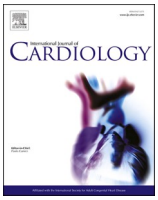
International Journal of Cardiology 419 (2025) 132716

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Cardiac magnetic resonance in patients with Takotsubo syndrome: Clinical correlates of T2 mapping

Luca Arcari [a,b,*], Giovanni Camastra [a], Federica Ciolina [c], Emanuela Belmonte [a], Domenico De Santis [d], Massimiliano Danti [c], Damiano Caruso [d], Viviana Maestrini [b], Francesco Santoro [e], Natale Daniele Brunetti [e], Andrea Laghi [d], Stefano Sbarbati [c], Luca Cacciotti [a]

[a] Cardiology Unit, Madre Giuseppina Vannini Hospital, Rome, Italy
[b] Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University, Rome, Italy
[c] Radiology Unit, Madre Giuseppina Vannini Hospital, Rome, Italy
[d] Department of Medical-Surgical Sciences and Translational Medicine, Radiology Unit, Sant'Andrea University Hospital, Sapienza University of Rome, Via Di Grottarossa, 1035-1039, 00189 Rome, Italy
[e] Department of Medical and Surgical Sciences, Università degli Studi di Foggia, Foggia, Italy

ARTICLE INFO

Keywords:
Myocardial edema
T2 mapping
Takotsubo
GEIST score
Cardiac magnetic resonance imaging

ABSTRACT

Background: Extensive myocardial edema is a key feature of acute takotsubo syndrome (TTS) and it can be quantitatively assessed by T2 mapping cardiac magnetic resonance (CMR) imaging. Clinical correlates of myocardial edema in TTS are not well characterized.
Methods: Sixty patients with acute TTS underwent CMR with T2 mapping within one week of hospitalization. Disease severity was assessed by a validated risk score (GEIST-score).
Results: Mean age of the study population was 71 ± 12 years (92 % females). Mean mid-septal T2 time was 58 ± 6 ms. Higher T2 mapping values were found in patients with left ventricular ejection fraction (LVEF) ≤40 % (60 ± 6 ms vs 56 ± 5 ms; $p = 0.006$), male sex (66 ± 7 ms vs 58 ± 6 ms; $p = 0.010$), dyspnea on admission (63 ± 7 ms vs 58 ± 6 ms; $p = 0.006$), absence of an emotional trigger (60 ± 7 ms vs 57 ± 5 ms; $p = 0.039$), intermediate-to-severe GEIST-score (63 ± 7 ms vs 58 ± 6 ms; $p = 0.045$) and in-hospital complications (61 ± 1 ms vs 58 ± 6 ms; $p = 0.009$). A trend towards higher values was observed in patients who died at follow-up (62 ± 8 ms vs 58 ± 6 ms; $p = 0.098$). On linear regression analysis, T2 mapping did not correlate with the timing of CMR (Beta −0.182, $p = 0.170$), whereas after multivariable correction, lack of emotional trigger (Beta 0.262, $p = 0.031$), decreasing LVEF (Beta −0.254, $p = 0.024$) and increasing GEIST score (Beta 0.282, $p = 0.024$) remained independently associated with T2 mapping.
Conclusions: In patients with acute TTS undergoing a timely CMR within the first week after admission, T2 mapping was not affected by timing of the examination, was higher in patients displaying high-risk features, and independently associated with the GEIST risk score.

1. Introduction

Takotsubo syndrome (TTS) is an acute heart failure condition characterized by a transient impairment of left ventricular (LV) systolic function and substantial risk of in-hospital and long-term adverse outcomes [1]. In the acute phase, myocardial tissue changes include widespread myocardial edema and extracellular volume expansion [2], conditioning transient LV hypertrophy [3], marking a peculiar systemic and local inflammation with monocyte infiltration [4,5]. Cardiac magnetic resonance (CMR) imaging is a central diagnostic modality in patients with TTS [6] since it can accurately measure left and right ventricular function and identify myocardial edema and scar to inform about differential diagnosis [7] and risk stratification [8]. T2-STIR sequences have been classically employed to assess myocardial edema. However, they are affected by several limitations, including their assessment, which is visually qualitative or no more than semi-

* Corresponding author at: Cardiology Unit, Madre Giuseppina Vannini Hospital, Via Di Acqua Bullicante 4, 00177 Rome, Italy.
E-mail address: luca.arcari@uniroma1.it (L. Arcari).

https://doi.org/10.1016/j.ijcard.2024.132716
Received 2 August 2024; Received in revised form 25 October 2024; Accepted 4 November 2024
Available online 10 November 2024

quantitative [9]. More recently, T2 mapping CMR has enabled a quantitative analysis of myocardial edema [10]. This technique has been validated in vivo against the histologic assessment of myocardial water content [11]and, when implemented at the clinical level, offers a higher accuracy for the detection of myocardial inflammation as compared to less recent approaches [12]. Previous studies using T2 mapping imaging in TTS described the relationship between the distribution and intensity of myocardial edema to cardiac function and electrocardiographic changes [2,13,14] as well as to the timing of myocardial systolic dysfunction recovery [13], with mid-septal T2 mapping values reliably representing a proxy of the global burden of myocardial edema [2]. However, clinical characteristics associated with myocardial edema intensity and as to whether this relates to the overall severity of the disease remain unknown. The aim of the present study is to describe clinical correlates including in-hospital and long-term outcomes of CMR T2 mapping findings in patients with acute TTS.

2. Methods

2.1. Study population

This is a single-center observational study. Patients have been enrolled prospectively since the establishment of T1 and T2 mapping sequences at our Institution (October 2019 onward). All patients provided informed consent for the use of their data for research purposes, and the study complied with the Declaration of Helsinki. We analyzed data from consecutively hospitalized TTS patients who underwent a clinically indicated [15] and timely CMR examination with T2 mapping within one week from symptoms onset. Hospital admission was selected as a reference time as it was more reliable to be determined, since symptoms in TTS might be atypical or even absent in some cases. TTS diagnosis was established in the presence of i) transient regional wall motion abnormalities of the left or right ventricle extending beyond a single epicardial vascular distribution; ii) absence of culprit coronary artery disease; iii) transient ECG abnormalities; iv) rise of cardiac troponin and serum natriuretic peptide levels; and v) proof of recovery of left ventricular ejection fraction at follow-up in all surviving patients. The evaluation of patients and subsequent inclusion in the study was performed only after all diagnostic criteria were met. All patients underwent ECG and echocardiography on admission and coronary angiograms during in-hospital stay to exclude coronary artery disease and culprit coronary plaque. Based on the wall motion abnormalities detected on admission echocardiography, ballooning patterns were categorized as typical (apical) or atypical (mid-ventricular, basal, and focal) [16]. The kind of trigger preceding the acute event, if present, was reported and defined as emotional or physical [17]. Disease severity was assessed by using the GEIST score [18], calculated by assigning 20 points each for male sex and neurologic comorbidity, 30 points for the presence of right ventricular (RV) involvement, and then subtracting the value of 1-(left ventricular ejection fraction (LVEF)). In-hospital complications were defined as previously reported [19] and included the occurrence of pulmonary edema, major arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes, or any arrhythmias associated with hemodynamic instability needing electric cardioversion), and cardiogenic shock. Follow-up was performed within our institutional dedicated outpatient clinic according to an established and previously described protocol [20]. Briefly, patients were evaluated after 1 and 3 to 6 months after the acute event with serial ECG and echocardiography until detection of full recovery; annual follow-up is offered to high-risk patients whereas phone calls are used to update long-term outcomes in the others. None of the patients within our sample was included in the derivation or validation cohorts from the original GEIST risk-score study.

2.2. Cardiac magnetic resonance imaging

All examinations were performed on a 1.5 Tesla scanner (Magnetom Aera, Siemens Healthcare, Germany) with a similar acquisition protocol. For cine imaging, a balanced steady-state free precession sequence was used in combination with parallel imaging (GRAPPA, factor 2) and retrospective gating during expiratory breath-hold (TE/TR/flip-angle: 1.16 ms/ 44.80 ms/71°, spatial resolution 1.5 × 1.5 × 8 mm) as a gapless short axis (SAX) stack for assessment of cardiac volumes and function and single slice long-axis view (2-chamber, 3-chamber, and 4-chamber view). Calculation of left and right ventricular volumes and function was performed offline with commercially available software. A modified Look-Locker inversion recovery (MOLLI) was used for T1 mapping and performed in three midventricular SAX slices and one 4-chamber view at mid-diastole prior to and 20 min after contrast administration (0,1 mmol/Kg body weight of gadoteric acid (Claricyclic, GE)) for the assessment of native and post-contrast T1 values, respectively. Sequence parameters were set as follows: TE/TR/flip angle: 1.8 ms/306.20 ms/35°, acquired voxel size 1.6 × 1.6 × 8 mm and base resolution 256, 8 images corresponding to different inversion times, MOLLI scheme 5(3)3. For T2 mapping, we employed a T2-prepared steady-state free precession pulse sequence [21]: a T2-prepared steady-state free precession sequence was used to generate three T2W images with different T2 preparation times (0 ms, 25 ms, 55 ms) (Fig. 1). Late gadolinium enhancement (LGE) imaging was performed using gapless whole heart coverage of SAX slices and three long-axis (2-chamber, 3-chamber and 4-chamber view) 15 min after contrast media administration using a mid-diastolic inversion prepared 2-dimensional gradient echo sequence (TE/TR/flip-angle 3.19 ms/635 ms/25°, acquired voxel size 1.5 × 1.5x8mm) with an individually adapted prepulse delay to achieve optimally nulled myocardium.

2.3. Image analysis

All observers were board-certified cardiologists or radiologists, holding established experience and accreditation of CMR competencies. LV and RV volumes, LVEF, and RVEF, were calculated from the short-axis cine sequences. T1 mapping and T2 mapping values were assessed directly on the scanner through the vendor platform; areas of LGE were excluded from regions of interest to avoid the inclusion of any replacement scars. A standardized approach to T1 and T2 mapping measurement after acquisition was adopted by drawing a region of interest (ROI) within the mid-septal LV region (Fig. 2, **Panel A**); this methodology grants higher reproducibility [22], is indicated by consensus documents [23,24] and in the specific setting of TTS we previously demonstrated to be comparable to a single slice or global assessment [2]. Hence, we considered the mid-septal T2 mapping value as a proxy of global myocardial edema extent. The n-center normal value for mid-septal T2 mapping is 46 ± 2 ms, with an upper limit of normal range < 50 ms (mean value +2SD).

2.4. Statistical analysis

Continuous variables were presented as mean ± standard deviation if normally distributed by visual inspection of distribution curves or as median and interquartile range if non-normally distributed. Comparisons were made by using the Student's *t*-test or Mann-Whitney *U* test, as appropriate. Univariable and stepwise multivariable linear regression analysis was used to assess factors associated with mid-septal T2 mapping; all variables with a *p*-value <0.1 at univariable analysis, plus those with biological relevance, including age, sex, and time from admission to CMR were included in the multivariable model. A two-tailed p-value <0.05 was considered statistically significant. All tests were performed using SPSS version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

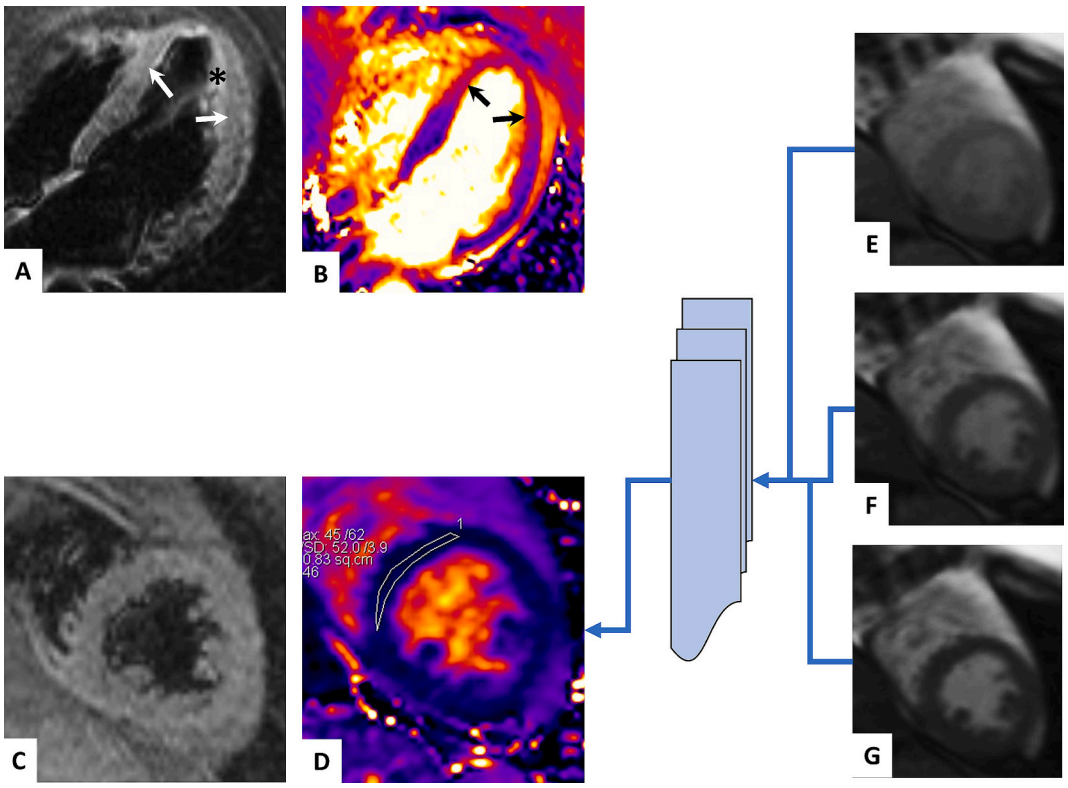


Fig. 1. long-axis 4-chamber view in T2-STIR (A) and T2 mapping (B) imaging. Qualitative visual evaluation reveals high signal intensity consistent with mid-apical edema (arrows in A and B); T2-STIR sequences are characterized by low signal-to-noise ratio, asterisk in (A) indicates slow flow artifact. Short-axis at mid left ventricular level in T2-STIR (C) and T2 mapping (D). T2 mapping allows parametric evaluation and quantification of edema (52 msec, in-center normal value <50 msec). Color-coded T2 mapping images are derived from 3 raw images with different echo times, acquiredduring a single breath-hold (E, F and G) and then merged into a single recontructed image (D).

3. Results

3.1. Patients' characteristics

The population consisted of 60 patients; the mean age was 71 ± 12 years, and most of them (55/60, 92 %) were females. Clinical, demographics and CMR data are summarized in Table 1, respectively. Neurologic comorbidities affected 8 (13 %) patients. Symptoms at presentation included chest pain in 35 (58 %) and dyspnea in 9 (15 %) patients, respectively. An identifiable trigger was detected in 50 (83 %) patients, emotional in 33 (55 %), and physical in 17 (28 %). Mean LVEF on echocardiography at hospital admission was 39 ± 9 %, apical ballooning was present in 42 (70 %), and atypical patterns in 18 (30 %). Median GEIST score was 0 (interquartile range − 1, 19). In-hospital complications occurred in 5 patients (8 %), and no in-hospital deaths were observed. At long-term follow-up, 6 deaths were recorded. CMR was performed at a median of 3 (interquartile range 2, 5) days after symptoms onset. Mean LVEF at CMR was 48 ± 10 %, with a significant improvement as compared with admission value ($p < 0.01$). Mean mid-septal native T1 and T2 mapping were 1139 ± 81 ms and 58 ± 6 ms, respectively. Mid-septal native T1 and T2 displayed an increase >4 SD in 63 % and 50 % of patients, respectively.

3.2. Factors associated with myocardial edema

Mid-septal T2 mapping (Fig. 2, **Panel B**) was higher in patients with LVEF ≤40 % (60 ± 6 vs 56 ± 5; $p = 0.006$), in males (66 ± 7 vs 58 ± 6; $p = 0.010$), in patients with dyspnea on admission (63 ± 7 vs 58 ± 6; p = 0.006), in the absence of an emotional trigger (60 ± 7 vs 57 ± 5; $p = 0.039$), in patients with in-hospital complications (61 ± 1 vs 58 ± 6; $p = 0.009$), and in patients with intermediate-to-severe [7] GEIST score (63 ± 7 vs 58 ± 6; $p = 0.045$) (panel B). A trend towards higher values was observed in patients with RV involvement (63 ± 7 vs 58 ± 6; $p = 0.096$) and neurologic comorbidity (62 ± 9 vs 58 ± 5; $p = 0.071$) as well as in those who experienced death after hospital discharge (62 ± 8 vs 58 ± 6; $p = 0.098$). Linear regression analysis for prediction of mid-septal T2 mapping is reported in Table 2. Factors associated with T2 mapping included male sex (β0.331, $p = 0.010$), absence of emotional trigger (β0.267, $p = 0.039$), dyspnea (β0.299, $p = 0.020$), admission LVEF (β-0.307, $p = 0.017$) and GEIST score (β0.356, $p = 0.005$). No relevant association was found regarding time from admission to CMR and T2 mapping (β −0.182, $p = 0.170$). On multivariable analysis, the absence of emotional trigger (β 0.262, $p = 0.031$), decreasing LVEF (β −0.254, $p = 0.024$), and increasing GEIST score (β 0.282, p = 0.024) remained independently associated with T2 mapping.

4. Discussion

In the present study, we report on the largest sample to date investigating CMR T2 mapping findings in acute TTS. We found that the intensity of myocardial edema varies according to several patients' characteristics - increasing with high-risk features such as dyspnea [25], male sex [26], low LVEF [27], and absence of an emotional trigger [17] - and independently associates with the overall disease severity as measured by the GEIST risk-score.

Myocardial edema is a key pathogenic change in acute TTS [6], and our finding that all patients had positive mid-septal T2 values is consistent with this notion. T2 mapping values that we found were, on average, >4 SD over the upper range of in-center normality, indicating a relevant increase in myocardial water content. Though comparison between populations imaged with different machines and sequences is often unreliable, the use of z-scores and increase of SD in addition to the

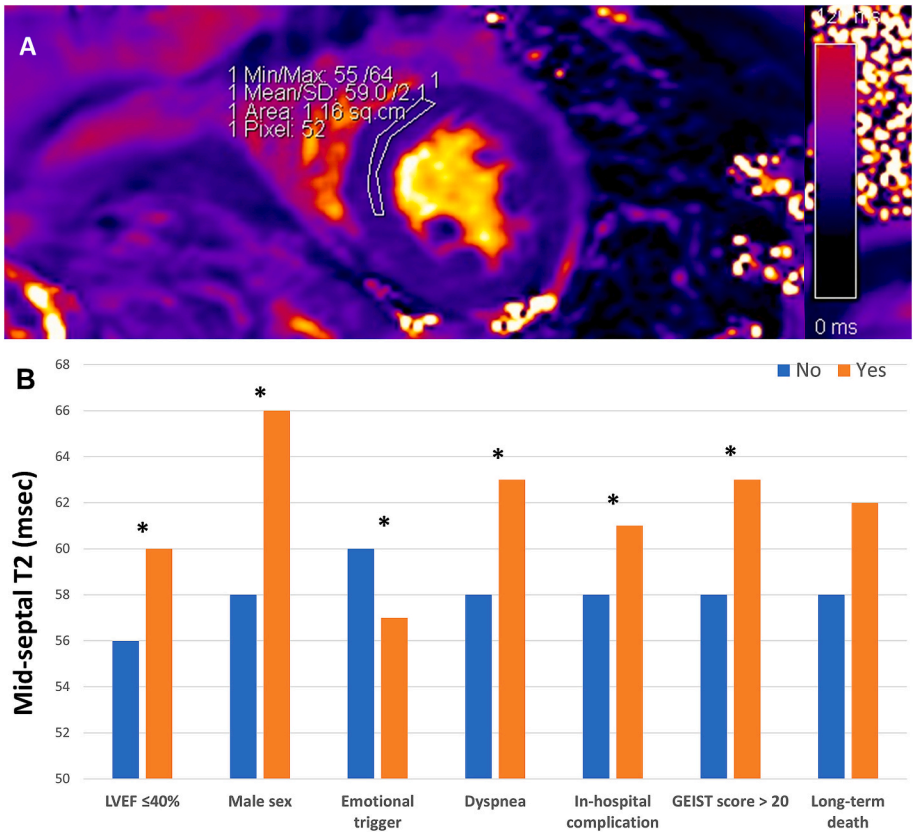


Fig. 2. depiction of the standardized approach to T2 mapping measurement after acquisition by drawing a region of interest (ROI) within the mid-septal LV region (**Panel A**). Histograms describing the LV mid-septal T2 mapping values in the study subgroups **(Panel B)** asterisks indicate $p < 0.05$.

absolute value allows paired evaluation of studies using different MRI equipment [28]. In patients with myocarditis, the share of those having such an increase in T2 mapping is lower [29], suggesting that in TTS myocardial edema could be more represented and potentially aid differential diagnosis as reported by Cau et al. [30].

The use of T2 mapping, a validated [31] quantitative method to assess the myocardial water content, and the relatively large size of our population enabled us to describe factors that could be associated with the intensity of edema. We found a relevant increase of native T1 too, consistently with this measure being a non-specific readout of several myocardial pathology, including edema [32]. Indeed, it can be found with an increase parallel to T2 mapping in those conditions characterized by increased myocardial water content [2,33,34]. In patients who underwent a timely CMR scan within one week from hospital admission, we found no significant relationship between the timing of the imaging assessment and T2 mapping, implying that myocardial edema could be relatively stable within this time frame. However, the presence of non-linear relationships that were missed in our sample, in which most patients underwent CMR more than 48 h after presentation cannot be excluded. A bimodal evolution of myocardial edema with dynamic changes especially on the first day has been described after acute myocardial infarction [35], though this fact seemed not to have a relevant impact at clinical level [36]. Both the extent and distribution of myocardial water content in TTS relate to ECG changes [2,37], including T-wave inversion and repolarization abnormalities that interestingly follow a bimodal pattern in the acute phase [38]. Whether these electrocardiographic changes are signs of fluctuating myocardial edema within the first days of TTS onset has to be clarified.

The reasons why some subgroups of patients experience a larger edema burden than others remain speculative; however, some hypotheses could be drawn from the present study. The association of increased myocardial T2 time with poorer cardiac function in TTS has been previously described multiple times [2,13,14], though it still remains unclear as to whether edema is a contributing factor [39] or just a consequence of myocardial dysfunction and stretching. Locally increased adrenergic drive represents an important physiopathological step for the disease onset [40,41], and it has been shown that this can be related to several factors. For example, patients with a physical trigger have higher norepinephrine levels than those without [42]. Men who develop TTS are characterized by larger impairment of cardiac function, worse outcomes [26], and more widespread contraction band necrosis [43], consistent with a larger catecholamine effect [44]. Our observation of higher T2 mapping levels in patients of male sex or without emotional triggers indicates that the extent of myocardial edema might be linked to the entity of adrenergic stimulation, leading to a higher degree of myocardial inflammation.

Finally, we compared the extent of myocardial edema with several prognostic factors and the GEIST severity score. This validated tool is derived from both cardiac and extracardiac variables and provides a comprehensive estimate of TTS severity in the setting of a disease that is characterized by recovery of LVEF after the acute phase and by an excess of both cardiovascular [45] and non-cardiovascular [46,47] long-term mortality. CMR can be used to assess several markers of adverse prognosis, including left and right ventricular function and atrial mechanics [48]. A CMR-based prognostic risk-score has been proposed [49], however, the absence of studies with large samples has prevented to date the validation of T2 mapping as a prognostic marker in TTS [50]. The independent association between mid-septal T2 values and the GEIST score points towards a potential prognostic relevance of this CMR measure. A trend towards higher T2 mapping values in patients who died at follow-up was observed as well, however, the low number of events prevented us from fully evaluating if the extent of myocardial edema can be considered a prognostic marker in TTS, as already demonstrated in other pathologies [51,52]. Altogether, the results of our

Table 1
clinical, demographics and CMR characteristics of the study population at baseline. Left ventricular ejection fraction (LVEF), angiotensin converting enzyme (ACE), angiotensin receptor blocker (ARB), angiotensin receptor neprilysin inhibitor (ARNI), sodium-glucose cotransporter-2 (SGLT-2). Left ventricle (LV), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), right ventricle (RV), RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV ejection fraction (RVEF), standard deviation (SD).

Variable	Value
Age (years)	71 ± 12
Male (%)	4 (7)
Comorbidities	
Hypertension (%)	41 (68)
Diabetes Mellitus (%)	5 (8)
Dyslipidemia (%)	23 (38)
Neurologic Disease (%)	8 (13)
Clinical presentation	
Chest Pain (%)	35 (58)
Dyspnea (%)	9 (15)
Stressful Trigger (%)	50 (83)
Emotional (%)	33 (55)
Physical (%)	17 (28)
Admission electrocardiographic findings	
ST-elevation (%)	20 (33)
T wave inversion (%)	29 (48)
Admission echocardiographic findings	
Apical Ballooning (%)	42 (70)
Admission echo LVEF (%)	39 ± 9
In-hospital therapy	
ACE-inhibitor/ARB (%)	50 (83)
Beta-blocker (%)	48 (80)
ARNI (%)	0 (0)
SGLT2-inhibitor (%)	0 (0)
Outcomes	
In-hospital complications (%)	5 (8)
Long-term death (%)	6 (10)
CMR findings	
Admission to CMR (days)	3 (2, 5)
LVEDV index (ml/m^2)	72 ± 17
LVESV index (ml/m^2)	38 ± 14
LVEF (%)	48 ± 10
LV mass index (g/m^2)	66 ± 16
RVEDV index (ml/m^2)	62 ± 15
RVESV index (ml/m^2)	28 ± 8
RVEF (%)	54 ± 8
Septal native T1 (ms)	1139 ± 81
Septal T1 > 4SD	38 (63)
Global native T1 (ms)	1107 ± 52
Septal T2 (ms)	58 ± 6
Septal T2 > 4SD	30 (50)
Global native T2 (ms)	56 ± 4

Table 2
Univariable and multivariable linear regression analysis results. Cardiac magnetic resonance (CMR), left ventricular ejection fraction (LVEF), right ventricle (RV), German Italian Spanish Takotsubo registry (GEIST). Bold indicates *p* value <0.05.

Variable	Univariable		Multivariable	
	Beta	P	Beta	P
Age	0.145	0.270	NS	NS
Sex (male)	0.331	**0.010**	NS	NS
Days to CMR	−0.182	0.170	NS	NS
Hypertension	−0.132	0.316	–	–
Diabetes	0.097	0.460	–	–
Neurologic comorbidity	0.235	0.071	NS	NS
Absence of Emotional Trigger	0.267	**0.039**	0.262	**0.031**
Dyspnea	0.299	**0.020**	NS	NS
LVEF (admission)	−0.307	**0.017**	−0.254	**0.024**
RV involvement	0.217	0.096	NS	NS
GEIST score	0.356	**0.005**	0.282	**0.024**

study bring some clinical implications. According to the European Society of Cardiology, CMR is a mandatory examination in patients with suspected TTS to confirm the etiology in patients with a working diagnosis of myocardial infarction with non-obstructed coronary arteries [15]. In this context, T2 mapping could be advised as a quick addition to the standard CMR protocol, useful to better stratify identify high-risk patients that could be considered for a more intensive and prolonged follow-up. Further studies with larger sample sizes and longer follow-ups are needed to clarify the prognostic relevance of T2 mapping in TTS.

4.1. Limitations

Some limitations apply to this study. The sample size is not powered for in-hospital and long-term outcome assessment. Furthermore, the low number of patients within certain subgroups, including patients of male sex, might have conditioned the lack of significance in the multivariable model. As previously noted [19], our population is characterized by low-risk features that might limit the generalizability of these findings.

5. Conclusions

In conclusion, we found that in patients with acute TTS undergoing a timely CMR in the first week after admission, the mid-septal T2 mapping was not affected by timing of the examination, was higher in patients displaying high-risk features and independently associated with the GEIST severity risk score. Larger studies are warranted to investigate the prognostic value of an early CMR with T2 mapping in patients hospitalized for TTS.

Funding

None.

CRediT authorship contribution statement

Luca Arcari: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giovanni Camastra:** Writing – review & editing, Methodology, Investigation, Data curation. **Federica Ciolina:** Writing – review & editing, Investigation, Data curation. **Emanuela Belmonte:** Writing – review & editing, Investigation. **Domenico De Santis:** Writing – original draft, Methodology. **Massimiliano Danti:** Writing – review & editing, Investigation. **Damiano Caruso:** Writing – review & editing, Validation, Methodology. **Viviana Maestrini:** Writing – review & editing, Supervision. **Francesco Santoro:** Writing – review & editing. **Natale Daniele Brunetti:** Writing – review & editing. **Andrea Laghi:** Writing – review & editing, Supervision. **Stefano Sbarbati:** Writing – review & editing, Supervision. **Luca Cacciotti:** Writing – review & editing, Supervision.

Declaration of competing interest

None declared.

References

[1] H. Medina de Chazal, M.G. Del Buono, L. Keyser-Marcus, L. Ma, F.G. Moeller, D. Berrocal, et al., Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review, J. Am. Coll. Cardiol. 72 (2018) 1955–1971, https://doi.org/10.1016/j.jacc.2018.07.072.

[2] L. Arcari, G. Camastra, F. Ciolina, L.R. Limite, M. Danti, M. Sclafani, et al., Myocardial oedema contributes to interstitial expansion and associates with mechanical and electrocardiographic changes in takotsubo syndrome: a CMR T1 and T2 mapping study, Eur. Heart J. Cardiovasc. Imaging (2023), https://doi.org/10.1093/EHJCI/JEAD035.

[3] C. Scally, W.K. Choo, A. Rudd, C. Neil, N. Siddiqi, A.M. Mezincescu, et al., The early dynamic of ECG in Takotsubo syndrome presenting with ST-elevation: a comparison with age and gender-matched ST-elevation myocardial infarction, Int. J. Cardiol. 320 (2020) 7–11, https://doi.org/10.1016/J.IJCARD.2020.07.025.

[4] C. Scally, H. Abbas, T. Ahearn, J. Srinivasan, A. Mezincescu, A. Rudd, et al., Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy, Circulation 139 (2019) 1581–1592, https://doi.org/10.1161/CIRCULATIONAHA.118.037975.
[5] F. Santoro, M.D. Costantino, F. Guastafierro, G. Triggiani, A. Ferraretti, N. Tarantino, et al., Inflammatory patterns in Takotsubo cardiomyopathy and acute coronary syndrome: a propensity score matched analysis, Atherosclerosis 274 (2018) 157–161, https://doi.org/10.1016/J.ATHEROSCLEROSIS.2018.05.017.
[6] I. Eitel, F. von Knobelsdorff-Brenkenhoff, P. Bernhardt, I. Carbone, K. Muellerleile, A. Aldrovandi, et al., Clinical characteristics and cardiovascular magnetic resonance findings in stress (Takotsubo) cardiomyopathy, JAMA 306 (2011) 277–286, https://doi.org/10.1001/jama.2011.992.
[7] B. Pathik, B. Raman, N.H. Mohd Amin, D. Mahadavan, S. Rajendran, A. D. McGavigan, et al., Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging, Eur. Heart J. Cardiovasc. Imaging 17 (2016) 1146–1152, https://doi.org/10.1093/ehjci/jev289.
[8] L. Arcari, L.R. Limite, C. Adduci, M. Sclafani, G. Tini, F. Palano, et al., Novel imaging and genetic risk markers in Takotsubo syndrome, Front. Cardiovasc. Med. 8 (2021) 948, https://doi.org/10.3389/FCVM.2021.703418/BIBTEX.
[9] H-Ici DO, J.P. Ridgway, T. Kuehne, F. Berger, S. Plein, M. Sivananthan, et al., Cardiovascular magnetic resonance of myocardial edema using a short inversion time inversion recovery (STIR) black-blood technique: diagnostic accuracy of visual and semi-quantitative assessment, J. Cardiovasc. Magn. Reson. (2012) 14, https://doi.org/10.1186/1532-429X-14-22.
[10] A.T. O'Brien, K.E. Gil, J. Varghese, O.P. Simonetti, K.M. Zareba, T2 mapping in myocardial disease: a comprehensive review, J. Cardiovasc. Magn. Reson. (2022) 24, https://doi.org/10.1186/S12968-022-00866-0.
[11] R. Fernández-Jiménez, J. Sánchez-González, J. Aguero, M. del Trigo, C. Galán-Arriola, V. Fuster, et al., Fast T2 gradient-spin-echo (T2-GraSE) mapping for myocardial edema quantification: first in vivo validation in a porcine model of ischemia/reperfusion, J. Cardiovasc. Magn. Reson. 171 (17) (2015) 1–9, https://doi.org/10.1186/S12968-015-0199-9.
[12] P. Thavendiranathan, M. Walls, S. Giri, D. Verhaert, S. Rajagopalan, S. Moore, et al., Improved detection of myocardial involvement in acute inflammatory cardiomyopathies using T2 mapping, Circ. Cardiovasc. Imag. 5 (2012) 102–110, https://doi.org/10.1161/CIRCIMAGING.111.967836.
[13] Y. Aikawa, T. Noguchi, Y. Morita, E. Tateishi, A. Kono, H. Miura, et al., Clinical impact of native T1 mapping for detecting myocardial impairment in takotsubo cardiomyopathy, Eur. Heart J. Cardiovasc. Imaging 20 (2019) 1147–1155, https://doi.org/10.1093/ehjci/jez034.
[14] L.S. Couch, K.E. Thomas, F. Marin, D. Terentes-Printzios, R.A. Kotronias, J. Chai, et al., The role of coronary blood flow and myocardial edema in the pathophysiology of Takotsubo syndrome, JACC Cardiovasc. Imaging (2024), https://doi.org/10.1016/J.JCMG.2024.02.017.
[15] R.A. Byrne, X. Rossello, J.J. Coughlan, E. Barbato, C. Berry, A. Chieffo, et al., ESC guidelines for the management of acute coronary syndromes, Eur. Heart J. 2023 (2023) 44, https://doi.org/10.1093/EURHEARTJ/EHAD191.
[16] C. Templin, J.R. Ghadri, J. Diekmann, L.C. Napp, D.R. Bataiosu, M. Jaguszewski, et al., Clinical features and outcomes of Takotsubo (stress) cardiomyopathy, N. Engl. J. Med. 373 (2015) 929–938, https://doi.org/10.1056/NEJMoa1406761.
[17] T. Pätz, F. Santoro, R. Cetera, I. Ragnatela, I. El-Battrawy, M. Mezger, et al., Trigger-associated clinical implications and outcomes in Takotsubo syndrome: results from the multicenter GEIST registry, J. Am. Heart Assoc. (2023) 12, https://doi.org/10.1161/JAHA.122.028511.
[18] F. Santoro, I.J. Núñez Gil, T. Stiermaier, I. El-Battrawy, F. Guerra, G. Novo, et al., Assessment of the German and Italian stress cardiomyopathy score for risk stratification for in-hospital complications in patients with Takotsubo syndrome, JAMA Cardiol. 4 (2019) 892, https://doi.org/10.1001/jamacardio.2019.2597.
[19] L. Arcari, L.R. Limite, L. Cacciotti, M. Sclafani, D. Russo, I. Passaseo, et al., Admission heart rate and in-hospital course of patients with Takotsubo syndrome, Int. J. Cardiol. (2018), https://doi.org/10.1016/j.ijcard.2018.07.145.
[20] M. Sclafani, L. Arcari, D. Russo, G. Tini, L.R. Limite, L. Cacciotti, et al., Long-term management of Takotsubo syndrome: a not-so-benign condition, Rev. Cardiovasc. Med. 22 (2021) 597, https://doi.org/10.31083/J.RCM2203071.
[21] S. Giri, Y.-C. Chung, A. Merchant, G. Mihai, S. Rajagopalan, S.V. Raman, et al., T2 quantification for improved detection of myocardial edema, J. Cardiovasc. Magn. Reson. 11 (2009) 56, https://doi.org/10.1186/1532-429X-11-56.
[22] D. Dabir, N. Child, A. Kalra, T. Rogers, R. Gebker, A. Jabbour, et al., Reference values for healthy human myocardium using a T1 mapping methodology: results from the international T1 multicenter cardiovascular magnetic resonance study, J. Cardiovasc. Magn. Reson. 16 (2014) 69, https://doi.org/10.1186/s12968-014-0069-x.
[23] V.O. Puntmann, S. Valbuena, R. Hinojar, S.E. Petersen, J.P. Greenwood, C. M. Kramer, et al., Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part i - analytical validation and clinical qualification, J. Cardiovasc. Magn. Reson. (2018) 20, https://doi.org/10.1186/s12968-018-0484-5.
[24] D.R. Messroghli, J.C. Moon, V.M. Ferreira, L. Grosse-Wortmann, T. He, P. Kellman, et al., Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI), J. Cardiovasc. Magn. Reson. 191 (19) (2017) 1–24, https://doi.org/10.1186/S12968-017-0389-8.
[25] L. Arcari, M.B. Musumeci, T. Stiermaier, I. El-Battrawy, C. Möller, F. Guerra, et al., Incidence, determinants and prognostic relevance of dyspnea at admission in patients with Takotsubo syndrome: results from the international multicenter GEIST registry, Sci. Rep. 10 (2020) 13603, https://doi.org/10.1038/s41598-020-70445-9.
[26] L. Arcari, I.J. Núñez-Gil, T. Stiermaier, I. El-Battrawy, F. Guerra, G. Novo, et al., Gender differences in Takotsubo syndrome, J. Am. Coll. Cardiol. 79 (2022) 2085–2093, https://doi.org/10.1016/J.JACC.2022.03.366.
[27] J.-R. Ghadri, I.S. Wittstein, A. Prasad, S. Sharkey, K. Dote, Y.J. Akashi, et al., International expert consensus document on Takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology, Eur. Heart J. 39 (2018) 2032–2046, https://doi.org/10.1093/eurheartj/ehy076.
[28] S. Razzaq, L. Haririsanati, K. Eyre, R. Garg, M. Chetrit, M.G. Friedrich, Inter-scanner comparability of Z-scores for native myocardial T1 and T2 mapping, J. Cardiovasc. Magn. Reson. (2024) 26, https://doi.org/10.1016/J.JOCMR.2023.100004.
[29] M. Spieker, S. Haberkorn, M. Gastl, P. Behm, S. Katsianos, P. Horn, et al., Abnormal T2 mapping cardiovascular magnetic resonance correlates with adverse clinical outcome in patients with suspected acute myocarditis, J. Cardiovasc. Magn. Reson. (2017) 19, https://doi.org/10.1186/S12968-017-0350-X.
[30] R. Cau, P. Bassareo, M. Deidda, G. Caredda, J.S. Suri, G. Pontone, et al., Could CMR tissue-tracking and parametric mapping distinguish between Takotsubo syndrome and acute myocarditis? A pilot study, Acad. Radiol. (0) (2021), https://doi.org/10.1016/j.acra.2021.01.009.
[31] R. Fernández-Jiménez, J. Sánchez-González, J. Aguero, M. Del Trigo, C. Galán-Arriola, V. Fuster, et al., Fast T2 gradient-spin-echo (T2-GraSE) mapping for myocardial edema quantification: first in vivo validation in a porcine model of ischemia/reperfusion, J. Cardiovasc. Magn. Reson. 17 (2015) 92, https://doi.org/10.1186/s12968-015-0199-9.
[32] V.O. Puntmann, E. Peker, Y. Chandrashekhar, E. Nagel, T1 mapping in characterizing myocardial disease, Circ. Res. 119 (2016) 277–299, https://doi.org/10.1161/CIRCRESAHA.116.307974.
[33] L. Arcari, R. Hinojar, J. Engel, T. Freiwald, S. Platschek, H. Zainal, et al., Native T1 and T2 provide distinctive signatures in hypertrophic cardiac conditions – comparison of uremic, hypertensive and hypertrophic cardiomyopathy, Int. J. Cardiol. (0) (2020), https://doi.org/10.1016/j.ijcard.2020.03.002.
[34] L. Arcari, J. Engel, T. Freiwald, H. Zhou, H. Zainal, M. Gawor, et al., Cardiac biomarkers in chronic kidney disease are independently associated with myocardial edema and diffuse fibrosis by cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 23 (2021) 71, https://doi.org/10.1186/s12968-021-00762-z.
[35] R. Fernández-Jiménez, M. Barreiro-Pérez, A. Martin-García, J. Sánchez-González, J. Agüero, C. Galán-Arriola, et al., Dynamic edematous response of the human heart to myocardial infarction, Circulation 136 (2017) 1288–1300, https://doi.org/10.1161/CIRCULATIONAHA.116.025582.
[36] T. Stiermaier, H. Thiele, I. Eitel, Early myocardial edema after acute myocardial infarction is stable and not bimodal in humans - evidence from a large CMR multicenter study, Int. J. Cardiol. 246 (2017) 87–89, https://doi.org/10.1016/j.ijcard.2017.05.064.
[37] F. Migliore, A. Zorzi, M.P. Marra, C. Basso, F. Corbetti, M. De Lazzari, et al., Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction, Heart Rhythm. 8 (2011) 1629–1634, https://doi.org/10.1016/j.hrthm.2011.04.035.
[38] W. Mitsuma, M. Kodama, M. Ito, K. Tanaka, T. Yanagawa, N. Ikarashi, et al., Serial electrocardiographic findings in women with Takotsubo cardiomyopathy, Am. J. Cardiol. 100 (2007) 106–109, https://doi.org/10.1016/j.amjcard.2007.02.062.
[39] R.M. Dongaonkar, R.H. Stewart, H.J. Geissler, G.A. Laine, Myocardial microvascular permeability, interstitial oedema, and compromised cardiac function, Cardiovasc. Res. 87 (2010) 331–339, https://doi.org/10.1093/cvr/cvq145.
[40] I.S. Wittstein, D.R. Thiemann, J.A.C. Lima, K.L. Baughman, S.P. Schulman, G. Gerstenblith, et al., Neurohumoral features of myocardial stunning due to sudden emotional stress, N. Engl. J. Med. 352 (2005) 539–548, https://doi.org/10.1056/NEJMoa043046.
[41] T. Kume, T. Kawamoto, H. Okura, E. Toyota, Y. Neishi, N. Watanabe, et al., Local release of catecholamines from the hearts of patients with tako-tsubo-like left ventricular dysfunction, Circ. J. 72 (2008) 106–108.
[42] Y. Sobue, E. Watanabe, T. Ichikawa, M. Koshikawa, M. Yamamoto, M. Harada, et al., Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality rate, Int. J. Cardiol. 235 (2017) 87–93, https://doi.org/10.1016/j.ijcard.2017.02.090.
[43] T. Murakami, T. Komiyama, S. Matsumoto, H. Kajiwara, H. Kobayashi, Y. Ikari, Examination of gender differences in patients with takotsubo syndrome according to left ventricular biopsy: two case reports, J. Med. Case Rep. 151 (15) (2021) 1–10, https://doi.org/10.1186/S13256-021-02856-9.
[44] I.S. Wittstein, Why sex matters in Takotsubo syndrome, J. Am. Coll. Cardiol. 79 (2022) 2094–2096, https://doi.org/10.1016/J.JACC.2022.04.005.
[45] E. Amelia, M.S. Rudd, P. Graham Horgan, M.B.C. Hilal Khan, T. David, M. Gamble, M. Jim McGowan, M. Arvind Sood, et al., Cardiovascular and non-cardiovascular prescribing and mortality after Takotsubo - comparison with myocardial infarction and general population, JACC Adv. (2023) 100797, https://doi.org/10.1016/J.JACADV.2023.100797.
[46] F. Scudiero, L. Arcari, L. Cacciotti, E. De Vito, R. Marcucci, I. Passaseo, et al., Prognostic relevance of GRACE risk score in Takotsubo syndrome, Eur Hear Journal Acute Cardiovasc Care (2019), https://doi.org/10.1177/2048872619882363, 2048872619882363.
[47] J.-L. Looi, T. Verryt, P. McLeod, C. Chan, J. Pemberton, M. Webster, et al., Type of stressor and medium-term outcomes after Takotsubo syndrome: what becomes of

the broken hearted? (ANZACS-QI 59), Heart Lung Circ. (2021), https://doi.org/10.1016/J.HLC.2021.09.021.

[48] R. Cau, A. Palmisano, J.S. Suri, F. Pisu, A. Esposito, L. Saba, Prognostic role of cardiovascular magnetic resonance in Takotsubo syndrome: a systematic review, Eur. J. Radiol. 177 (2024) 111576, https://doi.org/10.1016/J.EJRAD.2024.111576.

[49] A. Isaak, J. Bratz, D. Kravchenko, N. Mesropyan, I. Eckardt, L.M. Bischoff, et al., A novel and simple cardiac magnetic resonance score (PE2RT) predicts outcome in takotsubo syndrome, Eur. Radiol. 33 (2023) 5498–5508, https://doi.org/10.1007/S00330-023-09543-X.

[50] S. Humayra, N. Yahya, C.J. Ning, I.A. Mir, A.L. Mohamed, H.A. Manan, Systematic review of cardiovascular magnetic resonance imaging T1 and T2 mapping in patients with Takotsubo syndrome, Heliyon 10 (2024) e29755, https://doi.org/10.1016/j.heliyon.2024.e29755.

[51] Z. Xu, J. Wang, W. Cheng, K. Wan, W. Li, L. Pu, et al., Incremental significance of myocardial oedema for prognosis in hypertrophic cardiomyopathy, Eur. Hear J. Cardiovasc Imag. 24 (2023) 876–884, https://doi.org/10.1093/EHJCI/JEAD065.

[52] L. Bergamaschi, A. Landi, N. Maurizi, C. Pizzi, L.A. Leo, D. Arangalage, et al., Acute response of the noninfarcted myocardium and surrounding tissue assessed by T2 mapping after STEMI, Cardiovasc. Imag. (2024), https://doi.org/10.1016/J.JCMG.2023.11.014.