57 (22.9)	48 (21.6)	9 (34.6)	0.138
LGE (segments involvement), mean (SD)	1.4 $\pm$ 2.8	1.2 $\pm$ 2.6	2.4 $\pm$ 3.6	0.074
Pericardial effusion, n (%)	73 (29.3)	61 (27.5)	11 (42.3)	0.120
Pleural effusion, n (%)	56 (22.5)	47 (21.2)	8 (30.8)	0.272

Numbers in bold type indicate a significant difference.

Abbreviations: BPM, Beats Per Minute; BSA, body surface area; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; COPD, Chronic Obstructive Pulmonary Disease; EDV, end-diastolic volume; ESV, end-systolic volume; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left

ventricle ejection fraction; LVOTO, left ventricular outflow tract obstruction; RA, right atrium; RV, right ventricle; RVEF, right ventricular ejection fraction; SD, standard deviation; STIR, short tau inversion recovery; SV, stroke volume.

reported in **Supplemental Table 3** and **Table 2**. In univariable analysis, dyspnea was significantly associated with LVOTO (OR = 2.33, 95% CI: 1.01–5.38, $p = 0.048$). Among CMR parameters, LV basal septum wall thickness (OR = 1.34, 95% CI: 1.06–1.67, $p = 0.013$), LV mass (OR = 1.02, 95% CI: 1.01–1.04, $p = 0.001$), and the extent of myocardial edema assessed by T2-STIR segment involvement (OR = 1.29, 95% CI: 1.12–1.49, $p = 0.001$) were also significantly associated with LVOTO. In multivariable analysis, LV thickness (OR = 1.31, 95% CI: 1.03–1.66, $p = 0.026$) and the extent of myocardial edema assessed by T2-STIR segment involvement (OR = 1.38, 95% CI: 1.17–1.63, $p = 0.001$) remained independently associated with LVOTO. **Fig. 3**.

3.4. In-hospital complications and long-term follow-up

Patients with LVOTO experienced a higher rate of in-hospital complications compared with those without LVOTO (34.6% vs. 15.8%, $p = 0.018$). Specifically, pulmonary edema occurred more frequently in the LVOTO group (19.2% vs. 6.8%, $p = 0.027$), as cardiogenic shock (15.4% vs. 2.3%, $p = 0.001$). An exploratory multivariable logistic regression analysis was performed to assess the association between LVOTO and in-hospital complications after adjustment for age, sex, and LVEF. LVOTO remained independently associated with in-hospital complications (OR = 3.16, 95% CI: 1.08–9.26, $p = 0.035$), whereas age (OR = 0.98, 95% CI: 0.95–1.01, $p = 0.236$), sex (OR = 0.74, 95% CI: 0.16–3.43, $p = 0.703$), and LVEF (OR = 0.99, 95% CI: 0.96–1.02, $p = 0.752$) were not significantly associated with the outcome (Supplemental Table 4). The duration of hospitalization was similar between groups, with a median length of stay of 7 days (IQR: 5–10 days in both groups; $p = 0.257$). Over a mean follow-up of 20.23 ± 27.52 months (median 10 months, IQR: 2–24 months), 43 patients (17.2%) experienced out-of-hospital events, including 12 cases of heart failure hospitalization (28%), 10 TTS recurrences (23%), 16 deaths (37.2%), 4 arrhythmias (9.3%), 1 cerebrovascular event (2.3%).

The composite secondary outcome (all-cause mortality and long-term MACE) occurred in 37 patients (16.7%) without LVOTO and in 6 patients (23.1%) with LVOTO ($p = 0.416$).

Kaplan–Meier analysis showed no significant difference in event-free survival between patients with and without LVOTO (log-rank $p = 0.339$; **Fig. 4**). Consistently, univariable Cox regression analysis showed that LVOTO was not significantly associated with the composite secondary endpoint (HR 1.523, 95% CI 0.641–3.620; $p = 0.340$).

4. Discussion

We performed a CMR study in a large European retrospective registry

to assess the prevalence, clinical and imaging correlates, and outcomes of LVOTO in patients with TTS. The main findings of our analysis can be summarized as follows. First, LVOTO is not uncommon in TTS, being observed in approximately 10% of patients. Second, patients with LVOTO exhibit distinct CMR features, including increased wall thickness and mass, and a more extensive burden of myocardial edema. Third, among imaging parameters, the extent of myocardial edema is independently associated with the presence of LVOTO. Fourth, LVOTO identifies a subgroup of patients at higher risk of in-hospital complications, particularly acute heart failure and cardiogenic shock. Finally, despite its impact on early clinical course, LVOTO does not appear to be associated with worse long-term outcomes, as no significant differences were observed in mortality or out-of-hospital adverse events during follow-up.

Our findings confirm that LVOTO adversely affects the clinical course of TTS. The observed prevalence is consistent with prior multicenter echocardiographic studies, which have reported rates ranging from 6.7% to 18% [29,30]. However, compared with previous studies that have primarily focused on the clinical presentation and in-hospital management of TTS patients with LVOTO [29,30], the present sub-analysis of the EVOLUTION registry specifically investigated the association between LVOTO and morphological as well as tissue characterization abnormalities using CMR.

The pathophysiology of LVOTO during TTS remains incompletely understood. Current evidence suggests that it results from a catecholamine-mediated mechanism characterized by basal hypercontractility in the presence of mid-apical myocardial stunning [7,30,31]. This dynamic interplay creates the hemodynamic conditions that favor the development of LVOTO.

In addition, structural factors may contribute to a predisposition for obstruction. In our study, patients with LVOTO exhibited increased basal septal wall thickness and LV mass compared with those without LVOTO. From a mechanistic standpoint, increased wall thickness, a finding previously described during the acute phase of TTS and often referred to as “pseudohypertrophy” [32–35], particularly at the basal septum, could reduce the LVOT cross-sectional area, thereby facilitating the onset of dynamic obstruction. However, the contribution of a pre-

Table 2
Multivariable determinants of LVOTO in patients with Takotsubo syndrome.

Variables	OR	95% CI	p-value
Dyspnea	2.45	0.97–6.20	0.058
LV Thickness	1.31	1.03–1.66	0.026
T2 STIR	1.38	1.17–1.63	0.001

Determinants were identified through a multivariable logistic regression model adjusted for factors that reached statistical significance in univariable analysis and those considered to have biological relevance based on their potential association with LVOTO. Abbreviations: ESV, end-systolic volume; LV, left ventricle; LVOTO, left ventricular outflow tract obstruction; STIR, short tau inversion recovery.

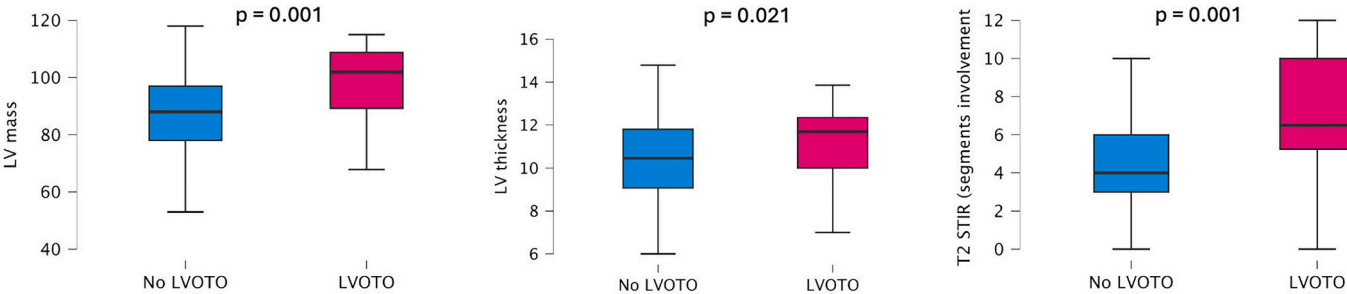


Fig. 2. Box plots of CMR parameters in patients with and without LVOTO. Abbreviations: CMR, cardiovascular magnetic resonance; LVOTO, left ventricular outflow tract obstruction.

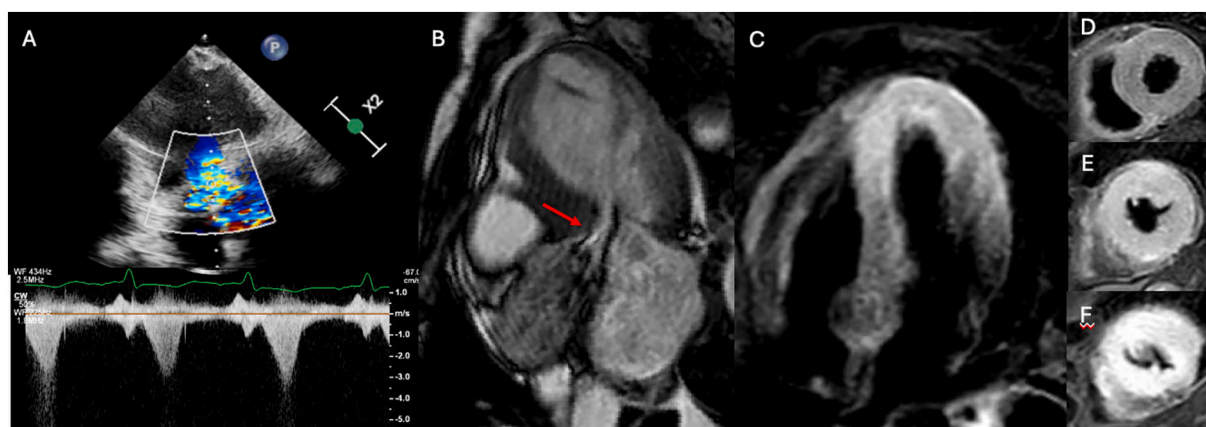


Fig. 3. Practical example of a Takotsubo syndrome patient with LVOTO assessed by echocardiography, with continuous-wave Doppler demonstrating a systolic intraventricular peak gradient of 53 mmHg (Panel A). Three-chamber balanced steady-state free precession (bSSFP) cine images show the presence of a flow artifact in the LVOT, indicated by the red arrow in Panel B during systole. Representative long-axis views (Panel C) and short-axis slices (Panels D–F; basal, mid-ventricular, and apical levels) on T2-weighted short tau inversion recovery (T2-STIR) imaging illustrate a positive T2-STIR signal involving all mid-ventricular and apical segments, defined as regions with a myocardium-to-skeletal muscle T2 ratio ≥ 1.9 .

Abbreviations: CMR, cardiovascular magnetic resonance; LVOTO, left ventricular outflow tract obstruction; bSSFP, balanced steady-state free precession; STIR, short tau inversion recovery. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

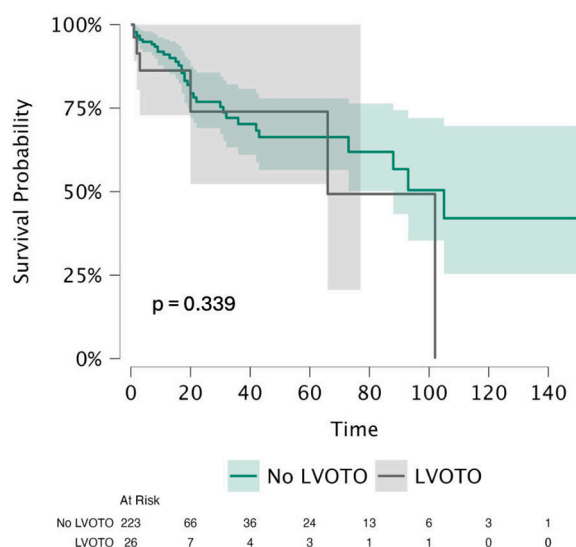


Fig. 4. Kaplan–Meier curves comparing patients with Takotsubo syndrome with and without LVOTO. The curves illustrate differences in long-term outcomes, including all-cause mortality and out-of-hospital adverse events, according to the presence or absence of LVOTO.

Abbreviations: LVOTO, left ventricular outflow tract obstruction;

existing versus an acutely accentuated geometric substrate cannot be definitively established. Given the lack of systematic structural characterization in our cohort, the presence of an underlying substrate cannot be excluded. Notably, the observation of a greater burden of myocardial edema on CMR, assessed by T2-STIR imaging, in patients with LVOTO offers additional pathophysiological insight and generates hypotheses for future longitudinal study. One possible explanation is that edema acts as a transient “space-occupying” process within the myocardial wall, contributing to wall thickening and further reduction of the LVOT lumen [32,34]. If confirmed in studies incorporating recovery-phase CMR imaging, this mechanism could represent a route by which myocardial injury and hemodynamic compromise reinforce one another; at present, however, this remains speculative rather than established. Interestingly, the lack of regional differences of myocardial edema in patients with and without LVOTO may suggest that LVOTO is

not driven by a distinct spatial pattern of myocardial injury, but rather by the overall burden and functional consequences of edema.

LVOTO identifies a distinct subgroup of patients with TTS in which in-hospital complications, particularly acute heart failure and cardiogenic shock, are more frequently observed, in line with previous studies [30,31]. Because in-hospital complications frequently occurred at clinical presentation, often before echocardiographic assessment and CMR, this association should be interpreted as descriptive rather than indicative of a temporal or predictive relationship. The underlying pathophysiological mechanism may be explained by dynamic obstruction to systolic ejection, whereby LVOTO increases LV afterload, initiating a vicious cycle that exacerbates myocardial dysfunction. This process is likely mediated by increased wall stress and an imbalance between myocardial oxygen supply and demand, ultimately impairing cardiac output. In this context, the combination of reduced forward flow and elevated filling pressures may synergistically contribute to the development of cardiogenic shock and acute heart failure; however, our cross-sectional data cannot establish the direction or sequence of this relationship, and this mechanistic interpretation remains speculative. Despite its clear association with a more severe acute presentation, LVOTO did not translate into worse long-term outcomes, as no significant differences were observed in all-cause mortality or out-of-hospital adverse events during follow-up. This apparent dissociation between early hemodynamic instability and long-term prognosis suggests that LVOTO primarily reflects a transient functional disturbance, rather than a marker of irreversible myocardial injury.

4.1. Limitations

This study has several limitations. First, its retrospective design limited the availability and completeness of certain clinically relevant data. Although the presence or absence of LVOTO was available for all patients, quantitative intraventricular pressure gradient measurements as a continuous variable were available in only 15 of the 26 patients with LVOTO. Therefore, a more detailed assessment of the severity of LVOTO based on continuous gradient measurements was not possible in all patients. Similarly, the exact time interval in hours from symptom onset to echocardiography, as well as the precise interval between echocardiography and CMR, were not systematically collected; only the interval between hospital admission and CMR acquisition was available. This precluded a more granular assessment of the temporal relationship between echocardiographic and CMR findings, which is particularly

relevant given the dynamic nature of LVOTO. In addition, because pre-event and post-recovery CMR data were not available, we cannot fully exclude the presence of pre-existing cardiomyopathy contributing to ventricular dilatation, hypertrophy, or dysfunction.

Although the registry is multicenter, the relatively small number of patients with TTS and LVOTO may limit the generalizability of our findings. In particular, the low number of patients with LVOTO did not allow us to derive a specific myocardial edema pattern characteristic of this subgroup. The limited number of LVOTO cases and in-hospital events restricted the complexity of the multivariable analyses and required the use of parsimonious models to minimize the risk of overfitting. Therefore, the exploratory multivariable analysis assessing the association between LVOTO and in-hospital complications should be interpreted with caution, and residual confounding cannot be excluded. Regarding long-term outcomes, the median follow-up was only ten months, with wide variability in follow-up duration across patients, and only six events were observed in the LVOTO group. The study is therefore insufficiently powered to demonstrate equivalence or the absence of a prognostic effect of LVOTO on long-term outcomes, and the wide confidence interval around the hazard ratio should be interpreted in this context. Moreover, T2 mapping was not available in all patients, further limiting the comprehensive assessment of myocardial edema.

Given the multicenter, multi-year design of the study, CMR examinations were performed using locally approved imaging protocols rather than a single harmonized acquisition protocol. Although all participating centers were required to include short- and long-axis cine, T2-STIR, and LGE sequences (Supplemental Table 1), variability in scanner field strength and sequence parameters across sites cannot be fully excluded and may have introduced additional heterogeneity into the edema assessment.

An inherent selection bias should also be acknowledged, as only TTS patients who underwent CMR were included, potentially leading to an underrepresentation of more clinically unstable cases. Additionally, CMR examinations were not performed on the same day as echocardiography, which may have limited the detection of transient features of TTS. Given the dynamic nature of LVOTO during the acute phase, changes in LVOTO status between echocardiography and CMR may have influenced the observed relationship between myocardial edema and LVOTO.

Importantly, in-hospital complications, particularly cardiogenic shock, often occur before CMR acquisition, which is usually performed after clinical stabilization. Consequently, the association between myocardial edema assessed by T2 mapping and cardiogenic shock should be interpreted mainly from a pathophysiological perspective rather than as a direct temporal relationship.

Future prospective, longitudinal studies are warranted to confirm our findings and to better define the role of CMR in the assessment and prognostic stratification of LVOTO in this setting.

5. Conclusion

In this multicenter cohort of patients with TTS, LVOTO was observed in approximately 10% of cases and was associated with a distinctive CMR phenotype, characterized by increased basal septal wall thickness, higher LV mass, and a greater burden of myocardial edema. Despite its substantial impact on the early clinical course, reflected by a higher rate of in-hospital complications, no statistically significant association was detected between LVOTO and long-term outcomes.

CRediT authorship contribution statement

Riccardo Cau: Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Francesco Santoro:** Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization, Writing – review & editing, Writing – original draft.

Gianluca Pontone: Visualization, Validation, Data curation, Writing – review & editing. **Giuseppe Muscogiuri:** Visualization, Validation, Methodology, Data curation, Conceptualization, Writing – review & editing. **Marco Gatti:** Visualization, Validation, Methodology, Data curation, Writing – review & editing. **Roberta Montisci:** Validation, Data curation, Conceptualization, Writing – review & editing. **Matteo Gravina:** Methodology, Writing – review & editing. **Sebastien Normant:** Validation, Formal analysis, Writing – review & editing. **Federica Catapano:** Visualization, Formal analysis, Data curation, Writing – review & editing. **Tommaso D'Angelo:** Investigation, Conceptualization, Writing – review & editing. **Antonio Esposito:** Visualization, Validation, Methodology, Data curation, Writing – review & editing. **Antonella Meloni:** Methodology, Data curation, Writing – review & editing. **Federica Ciolina:** Methodology, Formal analysis, Conceptualization, Writing – review & editing. **Francesco Negri:** Visualization, Methodology, Writing – review & editing. **Francesco Pisu:** Software, Methodology, Data curation. **Costanza Lisi:** Visualization, Data curation, Writing – review & editing. **Massimo Imazio:** Visualization, Validation, Data curation, Writing – review & editing. **Anna Palmisano:** Visualization, Validation, Methodology, Investigation, Data curation, Writing – review & editing. **Maria Francesca Marchetti:** Visualization, Resources, Methodology, Investigation, Data curation, Conceptualization, Writing – review & editing. **Nicola Galea:** Visualization, Data curation, Writing – review & editing. **Alessandra Volpe:** Resources, Data curation, Writing – review & editing. **Ludovica Lanzafame:** Methodology, Data curation, Writing – review & editing. **Giacomo Pambianchi:** Resources, Data curation, Writing – review & editing. **Alberto Clemente:** Visualization, Methodology, Writing – review & editing. **Jean Nicolas Dacher:** Resources, Methodology, Data curation, Writing – review & editing. **Leon Bischoff:** Visualization, Data curation, Writing – review & editing. **Julian Luetkens:** Resources, Methodology, Data curation, Writing – review & editing. **Luca Arcari:** Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Luca Saba:** Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization, Writing – review & editing.

Ethical approval

Approval by local Ethics Committee was obtained in each centre.

Clinical Trial Number: NCT06277297

Appendix A. Appendix

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Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2026.134777>.

Data availability

The data will be shared on reasonable request to the corresponding author, who will submit the request to the EVOLUTION group.

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