Late Gadolinium Enhancement on Cardiac MRI in Patients With Takotsubo Syndrome—Insights From the Multicenter EVOLUTION Registry

Abstract

Background: Late gadolinium enhancement (LGE) has traditionally been considered absent in Takotsubo syndrome (TS). However, accumulating evidence indicates the finding's presence during the acute phase in a subset of patients.

Objectives: To evaluate the frequency of LGE, identify factors associated with LGE presence, assess prognostic implications of LGE, and compare methods for quantifying LGE extent, in patients with TS undergoing cardiac MRI.

Methods: This retrospective study included 370 patients (338 female; 42 male; mean age 69.7±12 years) from the nine-center EVOLUTION registry from November 21, 2007 to December 22, 2024. The registry included patients with hospital admission for TS who underwent cardiac MRI within 10 days after symptom onset; patients were required to fulfill professional society criteria for TS diagnosis. Two radiologists independently reviewed LGE images to assess examinations for the visual presence of LGE, resolving discrepancies for further analyses. In patients with LGE, a radiologist quantified LGE extent visually and using semiautomated methods (2-SD, 3-SD, and 5-SD threshold methods relative to remote myocardial signal intensity; full-width at half-maximum method relative to LGE peak signal intensity). In-hospital adverse events (death or major cardiac or cerebrovascular events) were identified.

Results: The two radiologists identified LGE in 58 (15.7%) and 54 (14.5%) patients; by consensus, LGE was present in 58 (15.7%) patients. In multivariable analysis, LGE presence was independently associated with a shorter interval from presentation to cardiac MRI (OR per day=0.81, p=.003) and a greater extent of myocardial edema on T2-weighted STIR images (OR per segment=1.44, p<.001). The mean LGE extent by visual assessment was 25.5%. Among semiautomated methods, correlation with visual assessment of LGE extent was greatest for the 2-SD threshold method (ρ=0.93). In-hospital adverse events occurred in 88 (23.8%) patients and were not significantly associated with LGE presence (p=.44) or extent by any method (all p>.05).

Conclusion: LGE was identified in 15.7% of patients with TS and showed significant independent associations with greater myocardial edema extent and earlier MRI timing after presentation but was not associated with in-hospital adverse events.

Clinical Impact: The results may provide useful context when radiologists encounter LGE on cardiac MRI in patients with TS.

Highlights

Key findings: Among 370 patients with TS from a nine-center registry, LGE was detected in 15.7% and was independently associated with a shorter interval from presentation to cardiac MRI (OR per day=0.81) and greater myocardial edema extent (OR per segment=1.47). In-hospital adverse events were not significantly associated with LGE presence or extent.

Importance: These findings help to clarify the prevalence and clinical implications of LGE in patients with TS.

Keywords: Takotsubo syndrome; Cardiovascular Magnetic Resonance; LGE; quantitative analysis.

Introduction

Takotsubo syndrome (TS) is an acute reversible form of myocardial dysfunction characterized by distinctive left ventricular (LV) wall motion abnormalities and transient myocardial tissue changes, typically triggered by physical or emotional stress [1][2][3][4]. Cardiac MRI has emerged as the mainstay test for the noninvasive evaluation of cardiac morphology, function, and tissue characterization in TS, providing valuable prognostic information [4][5][6][7][8][9][10][11][12].

Late gadolinium enhancement (LGE) is a cardiac MRI parameter that plays a key prognostic role in various cardiovascular diseases [13][14][15][16][17][18][19]. LGE relies on the administration of an extracellular gadolinium-based contrast agent (GBCA), which accumulate in regions of expanded interstitial space due to delayed washout kinetics [15]. The significance of LGE in TS remains controversial. Historically, the absence of LGE was considered a hallmark feature of TS, supporting the diagnosis and aligning with the condition's absence of irreversible myocardial injury. Yet, accumulating literature has increasingly challenged this view. For example, case series and cohort studies have reported the presence of LGE in a subset of patients with TS, with LGE prevalence influenced by a variety of factors including the timing of MRI after clinical presentation as well as MRI technique [4][8][9][20][21][22][23][24][25][26]. A meta-analysis from 2025 of 21 studies including 703 patients with TS reported a prevalence of LGE on acute-phase MRI of 22.4%, with considerable heterogeneity depending on the sensitivity threshold used for diagnosing LGE [25].

From a histopathologic perspective, TS is characterized by transient myocardial alterations including interstitial edema and infiltration of inflammatory cells, particularly macrophages that may internalize gadolinium particles [27][28]. These processes are distinct from the extensive irreversible myocyte loss occurring in myocardial ischemic necrosis but nonetheless provide a plausible biologic substrate for the subtle or potentially reversible LGE patterns observed during the acute phase of TS. However, the clinical implications of LGE in patients with TS remain uncertain,

for example with respect to factors associated with the finding's presence and its prognostic implications.

The quantification of LGE extent in TS lacks standardization. Several semiautomated techniques are available, including signal intensity (SI) threshold methods that define enhancement using cutoffs ranging from 2 to 6 SDs above the SI of remote nonenhanced myocardium, as well as the full-width at half maximum (FWHM) method, which defines enhancement using a cutoff of 50% of the maximal SI within the area of LGE [15]. However, consensus is lacking regarding which technique offers the greatest reliability and reproducibility, contributing to the variable assessment protocols in current clinical practice.

The aims of this study were to evaluate the frequency of LGE, identify factors associated with LGE presence, assess prognostic implications of LGE, and compare methods for quantifying LGE extent, in patients with TS undergoing cardiac MRI.

Methods

Study Population

This retrospective study was approved by the institutional review boards of the participating centers, with a waiver of written informed consent.

The present study represented a subanalysis of the EVOLUTION (Exploring the eVolution in prognOstic capabiLity of mUlti-sequence cardiac magneTIc resOnance in patieNts affected by Takotsubo cardiomyopathy) registry. EVOLUTION was a retrospectively assembled registry across nine centers of patients with hospital admission for a diagnosis of TS who underwent a clinically indicated cardiac MRI examination within 10 days after symptoms onset. Patients were required to fulfill the criteria for TS in the Position Statement of the Heart Failure Association of the European Society of Cardiology [29]. Example criteria in this statement include regional wall motion

abnormalities extending beyond a single epicardial vascular territory, presence of a prior stressful trigger, absence of culprit atherosclerotic disease on invasive coronary angiography, new ECG abnormalities, elevations in serum natriuretic peptides or cardiac troponin levels, and complete recovery of LV dysfunction at follow-up. Patients were ineligible for registry entry if fulfilling any of the following criteria: age less than 18 years, preexisting cardiomyopathy, prior myocardial infarction, suspected or known prior irreversible myocardial damage, and significant valvular heart disease. The rationale and design of the EVOLUTION registry have been previously described in detail [30].

The EVOLUTION registry was searched for consecutive patients from November 21, 2007, to December 22, 2024, yielding 397 patients. Of these patients, six were excluded due to absence of LGE sequences on the cardiac MRI examination and 18 were excluded due to suboptimal quality of the LGE sequences. These exclusions resulted in a final study sample of 370 patients. **Figure 1** shows the patient selection process for the present study.

Information extracted from the registry database for patients in the current analysis included age, sex, BMI, weight, height, laboratory values (high-sensitivity cardiac troponin T [hs-cTnT], high-sensitivity cardiac troponin I [hs-cTnI], pro-B-type natriuretic peptide (proBNP) at the times of hospital admission and discharge, cardiovascular risk factors (hypertension, hyperlipidemia, obesity, smoking history, diabetes, coronary artery disease), comorbidities (chronic obstructive pulmonary disease, malignancy, neurologic disease, psychiatric disease), presenting symptoms (typical chest pain, dyspnea), presence of an emotional trigger, presence of a trigger physical, and interval in days between symptom onset and the cardiac MRI examination.

Cardiac MRI Examinations

The participating centers performed the cardiac MRI examinations using locally approved imaging protocols based on clinical indications [31][32]. The 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. **Table S1** summarizes protocols across participating centers, including scanner selection, LGE sequence, and contrast media details.

Cardiac MRI Postprocessing

The images from the cardiac MRI examinations were transferred from the participating centers to a single core laboratory for centralized postprocessing and analysis. The datasets were interpreted at the core laboratory by a radiologist (R.C) with 10 years of posttraining experience in cardiovascular imaging using commercially available software (CVI42, version 6.2; Circle Cardiovascular Imaging Inc., Calgary, Canada). The investigator performed quantitative assessment of LV and right ventricular (RV) volumetric and functional parameters on cine images following recommendations from the Society for Cardiovascular Magnetic Resonance and the European Association of Cardiovascular Imaging. The measured parameters included LV ejection fraction, LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV stroke volume (SV), RV ejection fraction, RV EDV, RV ESV, and RV SV.

The radiologist classified each examination in terms of the presence or absence of myocardial edema, defined as an area of myocardium showing hyperintensity on STIR images. The investigator placed ROIs on the STIR images to confirm areas of visually suspected myocardial edema; edema was required to show a SI ≥2 SD above that of remote myocardium or a SI ≥1.9 SD above that of skeletal muscle [33]. In patients with myocardial edema, the investigator recorded the number of myocardial segments with edema. The investigator also classified each examination in terms of the presence or absence of intracavitary LV thrombus, pericardial effusion, and pleural effusion. Additionally, the radiologist classified each examination in terms of the presence of absence of systolic anterior motion (SAM) of the mitral valve. Furthermore, the radiologist assessed each examination for the presence of apical, midventricular, basal, or focal ballooning, indicating TS variants. Finally, the radiologist classified each patient in terms of the presence or absence of wall

motion abnormalities; in patients with wall motion abnormalities, the radiologist classified the predominant pattern as hypokinesia or akinesia.

LGE Evaluation

The previously noted investigator (R.C) and another investigator (A.P, a radiologist with 4 years of posttraining experience in cardiovascular imaging) independently reviewed the cardiac MRI examinations to classify each patient for the presence versus absence of LGE using a qualitative visual assessment; a positive classification required the visual presence of LGE on both short- and long-axis LGE images. The two investigators discussed discrepancies to reach a consensus for the presence of LGE for each patient, for purposes of subsequent analyses.

For patients with LGE according to the consensus assessment, the first investigator recorded the number of myocardial segments with LGE; classified the involved segments as basal, mid, or apical (including the apical cap); recorded whether the involved segments showed transmural LGE; and recorded whether the involved segments showed wall motion abnormalities on cine images.

For patients with LGE according to the consensus assessment, the first investigator performed a quantitative assessment of LGE extent. The investigator first traced epicardial and endocardial contours of the LV on all slices on short-axis LGE images using the standardized American Heart Association 17-segment myocardial model [34]. Different semiautomated methods were then used to determine the quantification metrics. The investigator placed an ROI on a single slice on an area of myocardium remote to the region of LGE that did not show any visually apparent hyperenhancement, to serve as a reference region. The mean SI and SD of SI of the reference region were extracted. The software identified all LV pixels with a SI >2, >3, and >5 SD above the mean SI of the reference region, representing LGE extent according to the 2-SD, 3-SD, and 5-SD threshold methods, respectively. Additionally, the investigator placed an ROI on a single slice on the area of myocardium within the region of LGE that visually showed the maximum SI; the mean SI of this ROI was extracted as the peak SI of LGE [35][36]. The software identified all LV pixels with a SI exceeding half of the

peak SI, representing LGE extent according to the FWHM method. The investigator also performed a visual assessment of LGE extent by manually placing an ROI encompassing all pixels showing qualitative hyperenhancement on all slices on short-axis LGE images. For each quantification method, LGE extent was expressed both in absolute terms (i.e., grams) and in relative terms (i.e., as a percentage of LV myocardial mass). **Figure 2** depicts the quantification methods.

The same observer (R.C.) repeated the LGE quantification in a random subset of 20 patients with LGE after an interval of 6 weeks. The previously noted second investigator (A.P.) independently performed the LGE quantification in those same 20 patients without access to the first investigator's quantification results. These analyses in the random subset were used purely to assess intraobserver and interobserver agreement of the quantification metrics.

In-Hospital Adverse Events

The registry was reviewed to classify patients in terms of the presence versus absence of a composite endpoint of in-hospital adverse events during the hospital admission for the TS presentation. These adverse events included death or major cardiac or cerebrovascular events, in turn including pulmonary edema, arrhythmia, cardiogenic shock, ischemic stroke, and transient ischemic attack. Pulmonary edema was defined as the presence of respiratory distress and pulmonary rales in combination with pulmonary congestion, documented by chest radiography, respiratory failure (hypoxaemia-hypercapnia), tachypnoea (>25 breaths/min), or increased work of breathing [37]. Arrhythmia was defined as the presence of asystole, pulseless electrical activity, complete sinoatrial or atrioventricular block, new-onset atrial fibrillation, ventricular tachycardia, or ventricular fibrillation [38]. Cardiogenic shock was defined as a sustained systolic blood pressure below 90 mm Hg for at least 30 minutes or the need for vasopressors, inotropes, or mechanical circulatory support to maintain systolic blood pressure ≥90 mm Hg, accompanied by clinical signs of pulmonary congestion and impaired organ perfusion, the latter evidenced by at least one of the following: altered mental status; cold, clammy skin or extremities; oliguria (urine output ≤30

mL/hour); arterial lactate concentration ≥2 mmol/L (corresponding to ≥18 mg/dL)[39]. Stroke was defined as an ischemic cerebral infarction due to embolic or thrombotic occlusion of a major intracranial artery [40]. Transient ischemic attack was defined as the sudden onset of focal neurologic signs or symptoms that resolved within 24 hours [41].

Statistical Analysis

Normality of variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were summarized as mean ± SD or as median and IQR depending on their distribution; categorical variables were summarized as count with percentage. The time from presentation to cardiac MRI was compared between patients with and without an emotional trigger and between patients with and without a physical trigger. All study variables were compared between patients with and without LGE. Continuous variables were compared using the independent samples t test or the Mann-Whitney U test depending on their distribution; categorical variables were compared using the chi-square test or Fisher's exact test.

Univariable logistic regression analyses were performed to identify factors associated with the presence of LGE; tested factors included age, sex, hs-cTnT, cardiovascular risk factors, comorbidities, presenting symptoms, triggers, time to cardiac MRI, and the cardiac MRI features. Multivariable logistic regression analysis was then performed among variables showing statistically significant univariable associations. In the models, the number of segments involved by myocardial edema was classified as zero for patients without myocardial edema.

Intraobserver and interobserver agreement for the quantification metrics were assessed using the intraclass correlation coefficients (ICC) based on two-way models with absolute agreement, using mixed and random effects for intraobserver and interobserver agreement, respectively. An ICC ≥ 0.9 was considered to indicate excellent agreement. Spearman correlation coefficients were determined among pairwise combinations of LGE quantification metrics. Agreement between visually determined LGE extent and the other quantification metrics was assessed using Bland-Altman plots.

Patients with and without in-house adverse events were compared in terms of the presence of LGE and, in patients with LGE, in terms of the LGE quantification metrics. The presence of LGE was also compared between patients with and without the individual events contributing to the composite endpoint.

P values <.05 were considered statistically significant. Statistical analyses were performed using Python (version 3.10).

Results

Patients

The study sample of 370 patients included 338 women and 32 men. The patients had a mean age of 69.7±12.0 years. A total of 143 (42.2%) patients had an emotional trigger. The median interval from presentation to cardiac MRI was 5.0 days (IQR: 3-7 days) in patients with an emotional trigger versus 5.0 days (IQR: 3-7 days) in patients without an emotional trigger (p = .82). A total of 117 (35.0%) patients had a physical trigger. The median interval from presentation to cardiac MRI was 5.0 days (IQR: 3-7 days) in patients with a physical trigger versus 5.0 days (IQR: 3-7 days) in patients without a physical trigger (p=.53). A total of 290 (73%) patients showed wall motion abnormalities, including predominantly hypokinesia in 190 (65%) patients and predominantly akinesia in 100 (34%) patients.

Prevalence and Characteristics of LGE

Based on visual assessment, LGE was identified in 58 (15.7%) patients by investigator 1 and in 54 (14.5%) patients by investigator 2. Of four patients with a discrepancy, all had LGE based on consensus assessment. By the consensus assessment, LGE was identified in 58 (15.7%) patients.

The 58 patients showed LGE in a total of 319 myocardial segments (mean, 5.7 ± 2.5 segments per patient). Of the segments with LGE, eight were basal segments (in 1 patient), 107 were mid segments (in 18 patients), and 204 were apical segments (in 39 patients). All involved segments showed transmural LGE and had associated wall motion abnormalities.

Comparison of Patients Without and With LGE

Table 1 compares characteristics of patients without and with LGE. Patients with LGE, in comparison with those without LGE, were significantly older (72.8±9.1 vs 69.1±12.4 years, respectively; p=.01), had a significantly higher hs-cTnT (2715.9±3211.8 vs 1553.9±3185.6 ng/L, respectively; p=.02), had a significantly greater frequency of a physical trigger (34.0% vs 19.0%, respectively; p=.02), and had a significantly shorter interval from presentation to cardiac MRI (3.0 days [IQR 2.0, 5.0 days] vs 5.0 days [IQR 3.0, 8.0 days], respectively; p<.001). The two groups were not significantly different with respect to sex distribution, BMI, weight, height, other laboratory variables, cardiovascular risk factors, comorbidities, presenting symptoms, or presence of an emotional trigger (all p>.05).

Table 2 compares cardiac MRI findings between patients without and with LGE. Patients with versus without LGE showed a significantly smaller RV EDV (102.3 ± 30.4 vs 111.7 ± 34.7 mL, respectively; p=.04) significantly smaller RV ESV (49.9 ± 19.0 vs 56.0 ± 23.6 mL, respectively; p=.03), significantly greater frequency of myocardial edema (96.6% vs 69.6%, respectively; p<.001), and, among patients with myocardial edema, significantly greater number of segments with myocardial edema (6.7±2.7 vs 3.4±2.9, respectively; p<.001). The two groups were not significantly different with respect to other LV and RV function and volume

parameters; the frequency of SAM of the mitral valve; the frequency of TS variants; or the frequency of LV thrombus, pleural effusion, or pericardial effusion (all p>.05).

Factors Associated With LGE

Tables 3, 4, and **S2** present univariable and multivariable association with LGE. Factors showing significant univariable associations with LGE included older age (OR per year = 1.03, 95% CI: 1.00–1.06, p=.03), higher hs-cTnT level (OR per 300 pg/ml = 1.03, 95% CI: 1.00–1.05, p=.02), presence of a physical trigger (OR = 0.49, 95% CI: 0.25–0.96, p=.04), shorter time from symptom onset to cardiac MRI (OR per day = 0.80, 95% CI: 0.72–0.89, p<.001), presence of myocardia edema (OR = 12.07, 95% CI: 2.89–50.50, p<.001), a greater number of segments with myocardial edema (OR per segment = 1.48, 95% CI: 1.32–1.66, p<.001), and SAM of the mitral valve (OR = 2.34, 95% CI: 1.01–5.41, p=.046). In multivariable analysis, LGE showed significant independent associations with a shorter interval from presentation to cardiac MRI (OR per day = 0.82, 95% CI: 0.72–0.94, p=.004) and a greater number of segments with myocardial edema (OR per segment = 1.44, 95% CI: 1.27–1.64, p<.001).

LGE Quantification

All quantitative metrics of LGE extent demonstrated excellent intraobserver and interobserver agreement (**Table S3)**. **Table 5** provides summary values for the quantitative metrics among patients with LGE. In terms of relative measurements, the mean LGE extent was 26.8±12.0% for the 2-SD threshold method, 21.7±11.9% for the 3-SD threshold method, 12.2±11.1% for the 5-SD threshold method, 28.2±12.9% for the FWHM method, and 25.5±10.5% for the visual method. **Figure S1** shows correlations among pairwise combinations of quantification metrics. The correlation with visual LGE extent was strongest for the 2-SD threshold method in terms of both absolute extent (ρ=0.93) and relative extent (ρ=0.93). **Figure 3** shows results of the Bland–Altman analysis. The visual method showed the strongest agreement with the 2-SD

threshold and FWHM methods in terms of both absolute and relative differences. The 3-SD threshold and 5-SD threshold methods both underestimated the extent of LGE with respect to the visual method, with absolute and relative differences of -3.78 gm and -3.89%, respectively, for the 3-SD threshold method and of -12.30 gm and -13.31%, respectively, for the 5-SD threshold method.

In-Hospital Adverse Events

In-hospital adverse events occurred in 88 (23.8%) patients, including five with death, 27 with arrhythmia, 43 with pulmonary edema, 11 with cardiogenic shock, one with ischemic stroke, and one with transient ischemic attack. The frequency of in-hospital adverse events was not significantly different between patients with and without LGE (19.0% vs 24.7%, respectively; p=.44). The two groups also did not show significant differences in terms of the frequencies of any of the composite outcome components (all p>.05; formal comparison not performed for the two outcomes with a single occurrence) (**Table S4**). In patients with LGE, no quantitative measure of LGE extent showed a significant association with in-hospital adverse events (all p>.05) (**Table S5**).

Discussion

This nine-center registry study evaluated 370 patients with TS who underwent cardiac MRI after clinical presentation. The study had several major findings. First, LGE was observed in 15.7% of patients with TS. Second, the presence of LGE was independently associated with greater extent of myocardial edema and a shorter interval from presentation to cardiac MRI. Third, among the quantitative approaches for measuring LGE extent, the 2-SD threshold method showed the strongest correlation with visual LGE quantification. Finally, the presence and extent of LGE were not significantly associated with in-hospital adverse events.

LGE detection is mechanistically based on the differential distribution kinetics of GBCAs between normal and pathologically altered myocardium [15]. Extracellular GBCA does not cross intact cell membranes and typically distributes within the interstitial space, where it is rapidly

cleared via venous and lymphatic pathways [15]. In pathologic states, however, expansion of the extracellular space results in delayed GBCA washout and increased signal retention [15]. In TS, histologic studies have demonstrated upregulation of extracellular matrix proteins, particularly collagen-1 and fibronectin, suggesting a transient expansion of the extracellular compartment [27][28][42]. This increase in extracellular volume may alter GBCA kinetics, contributing to the LGE observed on cardiac MRI in patients with TS [43]. Postmortem findings further support this mechanism, with consistent reports of contraction band necrosis, interstitial edema, and mononuclear inflammatory infiltrates [27].

Quantification of LGE extent can vary substantially depending on the measurement method used, and consensus is lacking on the optimal quantification approach for use in TS. To our knowledge, this study is the first to evaluate different semiautomated techniques for LGE quantification specifically in patients with TS. Correlation with visual determination of LGE extent was greatest for the 2-SD threshold method, potentially supporting this method's use for standardized LGE quantification in TS in clinical practice. In contrast, an earlier study in hypertrophic cardiomyopathy observed greatest correlation with visual assessment using a 6-SD threshold method[44]suggesting a difference in LGE thresholding between TS and other cardiac pathologies [45][46][47]. This discrepancy may relate to the mild diffuse signal increase on LGE images that is characteristically observed in TS, reflecting transient myocardial edema rather than replacement fibrosis [28][42]. This enhancement pattern, with a mild SI increase, corresponds with the pharmacokinetics of GBCA in non-necrotic myocardium whereby temporary extracellular volume expansion leads to slower washout but limited GBCA accumulation [15]. In this low-contrast condition, a 2-SD cutoff preserves sensitivity for LGE, whereas the higher thresholds validated in conditions associated with dense focal fibrosis may miss subtle enhancement of TS and thus underestimate LGE extent. Additionally, the FWHM method yielded the highest LGE extent; this observation is counter to what has been observed in other conditions associated with cardiac fibrosis, where FWHM has generally underestimated LGE extent compared to SD-based threshold

methods [35][36]. This finding may reflect an additional unique aspect of the diffuse low-contrast LGE pattern of TS whereby the pixel-intensity histogram exhibits a shallow peak [28], [42]. In this context, the half-maximum threshold may fall below typical SI thresholds used for LGE quantification, thereby capturing peripheral or borderline-intensity pixels that would otherwise be excluded by stricter SD-based criteria.

The likelihood of LGE was significantly associated with a shorter interval from symptom onset to cardiac MRI. This finding is consistent with the transient time-dependent nature of LGE in TS, whereby patients imaged early after symptom onset are more likely to demonstrate reversible tissue changes and a delay until imaging introduces the possibility of missing LGE that had previously existed [25]. This temporal sensitivity is likely a primary contributor to the variability in reported LGE prevalence within the available literature. Data from patients who underwent longitudinal cardiac MRI examinations further support the predominantly transient nature of myocardial changes in TS; for example, Nakamora et al., reported complete disappearance of initially detected LGE after 12 months in five patients with TS and LGE [21].

In univariable analysis, a physical trigger was associated with a significantly lower frequency of LGE. This finding should be interpreted with caution and does not necessarily imply a lower degree of myocardial injury or a more benign clinical course in patients with a physical trigger. Indeed, TS triggered by physical stress has been consistently associated with worse short- and long-term outcomes [48]. Rather, the lower prevalence of LGE in patients with a physical trigger in the current analysis likely reflected the longer time from presentation to cardiac MRI in this group, providing time for resolution of LGE given the finding's transient nature. Patients exposed to physical triggers may be clinically unstable and thus unable to undergo cardiac MRI until a delayed time point, contributing to this timing difference. In multivariable analysis accounting for the time from presentation to cardiac MRI, a physical trigger was not independently associated with LGE.

In-hospital adverse events were not significantly associated with the presence or extent of LGE. This finding may reflect a selection bias in that patients with the most severe presentations of TS, and who were thus at greatest risk of complications, may have been too unstable to have undergone cardiac MRI and thus not been included in the study. This bias may have diluted or masked potential prognostic associations between LGE and adverse events.

In ischemic myocardial infarction, transmural LGE reflects irreversible myocyte necrosis and follows a coronary artery territory. In TS, transmural LGE may represent an overall homogeneous distribution of GBCA from endocardium to epicardium resulting from the previously noted transient extracellular matrix expansion and should not be interpreted as a marker of irreversible myocardial injury. Nonetheless, when cardiac MRI is performed early after symptom onset in patients with TS, LGE images can yield insights beyond that obtained from wall motion assessment on cine images alone. For example, transmural LGE spatially matching regional wall motion abnormalities provides complementary information regarding the distribution of myocardial tissue abnormalities and helps support the differential diagnosis among acute chest pain syndromes.

This study had limitations. First, the study was conducted retrospectively. Second, although the registry was multicenter in design, only 58 patients had LGE, limiting the stability of multivariable models and potentially reducing overall generalizability. Third, because of the study's cross-sectional nature with evaluation of cardiac MRI at a single time point, we could not explore the temporal dynamics of LGE disappearance or the evolution of LGE in relation to myocardial functional recovery. Fourth, we assessed potential associations of LGE with in-hospital adverse events; we did not explore associations with longer-term outcomes. Fifth, the evaluation of semiautomated LGE quantification methods used subjective visual assessment as the reference standard; an objective marker of myocardial tissue abnormalities, independent of MRI findings, was unavailable for this purpose. Sixth, due to the lack of both a histologic reference standard and long-term follow-up MRI data, we cannot exclude that the observed LGE in part reflected myocardial fibrosis or other irreversible injury rather than transient extracellular space expansion; this

possibility may be supported by the detection of regions of LGE meeting the more stringent criteria (i.e., the 5-SD threshold method) that required areas of LGE with relatively higher SI. Seventh, myocardial edema was assessed using conventional T2-weighted STIR sequences, which are limited by a relatively low SNR and susceptibility to motion and surface coil artifacts. Alternatively, quantitative T1 and T2 mapping could provide more robust and reproducible tissue characterization. Finally, this study did not assess potential impacts of the selection of MRI scanner, LGE sequence, or administered contrast agent on LGE quantification. These protocol elements serve as sources of variability in SI measurements and could thus alter semiautomated assessments based on SD thresholds or peak voxel values. To address the various identified study limitations, future investigations in patients with TS could prospectively perform longitudinal standardized cardiac MRI examinations with longer-term clinical follow-up, including a broader range of outcome measures, after patients' acute presentation.

Conclusion

In a multicenter registry, LGE was identified on initial cardiac MRI in 15.7% of patients with TS. LGE showed significant independent associations with greater myocardial edema extent and earlier timing of MRI after clinical presentation but was not associated with in-hospital adverse events. The 2-SD threshold method for quantifying LGE extent demonstrated the strongest agreement with visual assessment of LGE extent. These results may provide useful context when radiologists encounter LGE on cardiac MRI in patients with TS.

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Tables

Table 1: Summary of study characteristics in all patients and in patients stratified by presence versus absence of LGE

Variable	All Patients (n=370)	Patients Without LGE (n=312)	Patients With LGE (n=58)	P
Age (y), mean ± SD	69.7 ± 12.0	69.1 ± 12.4	72.8 ± 9.1	.01
Sex				>.99
Female, n (%)	338 (91.4)	285 (91.3)	53 (91.4)	
Male,	32 (11.6)	27 (8.7)	5 (8.6)	
BMI, mean ± SD	25.0 ± 4.6	25.1 ± 4.5	24.8 ± 4.8	.71
Weight (kg), mean ± SD	66.2 ± 12.3	66.3 ± 12.3	65.4 ± 12.0	.64
Height (cm), mean ± SD	162.7 ± 7.4	162.6 ± 7.3	162.8 ± 7.9	.89
Laboratory data				
hs-cTnT, mean ± SD	1763.1 ± 3216.2	1553.9 ± 3185.6	2715.9 ± 3211.8	.02
hs-cTnI, mean ± SD	4.2 ± 5.3	3.9 ± 5.3	8.3 ± 4.5	.14
proBNP at admission, mean ± SD	5896.5 ± 9574.3	6183.5 ± 10242.2	4488.5 ± 5055.3	.17
proBNP at discharge, mean ± SD	2894.9 ± 5231.4	3035.1 ± 5782.8	2364.2 ± 2096.4	.33
Cardiovascular risk factors				
Hypertension, n (%)	230 (62.8)	191 (61.6)	39 (69.6)	.32
Dyslipidemia, n (%)	184 (50.3)	151 (48.7)	33 (58.9)	.21
Obesity, n (%)	45 (12.4)	39 (12.7)	6 (10.7)	.85
Smoking history, n (%)	62 (16.9)	55 (17.7)	7 (12.5)	.63
Diabetes, n (%)	50 (13.7)	45 (14.5)	5 (8.9)	.36
CAD, n (%)	50 (13.7)	45 (14.6)	5 (8.9)	.36
Comorbilities				
COPD, n (%)	31 (8.5)	26 (8.5)	5 (8.9)	.80
Malignancy, n (%)	64 (17.6)	53 (17.3)	11 (19.6)	.81
Neurologic disease, n (%)	36 (9.9)	29 (9.4)	7 (12.5)	.65
Psychiatric disesase, n (%)	44 (12.2)	34 (11.1)	10 (17.9)	.23
Presnting symptoms				
Typical chest pain, n (%)	216 (60.7)	176 (58.7)	40 (71.4)	.10
Dyspnea, n (%)	125 (35.9)	104 (35.5)	21 (38.2)	.82
Triggers				
Emotional trigger, n (%)	143 (42.2)	125 (44.0)	18 (32.7)	.16
Physical trigger, n (%)	117 (35.0)	106 (38.0)	11 (20.0)	.02
Time from presentation to cardiac MRI (days), median [IQR]	5.0 [3.0, 7.0]	5.0 [3.0, 8.0]	3.0 [2.0, 5.0]	<.001

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; hs-cTnT, high-sensitivity cardiac troponin-T; hs-cTnI, high-sensitivity cardiac troponin-T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LGE, late gadolinium enhancement

Table 2: Summary of cardiac MRI findings in all patients and in patients stratified by presence versus absence of LGE

Variable	All Patients (n=370)	Patients Without LGE (n=312)	Patients With (n=58)	P
LV and RV volumetric and functional parameters				
LV EF (%), mean ± SD	47.7 ± 12.0	48.0 ± 12.3	45.9 ± 10.7	.18
LV EDV (ml), mean ± SD	129.8 ± 43.2	131.0 ± 44.5	123.4 ± 35.4	.16
LV ESV (ml), mean ± SD	68.9 ± 31.4	69.5 ± 32.6	65.8 ± 24.1	.32
LV SV (ml), mean ± SD	60.9 ± 22.6	61.5 ± 22.7	57.5 ± 21.6	.20
RV EF (%), mean ± SD	50.9 ± 11.7	50.7 ± 12.0	51.9 ± 9.9	.44
RV EDV (ml), mean ± SD	110.2 ± 34.2	111.7 ± 34.7	102.3 ± 30.4	.04
RV ESV (ml , mean ± SD	55.0 ± 23.0	56.0 ± 23.6	49.9 ± 19.0	.03
RV SV (ml), mean ± SD	56.5 ± 21.4	57.1 ± 21.7	53.0 ± 19.1	.15
Myocardial edema (presence), n (%)	271 (73.2)	215 (68.9)	56 (96.5)	<.001
Myocardial edema (segments involved)[a], mean ± SD	3.9 ± 3.1	3.4 ± 2.9	6.7 ± 2.7	<.001
SAM of mitral valve, n (%)	17 (4.6)	12 (3.8)	5 (8.6)	.07
TS variants				
Apical ballooning, n (%)	282 (76.8)	235 (75.8)	47 (82.5)	.36
Midventricular ballooning, n (%)	51 (13.9)	47 (15.2)	4 (7.0)	.15
Basal ballooning, n (%)	13 (3.6)	12 (3.9)	1 (1.8)	.70
Focal Balloning, n (%)	26 (7.1)	22 (7.1)	4 (6.9)	.99
LV thrombus, n (%)	7 (1.9)	5 (1.6)	2 (3.4)	.31
Pericardial effusion, n (%)	115 (31.1)	96 (30.7)	19 (32.7)	.91
Pleural effusion, n (%)	91 (24.6)	79 (25.3)	12 (20.7)	.54

EDV, end-diastolic volume; ESV, end-systolic volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, LV ejection fraction; RV, right ventricular; RVEF, RV ejection fraction; SV, stroke volume; TS, Takotsubo syndrome; SAM, systolic anterior motion

[a]Summarized among patients with myocardial edema

Table 3: Summary of variables showing significant univariable associations with presence of LGE. All univariable results shown in Table S2.

Variable	OR	95% CI	p
Age (per year)	1.03	1.00, 1.06	.03
hs-cTnT (per 300 pg/ml)	1.0001	1.00, 1.05	.02
Physical trigger (present)	0.49	0.25, 0.96	.04
Time to cardiac MRI (per day)	0.80	0.72, 0.89	<.001
Myocardial edema (present)	12.07	2.89, 50.50	<.001
Myocardial edema (segments involved)	1.48	1.32, 1.66	<.001
SAM of mitral valve (present)	2.34	1.01, 5.41	.046

LGE, late gadolinium enhancement; hs-cTnT, high-sensitivity cardiac troponin-T; SAM, systolic anterior motion

Table 4: Results of multivariable logistic regression model to identify associations with LGE, among factors showing significant independent associations.

Variable	OR	95% CI	p
Age (per year)	1.03	0.99, 1.06	.10
hs-cTnT (per 300 pg/ml)	1.01	0.99, 1.0	.30
Physical trigger (present)	0.62	0.29, 1.34d	.20
Time to cardiac MRI (per day)	0.82	0.72, 0.94	.004
Myocardial edema (segments involved)	1.44	1.27, 1.64	<.001
SAM of mitral valve (present)	2.36	0.89, 6.23	.08

SAM, systolic anterior motion; hs-cTnT, high-sensitivity cardiac troponin-T; LGE, late gadolinium enhancement

Table 5: Summary of Measurements of LGE Extent, Including Semiquantitative and Visual Methods

Method	Extent (Mean ± SD)
2-SD threshold	
Absolute (gm)	24.6 ± 12.0
Relative (%)	26.8 ± 12.0
3-SD threshold	
Absolute (gm)	19.7 ± 10.8
Relative (%)	21.7 ± 11.9
5-SD threshold	
Absolute (gm)	11.2 ± 9.2
Relative (%)Relative (%)	12.2 ± 11.1
FWHM	
Absolute (gm)	26.1 ± 14.6
Relative (%)Relative (%)	28.2 ± 12.9
Visual	
Absolute (gm)	23.5 ± 10.6
Relative (%)	25.5 ± 10.5

Data are presented only for patients with LGE.
FWHM, full width at half maximum; LGE, late gadolinium enhancement.

Figures Legends

Figure 1: Flowchart of patient selection. TS = Takotsubo syndrome. LGE = late gadolinium enhancement.

Figure 2: Various methods for quantification of extent of late gadolinium enhancement (LGE) in 67-year-old patient with Takotsubo syndrome. (A) Axial short-axis LGE image at mid-ventricular level shows faint transmural delayed enhancement involving anterior, anteroseptal, inferoseptal, and inferior segments . (B-F) Axial images (same underlying slice as in A) show quantification of LGE extent by 2-SD threshold method (B), 3-SD threshold method (C), 5-SD threshold method (D), full-width half maximum method (E), and visual method (F). In each image, red contour delineates endocardial border, and green contour delineates epicardial border. Orange-shaded pixels indicate pixels included in quantification of LGE extent for each method. For 2-SD, 3-SD, and 5-SD threshold methods, blue contour indicates ROI drawn in remote myocardium without visually apparent hyperenhancement to define reference myocardium. For FWH) method, purple contour indicates ROI placed within area of maximum signal intensity in region of LGE to define peak signal. For SD-based threshold and FWHM methods, semiautomated technique quantified LGE extent (orange-shaded pixels) based on ROI-derived information. For visual method, radiologist manually identified LGE extent (orange-shaded pixels).

Figure 3: Bland-Altman plots indicating agreement between visual method and other methods for quantification of LGE extent in patients with TS and LGE. In each plot, solid horizontal centerline indicates mean difference between methods (i.e., systematic bias), and dashed horizontal top and bottom lines indicate upper and lower 95% limits of agreement, respectively, between methods. (A-D) Plots for agreement between visual method and 2-SD threshold method (A), 3-SD threshold method (B), 5-SD threshold method (C), and FWHM method (D), based on absolute measurements in grams.

(E-H) Plots for agreement between visual method and 2-SD threshold method (E), 3-SD threshold method (F), 5-SD threshold method (G), and FWHM method (H), based on relative measurements (with respect to left ventricular mass) in percentages.

LGE = late gadolinium enhancement; TS = Takotsubo syndrome; FWHM = full-width half maximum