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CMR Findings Across Disease Phases in Takotsubo Syndrome: Insights From the Multicenter EVOLUTION Registry

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Takotsubo syndrome (TS) is characterized by transient left ventricular dysfunction accompanied by dynamic changes in myocardial tissue; however, differences in cardiac magnetic resonance (CMR) findings across disease phases remain incompletely characterized, particularly in large multicenter cohorts. This retrospective analysis from the multicenter EVOLUTION registry included 439 consecutive patients with TS (400 females; mean age 70.01 ± 11.59 years), stratified according to the time from symptom onset to CMR into acute (1 to 72 hours), subacute (4 to 21 days), and late (≥22 days) acquisition groups. Among these, 146 (33%) were classified as acute, 266 (60%) as subacute, and 27 (6%) as late. Biventricular systolic function was higher in patients imaged at later time points (both p = 0.001). Myocardial edema and late gadolinium enhancement (LGE) were more prevalent and extensive in patients imaged earlier and less evident in those imaged later. In multivariable analysis, T2-mapping Z-score and LGE extent were independently associated with earlier timing of CMR. T2-mapping Z-score decreased by approximately 0.22 units per day, corresponding to an average relative decline of 3% to 4% per day. In conclusion, cross-sectional CMR assessment in TS demonstrates that patients imaged at later time points exhibit more preserved systolic function and lower prevalence of myocardial edema

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and LGE, supporting the dynamic and reversible nature of myocardial injury in this condition; however, longitudinal studies with serial imaging are needed to confirm these findings.

Takotsubo syndrome (TS) is a transient yet clinically significant cardiac condition characterized by acute and reversible left ventricular (LV) systolic dysfunction, typically precipitated by emotional or physical stress.[1–4] Beyond the transient wall motion abnormalities and LV ejection fraction (LVEF) impairment that define its acute phase, TS is associated with dynamic alterations in myocardial tissue composition that cannot be fully captured by conventional imaging.[3]

In this setting, cardiac magnetic resonance (CMR) plays a pivotal role by enabling comprehensive tissue characterization that extends well beyond the evaluation of systolic dysfunction, uncovering myocardial abnormalities that may persist despite apparent functional recovery.[4–11] However, despite growing evidence supporting the diagnostic and prognostic relevance of these advanced CMR markers, differences in tissue abnormalities across the various phases of TS remain insufficiently characterized. To the best of our knowledge, the multicenter EVOLUTION registry is the first study to systematically stratify patients according to the timing of CMR relative to symptom onset. The present work aims to delineate the distribution of CMR abnormalities across different disease phases of TS in patients enrolled in the multicenter EVOLUTION registry.

Methods

Study population

The rationale and design of the EVOLUTION Registry have been previously described in detail.[12] In brief, EVOLUTION was a retrospective, multicenter study of patients with a diagnosis of TS who fulfilled the criteria outlined in the Position Statement of the Heart Failure Association of the European Society of Cardiology and were referred for clinical CMR imaging. Diagnostic criteria include 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 or coronary computed tomography angiography. Additional criteria comprise new electrocardiographic abnormalities, elevated serum natriuretic peptides with an increase in cardiac troponin levels, and recovery of left ventricular dysfunction at follow-up.

Between November 21, 2007 and December 22, 2024, consecutive patients who underwent completed CMR studies at 10 sites were enrolled. Exclusion criteria were applied as previously described.[12] CMR studies were performed at each participating center according to clinical indication and locally approved imaging protocols.[13,14] CMR protocols included mandatory sequences: cine imaging in short- and long-axis views, T2-weighted imaging in short- and long-axis views, and LGE imaging in short- and long-axis views. T2 mapping was performed as an optional sequence and was available in 287 patients (Supplementary Table 1).

The study was approved by local institutional review boards in accordance with the Declaration of Helsinki, with a waiver of written informed consent.

CMR image postprocessing

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 interpreted by an experienced observer with over 10 years of expertise in cardiovascular imaging, who was blinded to all clinical data. All quantitative measurements of left and right ventricular volumetric parameters were performed in a dedicated core laboratory, in accordance with recommendations from the Society for Cardiovascular Magnetic Resonance and the European Association of Cardiovascular Imaging.[13,14] 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. End-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) were calculated using the summation-of-disks method (Simpson's rule), and ejection fraction (EF) was derived as $(EDV-ESV)/EDV \times 100\%$. Left and right ventricular masses were indexed to body surface area to obtain LV and RV mass indices. 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.[15] LV dysfunction was defined as an LV ejection fraction below 50% as assessed by CMR.[16]

Offline CMR feature tracking analyses were performed to evaluate peak global longitudinal strain, global radial strain, and global circumferential strain. Longitudinal strain data were derived from 2-, 3-, and 4-chamber long-axis views, while radial and circumferential strain data were obtained from apical, midventricular, and basal short-axis views in all patients. The epi- and endocardial borders were traced in end-diastole on all images, after which an automatic computation was initiated to outline the borders throughout the cardiac cycle. The quality of tracking and contouring was visually validated and manually corrected as needed.

Myocardial edema was assessed both qualitatively and quantitatively. Qualitative assessment was visually performed on T2-weighted short-tau inversion recovery (T2-STIR) sequences, where edema was defined as local or regional areas of increased signal intensity with a nonischemic distribution pattern. To reduce the likelihood of artifacts, the presence of edema was confirmed only when visible in at least 2 orthogonal imaging planes. Quantitative assessment of myocardial edema was performed using T2 mapping. T2 mapping values were generated offline using the same dedicated CMR software. Endocardial and epicardial borders were manually traced and propagated through the image stack, with manual corrections applied when needed. To enable combined analysis across multicenter and multivendor data, T2 values were converted to z-scores.[17] using site-specific reference values, calculated as follows: (patient value − mean of reference range)/SD of the reference range.

The resulting z-score expresses how many SDs each patient's T2 value deviates from the mean of the normal range for the specific site, vendor, and field strength.

LGE was assessed using a multiparametric approach. First, a qualitative analysis was performed, with LGE recorded as a dichotomous variable (presence vs absence). To minimize false-positive findings, LGE was considered present only when detected in at least 2 orthogonal planes and exhibiting a nonischemic distribution pattern. Second, a semiquantitative analysis was conducted by assessing the number of myocardial segments with LGE according to the standardized 17-segment model of the American Heart Association. Finally, quantitative LGE burden was measured using semiautomated techniques, applying a signal intensity threshold >2 standard deviations above that of remote reference myocardium.[18] The remote myocardium was defined as visually normal myocardium without evidence of enhancement. The extent of LGE was expressed as a percentage of total left ventricular (LV) mass.

Statistical analysis

Continuous variables are presented as mean ± SD or median (interquartile range) as appropriate. Normality was assessed using the Kolmogorov-Smirnov test. Depending on the distribution, continuous variables were compared between groups using either the independent samples t-test or the Mann–Whitney U test. For comparisons among 3 or more groups, 1-way ANOVA or Kruskal–Wallis tests were used for continuous variables, with posthoc pairwise comparisons corrected for multiple testing using the Bonferroni method when applicable. Categorical variables were compared using the chi-square test or Fisher's exact test, with posthoc pairwise comparisons corrected for multiple testing as needed.

Associations between disease phases and demographic, clinical, laboratory, and CMR parameters were initially assessed using univariable logistic regression. Variables associated with disease phases at $p < 0.05$ in univariable analysis and not exhibiting collinearity (Spearman's $\rho < 0.7$) as well as relevant biological determinants, including age and sex were subsequently included in multivariable logistic regression models.

All tests were 2-tailed, and a p-value <0.05 was considered statistically significant. Statistical analyses were performed using JASP.

Results

Baseline characteristics

A total of 439 patients with TS were included (mean age 70.0 ± 11.6 years, 400 females). Based on the time interval between symptom onset and CMR, 146 (33%) patients were classified as acute (1 to 72 hours), 266 (60%) as subacute (4 to 21 days), and 27 (6%) as late (≥22 days) acquisition (Figure 1).

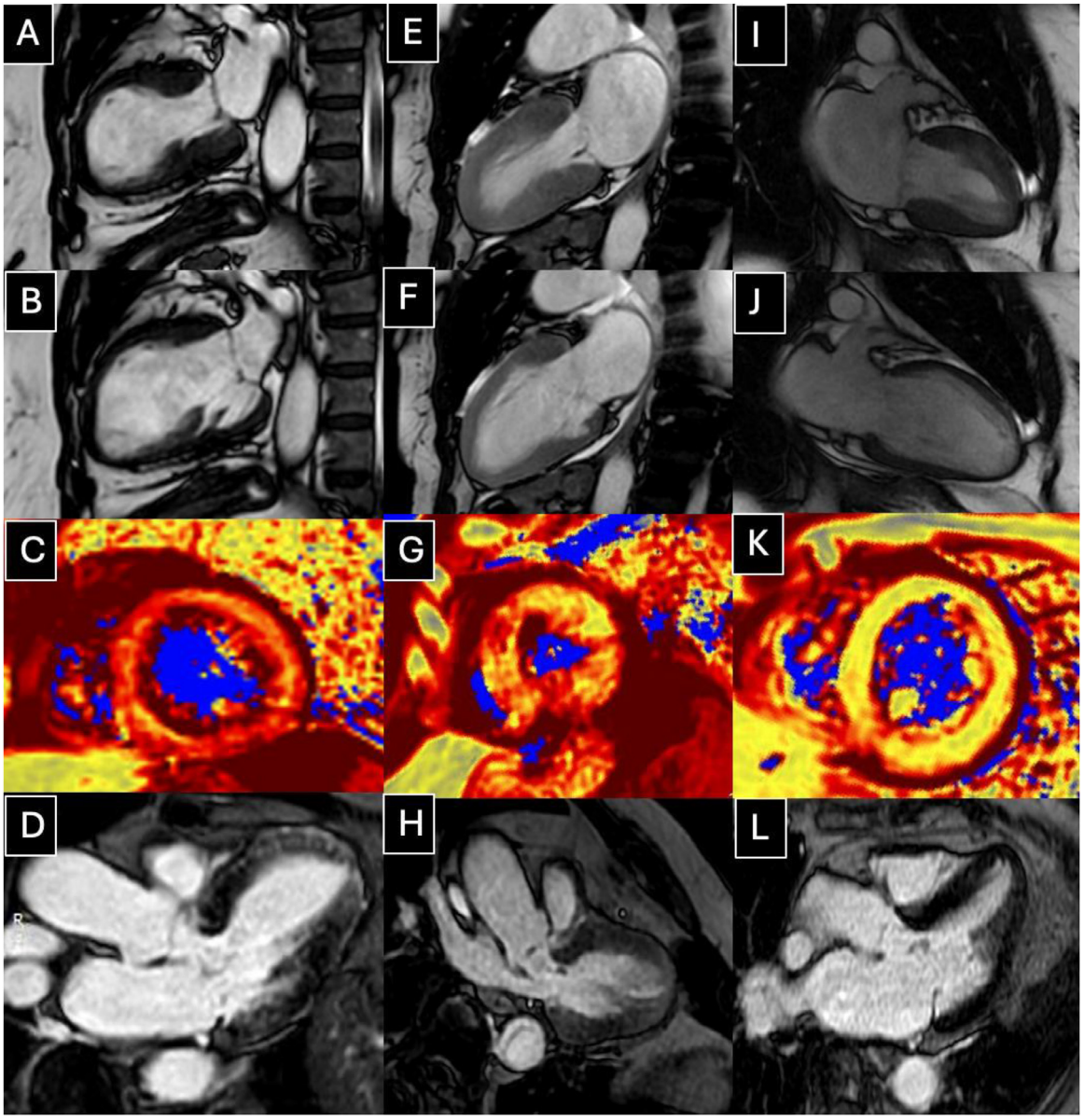


Figure 1. Representative CMR findings across different phases of Takotsubo syndrome. Panels show examples of individual patients in the acute (1–72 h, A–D), subacute (4–21 days, E–H), and late phases (≥22 days, I–L). In the acute phase, patients demonstrate markedly reduced left ventricular ejection fraction with typical wall motion abnormalities (panels A and B, systole and diastole, respectively), along with abnormal LGE, and elevated T2-mapping in segments with wall motion abnormalities (panels C and D, respectively). In the subacute phase, systolic function partially recovers (panels E and F), edema is reduced (panels G), and LGE is less extensive (panel H). In the late phase, LV function normalizes (panels I and J), edema is minimal (panel K), and LGE is absent (panel L).

The baseline clinical characteristics of the overall study cohort are summarized in Table 1.

Cardiovascular risk factors were frequently observed in the study population. Hypertension and dyslipidemia were the most common, affecting 61.7% and 52.1% of patients, respectively, while diabetes was present in 14.5% of cases. Nearly 1 in 5 patients reported a history of smoking, and 13.6% met criteria for obesity. A family history of coronary artery disease was documented in 14.8% of cases. Regarding comorbidities, malignancies were reported in 17.7% of patients, followed by neurological disorders in 11.1%, psychiatric conditions in 13.4%, and chronic obstructive pulmonary disease (COPD) in 7.9%. At clinical presentation, over half of the patients (57.8%) experienced typical chest pain, whereas dyspnea was noted in 34.1%. The average hospital stay was 9.4 ± 8.2 days. Emotional triggers were identified more frequently than physical ones (37.5% vs 30.5%), although approximately one-third of patients (31.8%) presented without any recognizable precipitating factor. Regarding TS phenotypes, apical ballooning was by far the dominant pattern (71%), while midventricular ballooning accounted for 18.4%, focal ballooning for 7%, and basal ballooning for only 3.6% of cases.

Cardiovascular magnetic resonance findings

CMR characteristics across disease phases are summarized in Table 2.

Significant difference in LV systolic function was observed across the acute, subacute, and late phases. LVEF increased from 42.8 ± 10.5% in the acute phase to 48.4 ± 11.8% in the subacute phase and 60.8 ± 8.6% in the late phase (overall p = 0.001).

LV volumes showed significant differences across the phase. LVESV significantly decreased from acute to subacute and late phases (p = 0.001), whereas LVEDV did not differ significantly between groups. Stroke volume increased modestly (from 57.9 ± 17.0 mL to 61.6 ± 24.4 mL and 68.8 ± 17.9 mL, p = 0.038), with posthoc significance only between the acute and late phases (p = 0.042). RV systolic performance also improved over time, increasing from 52.7 ± 8.9% (acute) to 53.4 ± 9.2% (subacute) and 60.6 ± 7.1% (late), (p = 0.001). Tukey posthoc testing confirmed significant differences for both acute versus late and subacute versus late (both p = 0.001), while acute versus subacute was not significant (p = 0.834).

Regarding myocardial strain analysis, GLS differed significantly across phases (from −8.44 ± 7.76%, to −10.76 ± 6.53%, to −11.05 ± 10.12%, p = 0.008). posthoc analyses revealed a borderline difference between acute and subacute (p = 0.054), but no significant difference between acute and late groups. GRS increased significantly (20.4 ± 7.5%, 22.2 ± 26.6%, 26.6 ± 8.3%, p = 0.001), with significant differences for acute versus late(p = 0.001) and subacute versus late (p = 0.016). GCS did not differ significantly across phases.

Myocardial edema was highly prevalent in the acute phase. T2-STIR positivity declined from 93.1% in acute to 71.0% in subacute and 25.9% in late phases (p = 0.001 for all pairwise comparisons). The extent of edema (segmental involvement) also significantly decreased (5.27 ± 2.88, 3.83 ± 3.43, 1.48 ± 2.62, p = 0.001).

T2 mapping was available in 287 of 439 patients (65.4%), including 95 of 146 (65.1%) in the acute group, 177 of 266 (71.9%) in the subacute group, and 15 of 27 (55.5%) in the late acquisition group. T2 mapping Z-scores showed a similar temporal decline (5.77 ± 3.52, 5.09 ± 2.88, 2.78 ± 1.77, p = 0.002), with significant differences for acute versus late and subacute versus late. LGE was observed in 23.9% of acute and 15.9% of subacute patients (p = 0.017), while no LGE was detected in the late group. The extent of LGE declined significantly across groups (p = 0.001). Notably, LGE was consistently confined to myocardial segments demonstrating concomitant edema and regional wall motion abnormalities.

Association between CMR findings and timing from symptom onset

The univariable and multivariable associations between time from symptom onset and CMR acquisition are presented in Tables 3 and 4. In univariable analysis, several CMR parameters demonstrated

Table 1
Baseline characteristics of patients with Takotsubo syndrome

Variables	Overall (*n* = 439)	Acute phase (*n* = 146)	Subacute phase (*n* = 266)	Chronic phase (*n* = 27)	p-value
Age, mean (SD)	70.01 ± 11.59	70.89 ± 9.92	70.01 ± 12.56	65.64 ± 9.58	0.101
Sex (Male), n (%)	39 (8.8%)	16 (10.9%)	22 (8.3%)	1 (3.7%)	0.409
BPM, mean (SD)	80.77 ± 19.89	81.03 ± 17.87	81.42 ± 21.06	72.60 ± 17.08	0.126
Troponin, mean (SD)	1938.42 ± 3245.83	1680.42 ± 2386.84	2149.81 ± 3732.08	1180.16 ± 1148.54	0.265
proBNP, mean (SD)	4767.65 ± 8649.43	2960.16 ± 4279.12	6045.87 ± 10436.84	1436.53 ± 1903.47	**0.011**
Hypertension, n (%)	271 (61.7)	98 (67.1%)	157 (59%)	16 (59.2%)	0.126
Dyslipidemia, n (%)	229 (52.1)	74 (50.7%)	141 (53%)	14 (51.8%)	0.987
Obesity, n (%)	60 (13.6)	21 (14.4%)	32 (12%)	7 (25.9%)	0.114
Smoke, n (%)	80 (18.2)	31 (21.3%)	45 (16.9%)	4 (14.8%)	0.625
Diabetes, n (%)	64 (14.5)	22 (15.1%)	38 (14.3%)	4 (14.8%)	0.941
CAD, n (%)	65 (14.8)	16 (11%)	45 (16.9%)	4 (14.8%)	0.306
COPD, n (%)	35 (7.9)	7 (4.8%)	27 (10.1%)	1 (3.7%)	0.131
Malignancies, n (%)	78 (17.7)	33 (22.6%)	42 (15.8%)	3 (11.1%)	0.113
Neurological disease, n (%)	49 (11.1)	18 (12.3%)	29 (10.9%)	2 (7.4%)	0.712
Psychiatric disease, n (%)	59 (13.4)	16 (11%)	40 (15%)	3 (11.1%)	0.561
Typical chest pain, n (%)	254 (57.8)	94 (64.4%)	143 (53.8%)	17 (63%)	**0.005**
Dyspnea, n (%)	150 (34.1)	42 (28.8%)	102 (38.3%)	6 (22.2%)	0.149
Emotional trigger, n (%)	165 (37.5)	56 (38.4%)	97 (36.5%)	12 (44.4%)	0.565
Physical trigger, n (%)	134 (30.5)	44 (30.1%)	83 (31.2%)	7 (25.9%)	0.942
No trigger, n (%)	140 (31.8)	46 (31.5%)	82 (30.8%)	12 (44.4%)	0.582
T-wave inversion, n (%)	168 (38.2)	57 (39%)	97 (36.5%)	14 (51.8%)	0.511
ST-segment elevation, n (%)	98 (22.2)	34 (23.3%)	61 (22.9%)	3 (11.1%)	0.212
Duration of hospitalization, mean (SD)	9.38 ± 8.19	8.34 ± 5.30	10.18 ± 9.45	7.30 ± 5.93	0.157
Apical ballooning, n (%)	312 (71)	105 (71.9%)	195 (73.3%)	12 (44.4%)	**0.015**
Midventricular ballooning, n (%)	81 (18.4)	28 (19.2%)	48 (18%)	5 (18.5%)	0.852
Basal ballooning, n (%)	16 (3.6)	4 (2.7%)	12 (4.5%)	/	0.432
Focal ballooning, n (%)	30 (7)	13 (8.9%)	14 (5.2%)	3 (11.1%)	0.246

BPM = beats per minute; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SD = standard deviation.
Bold value indicate statistically significant differences.

Table 2
CMR findings across groups stratified by the timing of CMR relative to symptom onset

Variables	Acute phase (*n* = 146)	Subacute phase (*n* = 265)	Chronic phase (*n* = 27)	p-value	p-value†	p-value‡	p-value§
CMR timing (days), mean (SD)	1.96 ± 0.84	7.39 ± 3.6	35.40 ± 15.60	**0.001**	**0.001**	**0.001**	**0.001**
LVEF, mean (SD)	42.80 ± 10.46	48.42 ± 11.80	60.80 ± 8.60	**0.001**	**0.001**	**0.001**	**0.001**
EDV LV, mean (SD)	132.53 ± 32.61	129 ± 48.15	117.41 ± 33.96	0.232	0.704	0.210	0.373
ESV LV, mean (SD)	74.82 ± 28.15	66.40 ± 34	47.63 ± 20.73	**0.001**	**0.027**	**0.001**	**0.009**
SV LV, mean (SD)	57.86 ± 17	61.64 ± 24.40	68.75 ± 17.90	**0.038**	0.216	**0.042**	0.242
RVEF, mean (SD)	52.74 ± 8.93	53.38 ± 9.15	60.59 ± 7.12	**0.001**	0.834	**0.001**	**0.001**
RV impairment, n (%)	32 (21.9%)	50 (18.8%)	1 (3.7%)	0.266	0.993	0.289	0.238
EDV RV, mean (SD)	107.51 ± 31.17	110.29 ± 34.68	107.59 ± 29.68	0.701	0.701	0.989	0.915
ESV RV, mean (SD)	51.76 ± 22.15	52.06 ± 21.14	45.36 ± 16.11	0.294	0.990	0.324	0.265
SV RV, mean (SD)	57.81 ± 15.62	59 ± 20.73	62.35 ± 17.18	0.259	0.820	0.228	0.334
T2 STIR, n (%)	136 (93.1)	189 (71)	7 (25.9%)	**0.001**	**0.001**	**0.001**	**0.001**
T2 STIR (segments involvement), mean (SD)	5.27 ± 2.88	3.83 ± 3.43	1.48 ± 2.62	**0.001**	**0.001**	**0.001**	**0.001**
LGE, n (%)	35 (23.9%)	43 (15.9)	/	**0.017**	0.097	**0.030**	0.255
LGE (segments involvement), mean (SD)	1.84 ± 3.09	0.82 ± 2.05	/	**0.001**	**0.002**	**0.005**	0.308
LGE 2 SD, mean (SD)	25.21 ± 13.40	24.13± 11.25	/	0.661	**0.661**	/	/
T2 mapping, mean (SD)* (*n* = 287)	62.51 ± 7.47 (*n* = 95)	61.18 ± 6.17 (*n* = 177)	57.8. ± 3.73 (*n* = 15)	**0.028**	0.308	0.119	**0.027**
T2 mapping Z score, mean (SD)* (*n* = 287)	5.77 ± 3.52 (*n* = 95)	5.09 ± 2.88 (*n* = 177)	2.78 ± 1.77 (*n* = 15)	**0.002**	0.194	**0.002**	**0.015**
GLS, mean (SD)	−8.44 ± 7.76	−10.76 ± 6.53	−11.05 ± 10.12	**0.008**	0.054	0.995	0.520
GCS, mean (SD)	−10.62 ± 8.42	−13.23 ± 12.49	−14.53 ± 9.23	0.152	0.067	0.210	0.826
GRS, mean (SD)	20.41 ± 7.53	22.23 ± 26.57	26.57 ± 8.31	**0.001**	0.086	**0.001**	**0.016**

CMR = cardiovascular magnetic resonance; EDV = end-diastolic volume; ESV = end-systolic volume; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; RA = right atrium; RV = right ventricle; RVEF = right ventricular ejection fraction; SD = standard deviation; STIR = short tau inversion recovery; SV = stroke volume.
Bold value indicate statistically significant differences.
* Available in 287 patients overall; group-specific n values are reported in the table.
† p-values for acute versus subacute phase in Tukey post hoc analysis.
‡ p-values for acute versus late phase in Tukey post hoc analysis.
§ p-values for late versus subacute phase in Tukey post hoc analysis.

significant relationships with imaging timing. Higher LVEF (β = 0.379, 95% CI: 0.215 to 0.344, p = 0.001), as well as increased LV and RV stroke volumes, were associated with longer intervals before CMR, reflecting progressive functional recovery over time. In contrast, markers typically observed in the early phase of TS—including larger LVESV (β = −0.227, 95% CI: −0.088 to −0.037, p = 0.001), greater edema burden on T2-STIR (β = −0.302, 95% CI: −1.067 to −0.573, p = 0.001), more extensive LGE (β = −0.171, 95% CI: −1.076 to −0.227, p = 0.003), and higher T2-mapping Z-scores (β = −0.220, 95% CI: −0.745 to −0.232, p = 0.001), were all significantly associated with earlier CMR examinations. Among strain parameters, only GRS correlated with delayed imaging (β = 0.217, 95% CI: 0.132 to 0.338, p = 0.001).

In the multivariable model, only LGE extent (β = −0.153, 95% CI: −0.805 to −0.039, p = 0.031) and T2-mapping Z-score (β = −0.215, 95% CI: −0.816 to −0.096, p = 0.014) remained independently associated with earlier CMR acquisition. Based on the regression coefficient, T2-mapping Z-scores decreased by approximately 0.22 units per day from symptom onset to CMR. This corresponds to an average relative decline of 3% to 4% per day (Figure 2).

Table 3
Univariables association of CMR timing in patients with Takotsubo syndrome

Variables	β	95% CI	p-value
LVEF, mean (SD)	0.280	[0.215, 0.344]	**0.001**
EDV LV, mean (SD)	−0.023	[−0.042, −0.003]	**0.024**
ESV LV, mean (SD)	−0.065	[−0.091, −0.038]	**0.001**
SV LV, mean (SD)	0.047	[0.005, 0.082]	**0.026**
RVEF, mean (SD)	0.179	[0.089, 0.269]	**0.001**
EDV RV, mean (SD)	0.002	[−0.025, 0.027]	0.929
ESV RV, mean (SD)	0.048	[0.019, 0.074]	**0.001**
SV RV, mean (SD)	0.040	[0.009, 0.096]	**0.049**
T2 STIR (segments involvement), mean (SD)	−0.820	[−1.067, −0.573]	**0.001**
LGE (segments involvement), mean (SD)	−0.651	[−1.076, −0.227]	**0.003**
T2 mapping Z score, mean (SD)*	−0.488	[−0.745, −0.232]	**0.001**
GLS, mean (SD)	−0.105	[−0.220, 0.011]	0.765
GCS, mean (SD)	−0.069	[−0.146, 0.008]	0.955
GRS, mean (SD)	0.235	[0.132, 0.338]	**0.001**

CMR = cardiovascular magnetic resonance; EDV = end-diastolic volume; ESV = end-systolic volume; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; RA = right atrium; RV = right ventricle; RVEF = right ventricular ejection fraction; SD, standard deviation; STIR, short tau inversion recovery; SV, stroke volume.
Bold value indicate statistically significant differences.
* Available in 287 patients overall.

Discussion

The main results of the current multicenter study can be summarized as follows: (1) biventricular systolic function differed across disease phases of TS, with more preserved function observed in patients evaluated in later phases; (2) myocardial edema was most frequently

Table 4
Multivariables associations of CMR timing in patients with Takotsubo syndrome

Variables	β	95% CI	p-value
LVEF, mean (SD)	0.263	[−0.028, 0.555]	0.076
EDV LV, mean (SD)	0.086	[−0.543, 0.714]	0.788
ESV LV, mean (SD)	−0.068	[−0.702, 0.567]	0.834
SV LV, mean (SD)	−0.146	[−0.783, 0.491]	0.652
RVEF, mean (SD)	0.056	[−0.108, 0.221]	0.502
ESV RV, mean (SD)	0.035	[−0.054, 0.124]	0.440
LGE (segments involvement), mean (SD)	−0.422	[−0.805, −0.039]	**0.031**
T2 mapping Z score, mean (SD)*	−0.455	[−0.816, −0.096]	**0.014**
GRS, mean (SD)	−0.095	[−1.185, 5.696]	0.136

Determinants were identified through a multivariable logistic regression model adjusted for factors that reached statistical significance in univariable analysis as well as for relevant biological determinants, including age and sex.
EDV = end-diastolic volume; ESV = end-systolic volume; GRS = global radial strain; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; RA = right atrium; RV = right ventricle; RVEF = right ventricular ejection fraction; SD = standard deviation; SV = stroke volume.
Bold value indicate statistically significant differences.
* Available in 287 patients overall.

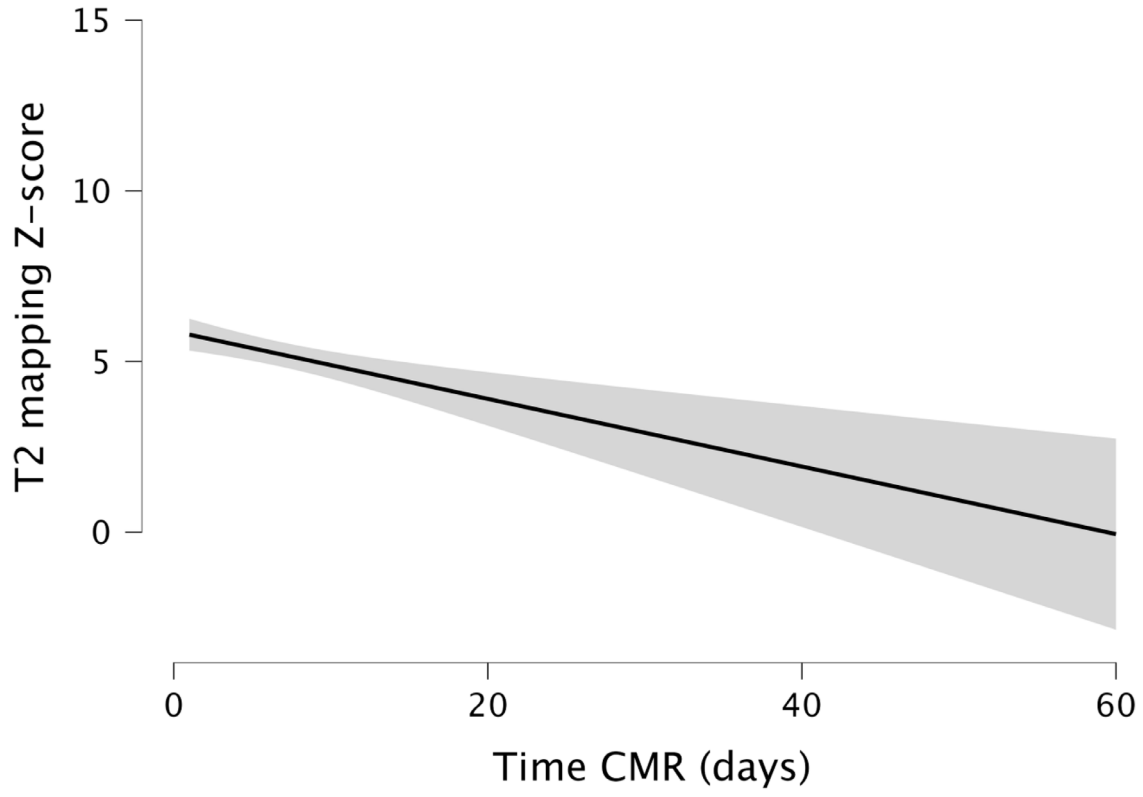
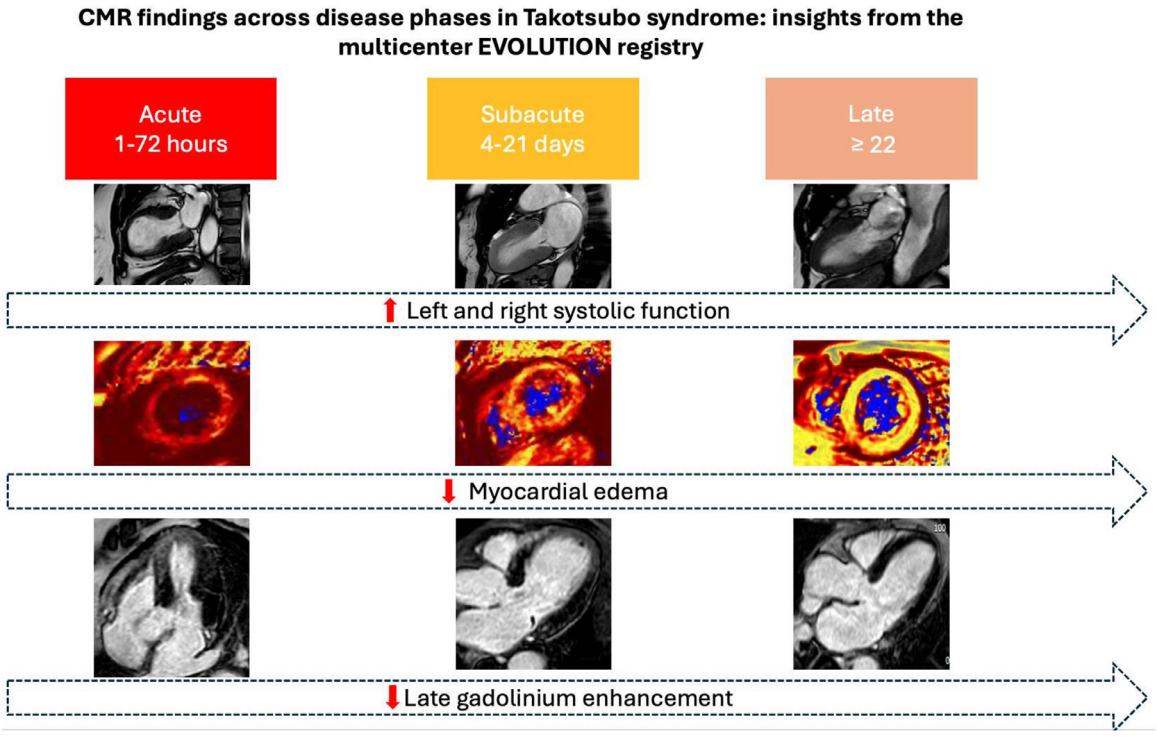


Figure 2. Temporal evolution of myocardial edema in Takotsubo syndrome assessed by T2 mapping. Scatterplot illustrating individual patient T2 mapping Z-scores (y-axis) as a function of time from symptom onset to cardiac magnetic resonance imaging (x-axis). A Loess smoothed curve (solid line) represents the overall trend of T2 values over time, with the shaded area indicating the 95% confidence interval.



Central illustration

detected in patients imaged in the early phase and was less prevalent in those assessed in later phases, whereas LGE, when present, was predominantly observed in early phases and was absent in patients evaluated in the late phase; and (3) among all CMR markers, T2-mapping Z-scores and LGE extent are the variables most strongly associated with early imaging, independently of confounders. Importantly, these findings reflect differences between groups of patients imaged at different time points rather than longitudinal changes within the same individuals.

In line with the transient nature of TS, global ventricular systolic function differed across disease phases in our cohort, with lower values observed in patients evaluated in the acute phase and progressively higher values in those assessed at later time points. While this pattern is consistent with the expected resolution of acute myocardial stunning that typifies TS,[19,20] it should be interpreted cautiously given the cross-sectional design of the study. The parallel reduction in LVEDV and LVESV further supports an association between timing of imaging and contractile performance. The modest increase in SV, which reached statistical significance only between the acute and late groups, is consistent with prior invasive hemodynamic data showing that TS is characterized by impaired LV contractility and a shortened systolic ejection period. In the acute phase, these abnormalities shift the pressure–volume loop rightward, resulting in increased LV end-diastolic and end-systolic volumes that help preserve SV despite a reduced ejection fraction.[21]

Right ventricular systolic function showed a similar association with timing of imaging, with higher values observed in patients evaluated later. The apparent delayed or less uniform RV response compared with the LV is consistent with previous research showing that RV involvement in TS is variable and may recover more slowly.[22] Myocardial strain analysis provided additional insight into differences in myocardial mechanics across groups. Among deformation parameters, GRS exhibited the largest variation, potentially reflecting differential involvement of myocardial fiber layers. Importantly, global strain values remained altered even in patients evaluated later, despite normalization of LVEF. This dissociation suggests that, beyond apparent recovery of conventional systolic function, a prolonged convalescent phase with persistent subclinical contractile dysfunction may exist in TS, consistent with prior evidence of long-lasting functional impairment.[23–25]

Myocardial edema was highly prevalent in the acute phase of TS, consistent with a transient inflammatory response and catecholamine-induced myocardial stunning at disease onset.[6,26,27] The lower prevalence of T2-STIR positivity and the decreasing extent of edema in patients imaged later reflect the expected resolution of myocardial inflammation and fluid accumulation over time.[28] The marked reduction in T2 abnormalities by the late group suggests that edema resorption is a relatively slow process, extending well beyond the early recovery of systolic function.[28]

Concerning LGE, it was present in about one-quarter of patients in the acute phase and less frequently in the subacute phase, but completely absent in the late-phase scans. This pattern aligns with previous data indicating that LGE in TS more often reflects transient myocardial injury.[4,8,9,29,30] Its absence in patients evaluated later underscores the largely reversible nature of myocardial tissue alterations in TS and helps distinguish TS from ischemic or inflammatory cardiomyopathies, which typically feature persistent LGE.[8]

Clinical implications

These findings have important clinical implications. The strong time dependence of edema and transient LGE underscores the need for early CMR, as delayed imaging markedly reduces diagnostic yield and increase the likelihood of false-negative findings. Quantitative T2-mapping emerged as one of the markers most strongly associated with early imaging, supporting their routine use when differentiating TS from other acute cardiomyopathies. Although LV and RV function appear more preserved in patients imaged later, strain analysis reveals that subtle myocardial dysfunction may still be present even when EF is normalized. However, the cross-sectional nature of these findings limits conclusions regarding the timeline of recovery. Importantly, the transient nature of LGE indicates reversible injury rather than permanent scar, preventing misclassification of TS as chronic myocardial disease.

Limitations

This study has several limitations. First, its retrospective and cross-sectional design did not allow longitudinal CMR assessment of the same patients across the different phases of TS. Instead, the acute, subacute, and late groups consisted of different patients imaged at varying time points, which limits the ability to draw definitive conclusions about individual temporal recovery patterns. Second, the timing of CMR was not standardized and was influenced by clinical and logistical factors, introducing potential selection bias. Third, although this represents one of the largest multicenter CMR cohorts in TS, the number of patients imaged in the late phase was relatively small, reducing statistical power for this subgroup.

In addition, T2-mapping was not available for all patients, as mapping sequences were incorporated into routine clinical practice only after the initial phase of patient enrollment. This resulted in heterogeneous availability of quantitative edema assessment across the cohort. Finally, despite multivariable adjustment, residual confounding cannot be fully excluded, and causality cannot be inferred due to the observational nature of the study.

Future prospective, longitudinal studies with standardized imaging follow-up are needed to validate our findings and more accurately clarify the temporal evolution of functional recovery and tissue characterization abnormalities in TS.

Conclusion

In this large multicenter cohort, cross-sectional CMR assessment across predefined time intervals from symptoms onset in TS revealed systematic differences in biventricular systolic function and tissue characterization parameters, with more preserved systolic function and lower prevalence of myocardial edema and transient LGE observed in patients imaged later. These findings are consistent with, but do not directly demonstrate, the dynamic and largely reversible nature of myocardial injury in TS. Because patients were assessed at different time points rather than undergoing serial imaging, these findings reflect cross-sectional associations rather than within-patient recovery trajectories. Prospective longitudinal studies with standardized follow-up are therefore warranted to confirm these observations and to more precisely characterize the temporal evolution of functional recovery and myocardial tissue remodeling in TS.

Data Availability

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

Ethical Approval

Approval by local Ethics Committee was obtained in each center.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2026.04.057.

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