European Journal of Radiology 177 (2024) 111576

Contents lists available at ScienceDirect

European Journal of Radiology

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

Review

Prognostic role of cardiovascular magnetic resonance in Takotsubo syndrome: A systematic review

Riccardo Cau [a], Anna Palmisano [b,c], Jasjit S. Suri [d], Francesco Pisu [a], Antonio Esposito [b,c], Luca Saba [a,*]

[a] Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato s.s. 554 Monserrato, Cagliari 09045, Italy
[b] Clinical and Experimental Radiology Unit, Experimental Imaging Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[c] School of Medicine, Vita-Salute San Raffaele University, Via Olgettina 58–60 20132, Milan, Italy
[d] Stroke Diagnostic and Monitoring Division, Atheropoint, Roseville, CA, USA

ARTICLE INFO

Keywords:
Takotsubo
CMR
Prognosis
Outcome

ABSTRACT

Background: Takotsubo syndrome (TS) is characterized by transient myocardial dysfunction with outcomes ranging from favorable to life-threatening. Cardiovascular magnetic resonance (CMR) has emerged as an essential tool in its diagnosis and management and is consistently recommended by current guidelines in the diagnostic work-up. However, the prognostic value of CMR in patients with TS remains undetermined. The aim of this study was to assess the prognostic value of CMR in managing patients with TS.

Method: PubMed, MEDLINE via Ovid, Scopus, and the Cochrane Library were searched to identify studies reporting the prognostic role of multiparameteric CMR in patients with TS with a follow-up $\geq$ 12 months. The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), defined as all-cause mortality, cardiac death, heart failure, sudden cardiac death, recurrence of TS, and cerebrovascular events.

Results: Five studies with 564 patients were included for reporting correlation of CMR parameters with MACCE. Primary endpoint occurred in 69 (12%) patients.

Among the CMR parameters assessed, myocardial strain parameters (including measurements of the left atrium, left and right ventricle), right ventricle involvement, and a CMR-based radiomics model demonstrated correlations with MACCE. Additionally, one study showed the predictive ability of a CMR score.

Conclusion: The current systematic review suggests that CMR may offer prognostic insights in TS patients, underscoring its potential clinical utility for integration into clinical practice. However, scarce data are currently available; hence, further research is needed.

1. Introduction

Takotsubo syndrome (TS) is an acute myocardial dysfunction commonly affecting mainly postmenopausal women, who have a 10-fold greater risk than men. It is characterized by transient regional myocardial contractility impairment, mainly involving apical segments[1,2]. Most of patients experience a complete recovery in 4 to 8 weeks however some individuals showed persistence of alteration and worse outcome [3,4]. In particular, a growing body of evidence reports complications in about 52 % of patients, including heart failure, cardiogenic shock, ventricular arrhythmia, and death [4]. In particular, various studies have reported higher long-term mortality rates among TS patients compared to the general population, with a ratio of 12.5 % [5], similar to patients with acute coronary syndrome [6] and ST-segment elevation myocardial infarction [7].

Given the potential for long-term adverse outcomes in TS patients, the identification of clinical, laboratory, and non-invasive imaging data related to adverse outcomes is undoubtedly valuable for risk stratification in TS patients. Different echocardiography features have demonstrated their ability to stratify TS patients [3,8–11]. Alashi et al. evaluated 650 TS patients using echocardiography with a median follow-up of 2.2 years, demonstrating that higher age (HR 1.35, 95 % CI

Abbreviations: **CMR**, Cardiovascular Magnetic Resonance; **LV**, left ventricle; **TS**, Takotsubo syndrome.

* Corresponding author at: Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato s.s. 554 Monserrato, Cagliari 09045, Italy.
E-mail address: lucasaba@tiscali.it (L. Saba).

https://doi.org/10.1016/j.ejrad.2024.111576
Received 18 May 2024; Received in revised form 8 June 2024; Accepted 14 June 2024
Available online 15 June 2024

1.17–1.55, P < 0.001), male sex (HR 1.75, 95 % CI 1.06–2.89, P = 0.032), lower baseline LVEF (HR 1.02, 95 % CI 1.01–1.04, P = 0.023), worse left ventricle (LV)-global longitudinal strain (HR 1.04, 95 % CI 1.01–1.14, P = 0.032), neurologic trigger (HR 2.66, 95 % CI 1.35–5.26, P < 0.001), and physical trigger (HR 2.64, 95 % CI 1.63–4.20, P < 0.001) were associated with mortality in multivariate Cox survival analysis [9]. The prognostic impact of echocardiography features was also reported in the recent systematic review and *meta*-analysis by Chiang et al. that evaluated 18 studies and 5168 patients. The authors demonstrated that reduced LVEF was associated with an increased risk of mortality in TS patients (HR 3.13; 95 % CI 1.392–7.031, P < 0.006) [8]. Nevertheless, while echocardiography represents the first-line non-invasive modality, it may be limited by anatomical window, suboptimal right ventricle evaluation, and its inability to evaluate myocardial tissue changes [12,13].

In this scenario, cardiovascular magnetic resonance (CMR) enables a comprehensive assessment of functional, morphological as well as tissue characterization changes that occurs during TS.

However, despite the emerging role of CMR in the diagnostic work-up of TS [14–18], few studies evaluated the prognostic values of CMR parameters in TS patients.

To investigate the potential role of CMR-based parameters in patients with TS, we conducted a systematic review of the literature.

2. Methods

A systematic search to identify studies reporting the prognostic role of CMR parameters in patients suffering from TS were performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19]. The PRISMA flowchart (Preferred Reporting Items for Systematic Reviews and Meta-analyses) illustrating the inclusion process is provided in the Fig. 1.

Ethics approval was not needed as this study utilized data from already published studies.

2.1. Search strategy and eligibility criteria

We systematically searched PubMed, MEDLINE via Ovid, Scopus, and the Cochrane Library for studies discussing the prognostic role of CMR parameters in TS. The search period was conducted in January 2024, starting from inception. Additionally, we examined the reference lists of eligible studies and recent systematic reviews to identify relevant research.

The search terms used in the search were (prognosis OR outcome) AND (‘apical ballooning syndrome’ OR ‘broken heart syndrome’ OR ‘stress cardiomyopathy’ OR ‘takotsubo syndrome’ OR ‘takotsubo cardiomyopathy’ OR ‘takotsubo cardiomyopath*’ OR ‘takotsubo’) AND (‘delayed gadolinium enhancement’ OR ‘late gadolinium enhancement’ OR ‘cardiac MRI’ OR ‘CMR’).

The search strategy was adapted for each database based on its specific nomenclature.

The criteria for eligible studies were as follows: 1) studies including patients with a diagnosis of TS; 2) an available CMR evaluation within 7 days from the index acute event; (3) studies that clearly described the clinical cohort and CMR parameters; (4) comprehensive CMR examinations according to published and established TS imaging protocols, including mandatory sequences such as cine-CMR, T2-STIR, and LGE [39]; and (5) a comprehensive report on long-term outcomes with a follow-up duration of ≥ 12 months.

2.2. Outcomes of interest

The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), defined as all-cause mortality, cardiac death, heart failure, sudden cardiac death, recurrence of TS, and cerebrovascular events, which were assessed as clinical outcome measures.

2.3. Study selection and quality assessment

The articles identified in the literature search underwent screening

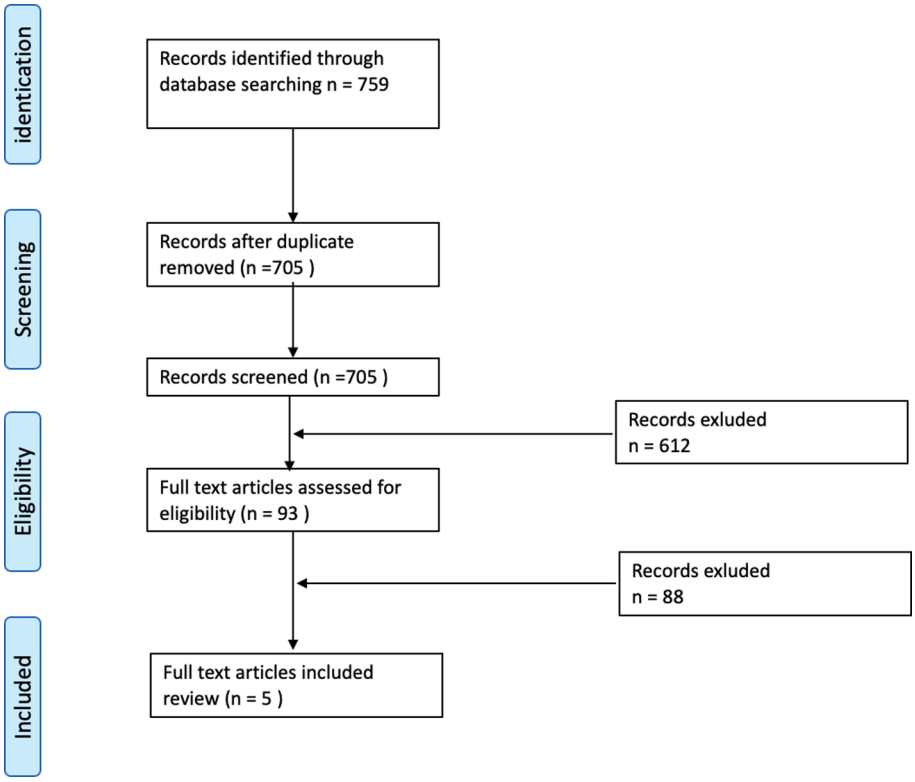

Fig. 1. PRISMA flow diagram of the study selection process.

(by title and abstract) by two independent reviewers (R.C. and F.P.). Articles deemed potentially relevant by any reviewer were retrieved for full-text review. Discrepancies during full-text review were resolved through consensus or, if necessary, by a third reviewer (L.S.).

Studies written in languages other than English were excluded. Conference abstracts, opinion papers, editorials, letters to editors, case reports, case series, review articles, and preclinical studies were excluded from this study.

2.4. Data collection process and data items

An electronic data extraction form was developed and defined prior to conducting the literature searches and study selection. The items extracted from each study included publication year, author, sample size, study design (retrospective of prospective), duration of follow-up, CMR parameters, clinical outcomes, and CMR performance.

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the included observational studies. It specifically assesses the following characteristics: (a) representativeness of the exposed cohort, (b) selection of the non-exposed cohort, (c) ascertainment of exposure, (d) demonstration that the outcome of interest was not present at the start of the study, (e) comparability of cohorts based on study design or analysis, (f) assessment of outcomes, (g) follow-up periods of sufficient length for outcomes to occur, and (h) adequacy of cohort follow-up. The NOS scales range from 0 to 9, where studies with a score of less than 5 are considered low quality, a score of 5 to 7 is deemed moderate quality, and a score of more than 8 is categorized as high quality. The details of the NOS quality assessment are summarized in Supplementary Table 1.

3. Results

3.1. Search results

Our initial search identified 759 potentially relevant articles, of which 705 remained after removing duplicates. Following the screening of titles and abstracts, we excluded 612 manuscripts for not meeting our inclusion criteria. Full texts of the remaining studies were obtained and reviewed. After further evaluation, only 5 studies met all inclusion criteria and were included in our analysis [20–24]. Fig. 1 displays the PRISMA flow chart summarizing the search strategy. Included studies were all observational investigations published between 2010 and 2023, involving patients from Europe. Amongst the included studies, three were retrospective, with the remainder prospective. The sample size of each study ranged from 58 to 152 subjects. A total of 564 patients suffering from TS were included, with 68 males (12 %) and 496 females (88 %). The mean ages of these individuals ranged from 68 to 72 years. The mean age of the subjects was 69.6 years. The demographic characteristics of the included patients are in line with current literature for both age of onset and gender [25,26].

Median follow-up period ranged from 13.3 to 60 months. The assessed clinical outcomes included myocardial infarction, stroke or transient ischemic attack, recurrence of TS, and all-cause mortality. The number of endpoints occurred was 69 (12 %, ranging from 10 % to 17 %). All five studies included reported a correlation between CMR parameters and outcomes. Two studies evaluated the prognostic role of myocardial strain, two investigations reported a correlation between right ventricle involvement and outcomes. One study proposed a combined CMR score to predict major adverse cardiac events.

None of the included studies demonstrated a correlation between T2-STIR, LVEF, LGE, and outcomes.

Characteristics of included studies are outlined in Table 1.

3.2. Right ventricle involvement and outcomes

Right ventricle involvement, defined by the presence of regional right ventricle contraction abnormalities, was correlated with clinical outcomes in two studies [21,24]. In one study, Isaak et al. evaluated the correlation of several CMR parameters with adverse outcomes in 79 patients suffering from TS. Univariate Cox regression analysis revealed an association between the occurrence of adverse outcome and right ventricle involvement (HR 4.96, 95 % CI 1.71–14.34, P = 0.003) [24].

In a second study, Stiermaier et al. investigated the impact of right ventricle dysfunction in a multicenter cohort of 134 TS patients using CMR, employing visual assessment and right ventricle strain parameters. In TS patients with visual dysfunction of the right ventricle, a higher number of adverse events were observed, although the difference did not reach statistical significance (HR 1.38, 95 % CI 0.49–3.88, P = 0.31) [21]. Additionally, the authors stratified the TS cohort based on right ventricle strain, revealing that patients with −17.24 % strain values exhibited increased long-term mortality (HR 2.98, 95 % CI 1.02–8.73, P = 0.03) [21].

3.3. Left atrial and ventricular strain and outcomes

Data correlating clinical outcome with atrial and ventricular strain parameters through CMR were provided in four studies [20–22,24]. In one study, Stiermaier et al evaluated the prognostic values of left ventricle CMR- feature tracking in a multicenter cohort of 141 patients with TS [20]. In multivariate model, patients with lower global longitudinal strain demonstrated a higher number of adverse events (HR 1.14 95 % CI 1.04–1.25, P = 0.006). No significant differences were observed regarding global circumferential strain and global radial strain. The authors found that patients with lower global longitudinal strain (Global longitudinal strain > -14.75 %) had shorter event-free survival on Kaplan-Meier analysis (log rank, P = 0.02) [20]. Conversely, the study by Isaak et al did not shown significant association between global longitudinal strain and outcome in univariate Cox regression analysis [24]. Instead, Backhaus explored the predictive value of atrial mechanism in patients with TS, reporting that left atrial reservoir function was an independent predictive factor in multivariate analysis after adjustment for established cardiovascular risk factors and LVEF (HR 1.10, 95 % CI 1.01–1.20; p = 0.037) [22].No significant association were found between right atrial functions and adverse outcomes [22].

3.4. Left ventricle ejection fraction and outcomes

Three studies have reported the association of outcome data in TS patients with LVEF measurements. No significant association of adverse outcomes with LVEF was identified in all included studies (HR 0.95, 95 % CI 0.91–0.99, P = 0.03, HR 0.9822, 95 % CI 0.3713–2.598; P = 0.971, and HR 0.98 (0.93–1.03), P = 0.383) [20,22,24].

3.5. Myocardial edema, late gadolinium enhancement, and outcomes

Two studies have reported the association of outcome data in TS patients with myocardial edema assessed using T2-STIR images. No significant association of adverse outcomes with myocardial edema was identified in all included studies (HR 0.18 95 % CI 0.04–0.74, P = 0.02, and HR 1.54 95 % CI 0.20–12.2, P = 0.680)[20,24].

One study evaluated the association of outcome in TS patient with late gadolinium enhancement (LGE), defined dichotomously as present or absent. No significant association of adverse outcomes with LGE was identified by Isaak et al. (HR 0.70 95 % CI 0.09–5.58, P = 0.73). None of the studies included evaluated the association of LGE location and extent with adverse outcome.

3.6. Combined CMR score, radiomics, and outcomes

The data correlating outcomes with the combined CMR score are limited and reported in only one study by Isaak et al.[24] This study evaluated the predictive performance of a CMR score, namely PE^2RT

Table 1
Characteristics of included studies.

Authors	Years	Patients	Study design	Age	Female	Symptom Onset to CMR Examination (days)	CMR protocol	CMR variables	Endpoints	Follow-up	Number of events	Results
Isaak et al	2023	79	Retrospective	68	72/79	4 days (IQR, 2–6)	Cine-CMR, T2-STIR, LGE, T1 mapping, and T2 mapping	CMR score that include pericardial effusion, pleural effusion, right ventricular involvement, and ventricular thrombus	cardiovascular death or new hospitalisation due to acute myocardial injury, arrhythmia, or chronic heart failure	13.3 months	14/79 (17 %)	Combined CMR parameters score was associated with MACE (HR 2.44; 95 %CI: 1.62–3.68; p < 0.001)
Backhaus et al.	2019	152	Retrospective	69	127/152	2 days (IQR, 2–4)	Cine-CMR, T2-STIR, and LGE.	Atrial strain parameters	Mortality	40.99 months	17/152 (11 %)	Left atrial reservoir strain predicted mortality (HR 1.10, 95 % CI 1.01–1.20; p = 0.037)
Stiermaier et al	2018	141	Prospective	72	129/141	2 days (IQR, 2–4)	Cine-CMR, T2-STIR, and LGE	Left ventricular strain parameters	Mortality	37 months	17/141 (12 %)	Global longitudinal strain was a predictive CMR parameters of mortality in multivariate model (HR 1.14 1.04–1.25, P = 0.006)
Mannil et al.	2020	58	Retrospective	68	56/58	4 days (IQR, 2–6 days)	Cine-CMR, T2-STIR, and LGE	CMR-based texture analysis	MACCE (composite of death from any cause, myocardial infarction, stroke or transient ischemic attack, or recurrence of TTS)	60 months	6/58 (10 %)	ML models showed a sensitivity of 82.9 % (confidence interval (CI) 80–86.2), specificity of 83.7 % (CI 75.7–92) and AUC of 0.88 (CI 0.83–0.92) in predictivity ability
Stiermaier et al	2018	134	Prospective	71	112/134	2 days (IQR 2–4)	Cine-CMR, T2-STIR, and LGE	Right ventricle involvement Right ventricular strain parameters	Mortality	37 months	15/134 (11 %)	Both right ventricle involvement and global right ventricle strain demonstrated an association with moritality (HR 1.38 95 % CI 0.49–3.88, p = 0.31, and HR 2.98 95 % CI 1.02–8.73, p = 0.03; respectively)

Abbreviations: CMR cardiovascular magnetic resonance; HR Hazard ratio; IQR interquartile range; LGE late gadolinium enhacement; T2-STIR T2 Short tau inversion recovery.

(including pleural effusion, pericardial effusion, right ventricular involvement, and ventricular thrombus), in a cohort of 79 TS patients followed up for a median of 13.3 months. The authors assigned one point for each defined cardiac complication, ranging from 0 (no complications) to 4 (all complications present). The proposed score, with a score higher or equal to 2, was an independent predictor of adverse outcome (HR, 7.98; 95 % CI: 1.34–47.40, P = 0.02). Additionally, they found that patients with a higher PE^2RT score had shorter event-free survival on Kaplan-Meier analysis (log-rank, P = 0.001) [24].

Similarly, the predictive ability of CMR-based radiomics models was evaluated in only one study by Mannil et al. [23] The radiomics model, after reducing dimensions of redundant features and those with poor intra-class correlation coefficients in texture analysis, comprises 10 features, including categories such as histogram, grey-level co-occurrence matrix, run-length matrix, absolute gradient, autoregressive model, and wavelet transform. The authors tested various machine learning models, including the artificial neural network Multilayer Perceptron, decision tree J48, NaïveBayes, RandomForest, and Sequential Minimal Optimization, to assess the 5-year outcome, including major adverse cardiac and cerebrovascular events.

The authors internally validated their model with ten-fold cross-validation, reporting that NaïveBayes showed higher predictive ability with a sensitivity of 82.9 % (CI 80–86.2), specificity of 83.7 % (CI 75.7–92), an AUC of 0.88 (CI 0.83–0.92), precision of 0.88 (0.83–0.92), and a precision-recall curve of 0.98 (0.97–0.99) [23].

4. Discussion

This systematic review demonstrates a significant association between CMR parameters and adverse outcomes in TS patients, including a composite of death from any cause, myocardial infarction, stroke or transient ischemic attack, or recurrence of TS.

In particular, our findings suggest that left atrial and ventricular strain impairment, as well as right ventricle dysfunction, were independent predictors of long-term adverse outcomes. Furthermore, incorporating a combined CMR score and radiomics may enhance the predictive capability of CMR.

Conversely, myocardial tissue abnormalities, including myocardial edema and LGE, were not associated with outcomes in the studies included in our systematic review.

The widespread adoption of CMR examination in patients with suspected TS can, in accordance with the ESC guidelines, rule out other causes of myocardial damage and contemporaneously stratify TS patients, allowing prompt clinical management and tailored therapy with consequent improvement in outcomes.

4.1. Myocardial strain

TS has emerged as a noteworthy manifestation of transient ventricular systolic dysfunction, characterized by a distinctive pattern of regional myocardial wall abnormalities, presenting predominantly as apical ballooning and hyperkinesis of the LV basal segment [1,2]. The evaluation of LV performance, quantified through LV ejection fraction, plays a crucial role in the diagnosis and management of TS patients. However, the measurement of LV ejection fraction takes into account global ventricular performance without discerning and identifying regional wall motion abnormalities. For instance, in the classical TS pattern, basal hyperkinesis can compensate for mid/basal regional dysfunction, resulting in only mild or moderate ejection fraction reduction [14,16].

The recently introduced CMR feature tracking allows for the objective and quantitative depiction of both regional and global transient impairments of myocardial contractility, even when ejection fraction is preserved or recovered in TS patients. It also demonstrates the compensatory increase in contractility in the longitudinal, radial, and circumferential directions, proving to be a superior measurement of LV performance compared to LV ejection fraction alone [20,27]. The different regional myocardial contraction impaired may be explained by the anatomical differences in the structural organization and molecular signaling of adrenoreceptors between the basal and apical myocardium, or to the altered distribution of epicardial blood flow following a prolonged, forceful left ventricular contraction [1,2,14].

Fig. 2 demonstrated an example of atrial and ventricular strain analysis in TS patients.

Additionally, myocardial strain assessment through CMR feature tracking has been demonstrated to be more accurate and reliable compared to speckle tracking in echocardiography [12].

Of interest, none of the studies included in the current systematic review reported a correlation of LV ejection fraction measured by CMR with adverse outcomes. These findings are in contrast with previous echocardiography studies [8,9]. This discrepancy could be explained by the rapidly reversible contractile impairment within several days to weeks during TS [28]. Indeed, CMR examinations are seldom performed on the same day as symptoms onset due to the limited availability of CMR scanners in “real world” clinical practice. The studies included conducted CMR examinations at median of 3 days after initial presentation, allowing for a potential partial or full recovery of LV ejection fraction. This data emphasizes two important aspects: (1) LV ejection fraction measured by CMR may be a suboptimal prognostic parameter in TS patients, especially if not performed in a short period of time from the initial presentation—ideally on the same day as echocardiography; (2) myocardial strain can better reflect regional wall motion abnormalities in TS patients, which persist for a longer period in comparison with LV ejection fraction reduction, representing a more robust marker for risk stratifying TS patients. However, the potential clinical application of CMR-feature tracking parameters, both in identifying subtle regional wall dysfunction and stratifying high-risk patients, demands rigorous validation through comprehensive prospective studies.

4.2. Right ventricle involvement

An additional critical aspect involves identifying the involvement of the right ventricle in patients with TS. Indeed, an impairment in right ventricle function have demonstrated to be linked to prolonged hospitalization and higher rate of adverse cardiac events [29,30]. A potential explanation of this phenomena may be related to an increased area of myocardial edema inflammation extended in right ventricle [30,31]. In this scenario, CMR represents the gold standard for assessing RV wall motion abnormalities and structure. It enables a comprehensive visualization of the complex anatomical shape of right ventricle, overcoming most of the echocardiography limitations, such as limited acoustic window, variations in body size or deformation (e.g. pectum excavatum), and changes in right ventricle anatomy due to pathology or surgical intervention [32].Scally et al. investigated the potential of CMR to improve the detection rate of right ventricular regional wall motion abnormalities in TS, demonstrating a twofold increase in sensitivity [33]. CMR has the unique ability of tissue characterization, enabling an assessment of myocardial tissue abnormalities that could be linked with long-term outcomes.

Finally, the utilization of CMR-based strain imaging may demonstrate greater sensitivity in detecting right ventricular involvement, enabling a more in-depth identification of subtle abnormalities in right ventricle contractility [21]. Careful evaluation of right ventricle involvement, along with the application of CMR-feature tracking, could provide important prognostic information and aid in clinical decision-making. Fig. 3.

4.3. Combined CMR models

In TS patients, several diagnostic and risk stratification scores based on clinical and/or echocardiography parameters have been proposed [10,34,35], while the role of combining CMR features has not been

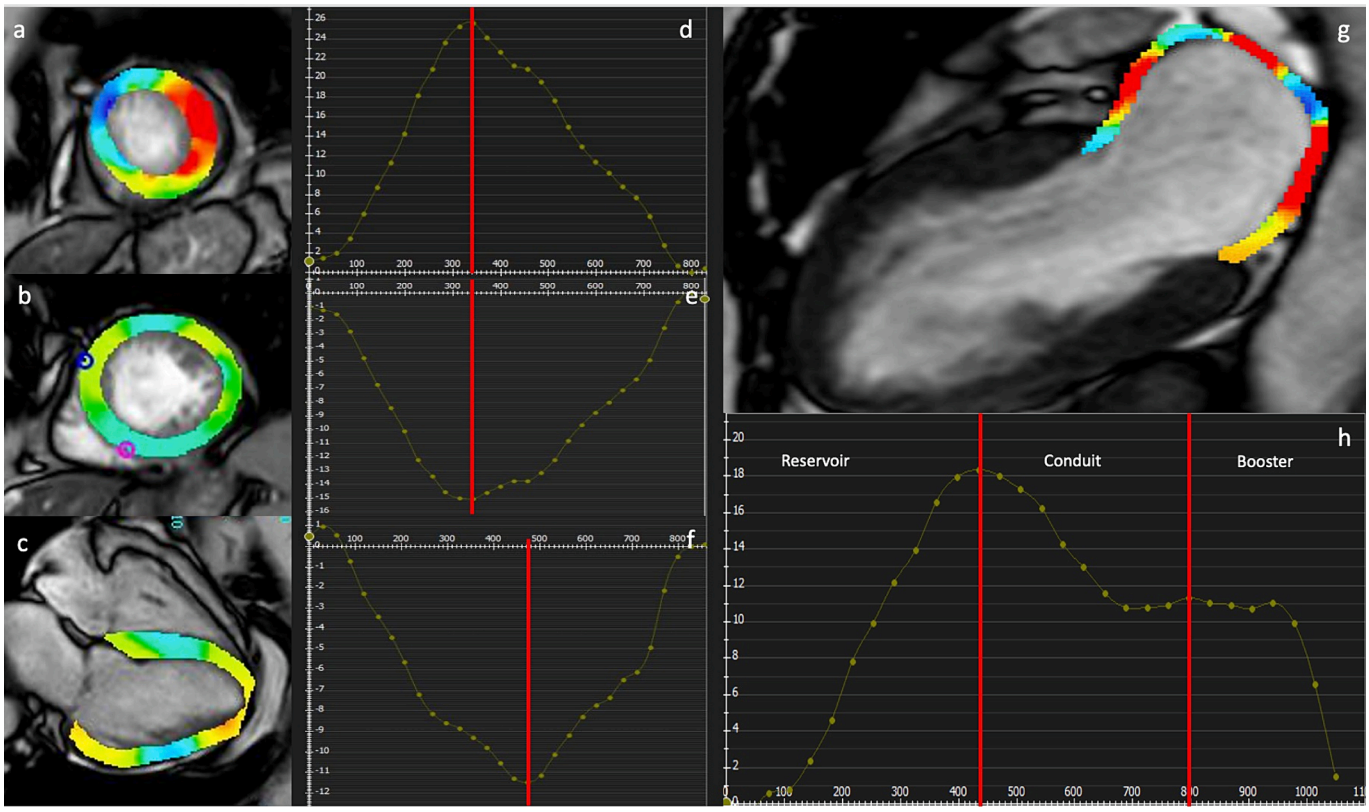

Fig. 2. Images of cardiovascular magnetic resonance-feature tracking in short- and long-axis in patients with Takotsubo syndrome. Examples of ventricular strain parameters in all three directions (Panel a: global radial strain, Panel b: global circumferential strain, Panel c: global longitudinal strain) with their corresponding strain curves. Panel g demonstrates an example of left atrium strain obtained in the two-chamber view with its corresponding reservoir, conduit, and booster curves (Panel h).

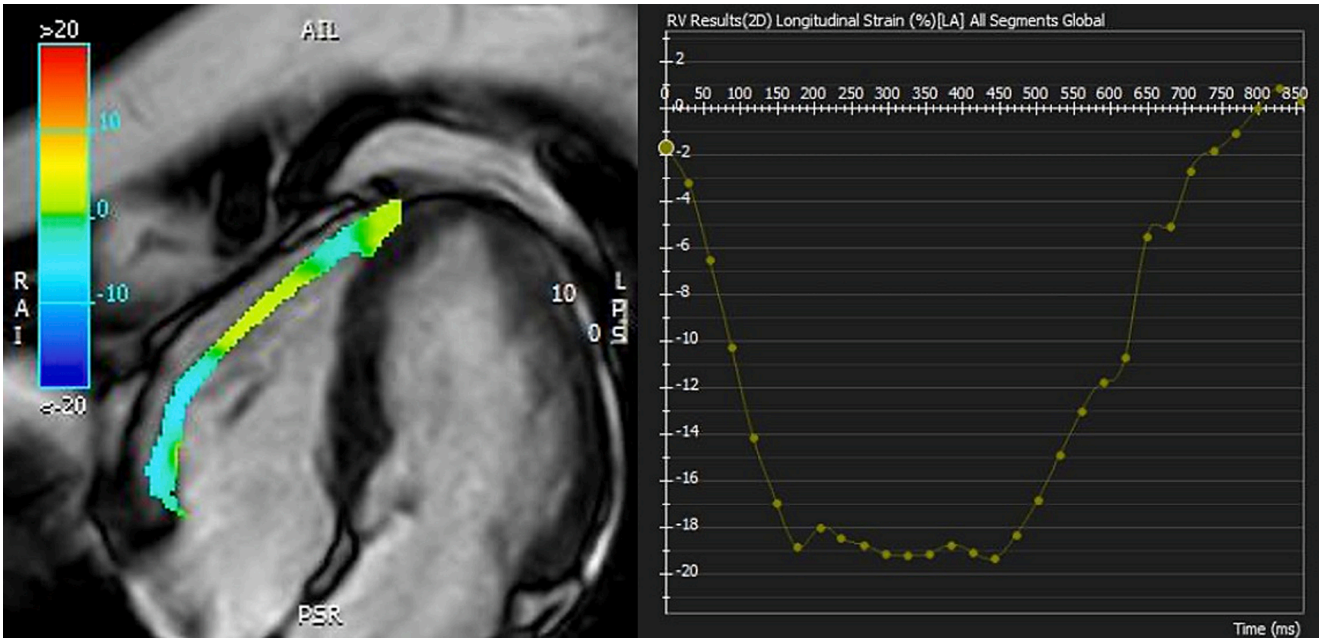

Fig. 3. Assessment of cardiovascular magnetic resonance-derived right ventricular global longitudinal strain in patients with Takotsubo syndrome.

extensively studied. A recent study by Isaak et al. developed a CMR score in a cohort of 79 TS patients, considering some easily assessable and readily available CMR parameters. This study demonstrated the predictive value of the CMR score in TS risk stratification [24].

Further prospective studies are needed to evaluate more in-depth the potential clinical application of a combined score, incorporating CMR parameters.

The recently published design and rationale of the EVOLUTION (Exploring the eVolution in prognOstic capabiLity of mUlti-sequence cardiac magneTIc resO-nance in patieNts affected by Takotsubo

cardiomyopathy) registry aims to develop a prognostic score that incorporates CMR-based morphologic and tissue characterization parameters beyond clinical and echocardiography parameters [36]. Implementing a combined score will result in earlier diagnosis, more tailored therapy, and improved patient outcomes.

4.4. AI and radiomics

In the incoming era of imaging-guided precision medicine, novel approaches to data science such as radiomics may help in stratify TS patients. Radiomics is a promising tool that automatically extracts extensive quantitative features from medical images by analyzing pixel grey level distribution. By calculating the relationship between adjacent voxels with similar or different signal intensity using standardized mathematical formulas, this approach enables the extraction of texture features that may not be discernible to the human eye [37].

Artificial intelligence (AI) can be combined with radiomics to streamline and optimize the diagnostic and prognostic processes,

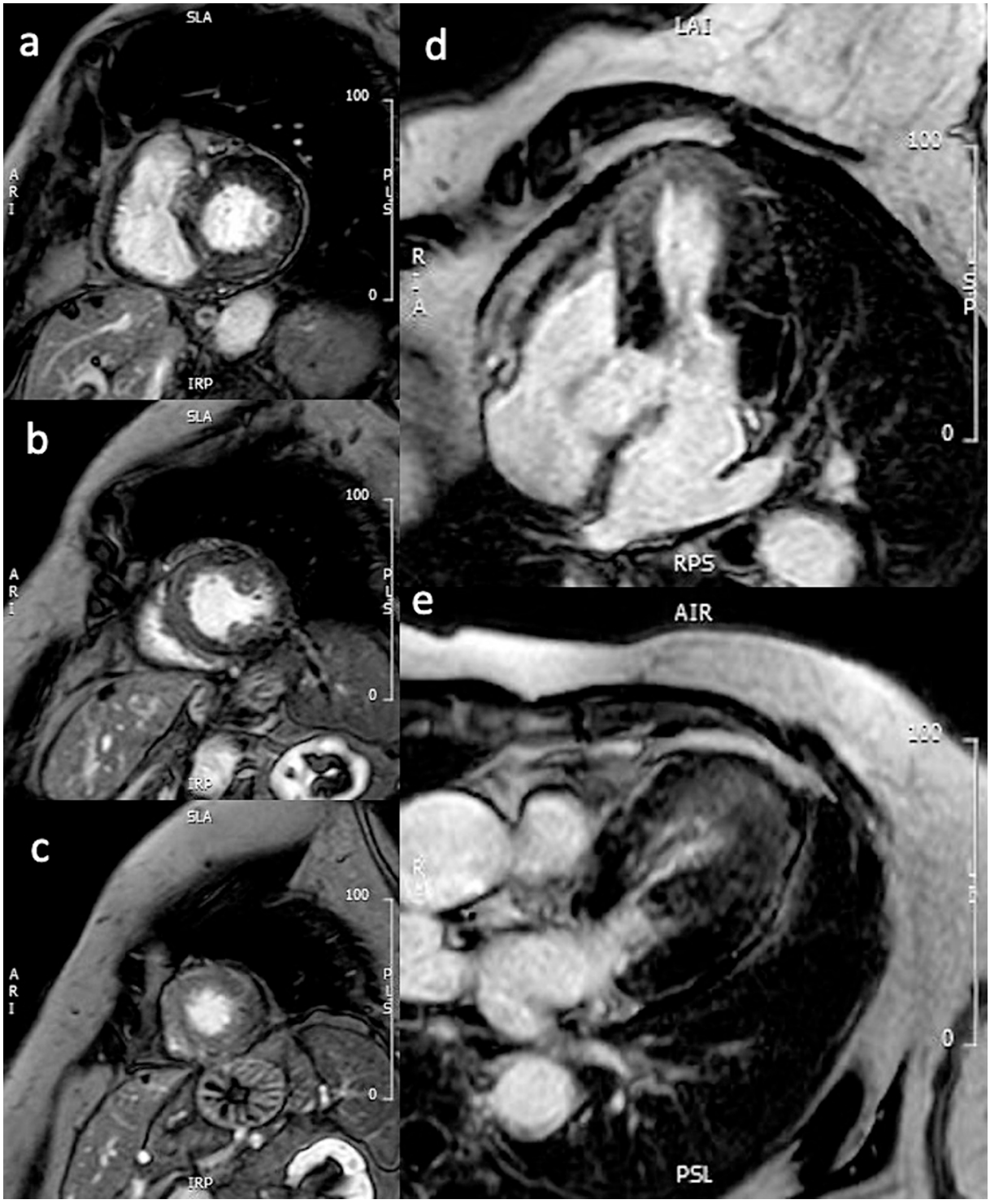

Fig. 4. Late gadolinium enhancement pattern in Takotsubo syndrome patients. Basal (Panel a), mid-ventricular (Panel b), and apical (Panel c) short-axis views showing mild transmural gadolinium enhancement in the mid-apical regions. Findings confirmed in the long-axis views (Panel d and Panel e).

facilitating not only big data analysis (including multi-omics) but also the unraveling of hidden patterns and insights within heterogeneous datasets [38]. The application of AI-based radiomics models in TS has been demonstrated in pivotal research by Mannil et al. This study showcased the prognostic value of texture analysis combined with AI models in TS patients [23]. Nevertheless, this proof-of-principle study, conducted across multiple centers and collecting CMR images from different scanners, is limited by the small cohort of patients enrolled, the explainability of the models, and the absence of external validation. The results of the EVOLUTION registry are anticipated to expand our knowledge regarding the clinical application of AI in TS patients [36].

4.5. Myocardial tissue abnormalities

CMR also enables the evaluation of myocardial tissue changes during TS, historically characterized by the presence of myocardial edema and absence of LGE [39]. However, several studies have demonstrated the presence of focal or patchy areas of LGE in the acute phase of TS [40–43] with controversial results about the prognostic impact of this finding [40,44,45]. Fig. 4 An immunohistologic analysis suggested that an increase in extracellular matrix rich in collagen-1, indicative of transient fibrosis, might explained the presence of LGE observed in TS patients [42].

None of the studies included in the present systematic review reported an association between presence of LGE, myocardial edema and adverse outcomes in TS patients.

The recently introduced CMR mapping sequences enable the quantitative assessment of myocardial relaxation time, encompassing both the increase in extracellular water (T2 mapping) and the expansion of the extracellular matrix (T1 mapping and extracellular volume fraction [ECV]) [46,47].In TS patients, increased T1 mapping values have been described persisting for more than 1 year after the acute event, and associated with compromised cardiac deformation, elevated natriuretic peptide levels, and persisting reduced maximal oxygen consumption during exercise testing at a cardiopulmonary stress test [48], along with prolonged left ventricular wall motion recovery time [49]. suggesting subtle, long-term, non-transient abnormalities associated with TS.

Similarly, higher T2 mapping values was related to ECG changes and TS complications [50,51], suggesting a potential predictive implication.

Fig. 5 exhibited the adoption of parametric mapping in TS patients.

Due to the recent introduction of parametric mapping techniques, none of the aforementioned studies evaluated the potential predictive value of these new mapping sequences. Further prospective studies, including the assessment of parametric mapping techniques, should be conducted to investigate the prognostic value of these new mapping parameters in TS patients more comprehensively.

4.6. Clinical implication

Recent evidence has demonstrated a non-negligible rate of adverse events at follow-up among patients with TS[10]. Identification of high-risk TS patients who may benefit from tailored therapy is crucial in clinical practice. In this scenario, CMR represents the reference standard in the assessment of left and right ventricular function and volumes, enabling a comprehensive assessment of functional changes in TS, including an accurate assessment of the right ventricle even in patients with suboptimal acoustic echocardiography windows [12]. Additionally, multiparametric CMR, including recently introduced parametric mapping techniques, with its unique non-invasive tissue characterization capabilities, can provide further information about myocardial tissue injury during TS and may be useful in clinical decision-making for the selection of management strategies [52,53].

4.7. Limitations

The following study limitations should be acknowledged. First, all

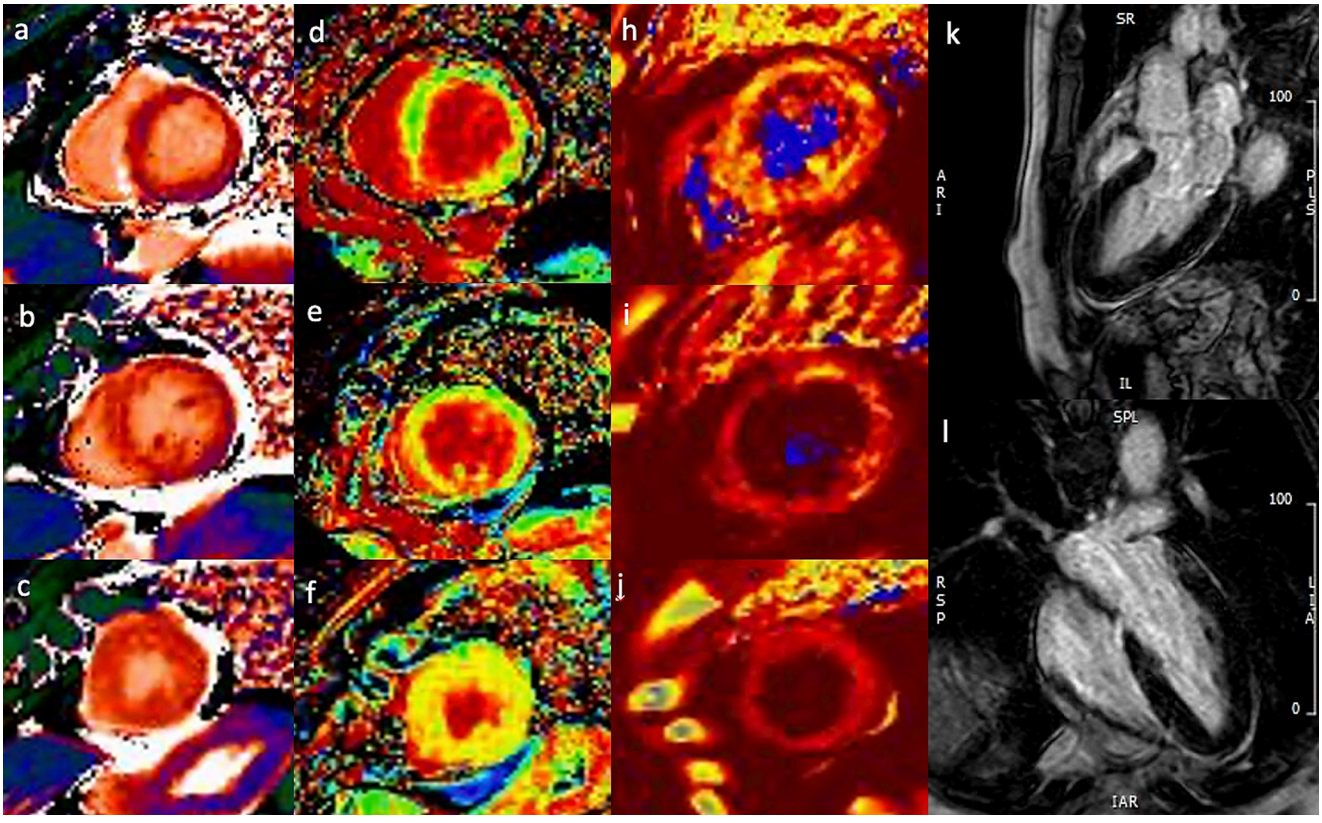

Fig. 5. Representative CMR mapping sequences in patients with Takotsubo syndrome revealed increased T1 (panels a to c), ECV (panels d to f), and T2 mapping (panels h to j) values detected in the mid to apical segments without corresponding gadolinium enhancement in the same segment (panels k-l).

the included studies are observational in nature, posing a potential risk of bias. The variability in cardiac magnetic resonance (CMR) scanners and field strengths may have influenced our findings, and it is hoped that a more widespread adoption of CMR examinations may facilitate a standardized protocol, including parametric mapping. Additionally, in most studies included, assessment and quantification of LGE were not available, limiting the ability to assess the relationship between the presence and extent of fibrosis and patient outcomes.

Second, in adherence to our inclusion and exclusion criteria, we excluded conference abstracts and publications other than full-length manuscripts. Additionally, this review exclusively considered English articles, potentially overlooking relevant studies published in other languages. Finally, the paucity of the existing literature combined with the heterogeneity of CMR parameters analyzed constrained our ability to conduct a *meta*-analysis.

5. Conclusion

The data reported in the present systematic review indicate the significance of various CMR parameters in predicting the long-term prognosis of patients with TS patients. These findings underscore the importance of incorporating CMR for risk stratification in a clinical setting. Nevertheless, further prospective multicenter studies are necessary to attain a more in-depth understanding of TS prognosis and the application of CMR in risk stratification.

CRediT authorship contribution statement

Riccardo Cau: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Anna Palmisano:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Data curation. **Jasjit S. Suri:** Writing – review & editing, Validation, Supervision, Methodology. **Francesco Pisu:** Writing – review & editing, Methodology, Data curation. **Antonio Esposito:** Writing – review & editing, Visualization, Validation, Data curation. **Luca Saba:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Data curation.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2024.111576.

References

[1] J.R. Ghadri, I.S. Wittstein, A. Prasad, et al., International expert consensus document on Takotsubo syndrome (Part I): Clinical characteristics, diagnostic criteria, and pathophysiology, Eur. Heart J. 39 (22) (2018) 2032–2046, https://doi.org/10.1093/eurheartj/ehy076.

[2] J.R. Ghadri, I.S. Wittstein, A. Prasad, et al., International expert consensus document on Takotsubo syndrome (Part II): Diagnostic workup, outcome, and management, Eur. Heart J. 39 (22) (2018) 2047–2062, https://doi.org/10.1093/eurheartj/ehy077.

[3] P. Francesco, P. Vincenzo, P. Giuseppe, et al., Long-term prognosis and outcome predictors in Takotsubo syndrome, JACC Hear. Fail. 7 (2) (2019) 143–154, https://doi.org/10.1016/j.jchf.2018.10.009.

[4] A.R. Lyon, E. Bossone, B. Schneider, et al., Current state of knowledge on Takotsubo syndrome: A Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology, Eur. J. Heart Fail. 18 (1) (2016) 8–27, https://doi.org/10.1002/ejhf.424.

[5] G. Parodi, B. Bellandi, S. Del Pace, et al., Natural history of tako-tsubo cardiomyopathy, Chest 139 (4) (2011) 887–892.

[6] B. Redfors, R. Vedad, O. Angerås, et al., Mortality in takotsubo syndrome is similar to mortality in myocardial infarction—A report from the SWEDEHEART registry, Int. J. Cardiol. 185 (2015) 282–289.

[7] T. Stiermaier, C. Moeller, K. Oehler, et al., Long-term excess mortality in takotsubo cardiomyopathy: Predictors, causes and clinical consequences, Eur. J. Heart Fail. 18 (6) (2016) 650–656.

[8] L.L.W. Chiang, S.L. Tsang, J.X. Lee, et al., Takotsubo cardiomyopathy with low ventricular ejection fraction and apical ballooning predicts mortality: A systematic review and meta-analysis, Heart Fail. Rev. 26 (2) (2021) 309–318, https://doi.org/10.1007/s10741-020-10018-0.

[9] A. Alashi, N. Isaza, J. Faulx, et al., Characteristics and outcomes of patients with Takotsubo syndrome: Incremental prognostic value of baseline left ventricular systolic function, J. Am. Heart Assoc. 9 (16) (2020) e016537, https://doi.org/10.1161/JAHA.120.016537.

[10] F. Santoro, I.J. Núñez Gil, T. Stiermaier, 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 (9) (2019) 892–899, https://doi.org/10.1001/jamacardio.2019.2597.

[11] I. El-Battrawy, F. Santoro, T. Stiermaier, et al., Incidence and clinical impact of recurrent Takotsubo syndrome: Results from the GEIST registry, J. Am. Heart Assoc. 8 (9) (2019) e010753, https://doi.org/10.1161/JAHA.118.010753.

[12] R. Citro, H. Okura, J.R. Ghadri, et al., Multimodality imaging in takotsubo syndrome: a joint consensus document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE), J. Echocardiogr. 18 (4) (2020) 199–224, https://doi.org/10.1007/s12574-020-00480-y.

[13] P.J. Jensch, T. Stiermaier, I. Eitel, Takotsubo syndrome-is there a need for CMR? Curr. Heart Fail. Rep. 18 (4) (2021) 200–210, https://doi.org/10.1007/s11897-021-00518-x.

[14] Cau R, Muscogiuri G, Palmisano V, et al. Base-to-apex Gradient Pattern Assessed by Cardiovascular Magnetic Resonance in Takotsubo Cardiomyopathy. *J Thorac Imaging*. Published online November 2023. doi:10.1097/RTI.0000000000000761.

[15] Cau R, Pisu F, Porcu M, et al. Machine learning approach in diagnosing Takotsubo cardiomyopathy: The role of the combined evaluation of atrial and ventricular strain, and parametric mapping. *Int J Cardiol*. Published online November 2022. doi:10.1016/j.ijcard.2022.11.021.

[16] Cau R, Bassareo P, Deidda M, et al. Could CMR Tissue-Tracking and Parametric Mapping Distinguish Between Takotsubo Syndrome and Acute Myocarditis? A Pilot Study. *Acad Radiol*. Published online 2021. http://www.sciencedirect.com/science/article/pii/S1076633221000155.

[17] J.P. Collet, H. Thiele, E. Barbato, et al., 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, Eur. Heart J. 42 (14) (2021) 1289–1367, https://doi.org/10.1093/eurheartj/ehaa575.

[18] Cau R, Bassareo P, Caredda G, Suri JS, Esposito A, Saba L. Atrial Strain by Feature-Tracking Cardiac Magnetic Resonance Imaging in Takotsubo Cardiomyopathy. Features, Feasibility, and Reproducibility. *Can Assoc Radiol J = J l'Association Can des Radiol*. Published online October 2021:8465371211042497. doi:10.1177/08465371211042497.

[19] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e1000097, https://doi.org/10.1371/journal.pmed.1000097.

[20] T. Stiermaier, T. Lange, A. Chiribiri, et al., Left ventricular myocardial deformation in Takotsubo syndrome: A cardiovascular magnetic resonance myocardial feature tracking study, Eur. Radiol. 28 (12) (2018) 5160–5170, https://doi.org/10.1007/s00330-018-5475-2.

[21] T. Stiermaier, T. Lange, A. Chiribiri, et al., Right ventricular strain assessment by cardiovascular magnetic resonance myocardial feature tracking allows optimized risk stratification in Takotsubo syndrome, PLoS One 13 (8) (2018) e0202146.

[22] S.J. Backhaus, T. Stiermaier, T. Lange, et al., Atrial mechanics and their prognostic impact in Takotsubo syndrome: A cardiovascular magnetic resonance imaging study, Eur. Hear. J. – Cardiovasc. Imaging 20 (9) (2019) 1059–1069, https://doi.org/10.1093/ehjci/jey219.

[23] M. Mannil, K. Kato, R. Manka, et al., Prognostic value of texture analysis from cardiac magnetic resonance imaging in patients with Takotsubo syndrome: a machine learning based proof-of-principle approach, Sci. Rep. 10 (1) (2020) 20537, https://doi.org/10.1038/s41598-020-76432-4.

[24] A. Isaak, J. Bratz, D. Kravchenko, et al., A novel and simple cardiac magnetic resonance score (PE2RT) predicts outcome in takotsubo syndrome, Eur. Radiol. (2023), https://doi.org/10.1007/s00330-023-09543-x.

[25] Y.J. Akashi, H.M. Nef, A.R. Lyon, Epidemiology and pathophysiology of Takotsubo syndrome, Nat. Rev. Cardiol. 12 (7) (2015) 387–397, https://doi.org/10.1038/nrcardio.2015.39.

[26] Y-Hassan S, De Palma R. Contemporary review on the pathogenesis of takotsubo syndrome: The heart shedding tears: Norepinephrine churn and foam at the cardiac sympathetic nerve terminals. *Int J Cardiol*. 2017;228:528-536. doi:https://doi.org/10.1016/j.ijcard.2016.11.086.

[27] A. Scatteia, A. Baritussio, C. Bucciarelli-Ducci, Strain imaging using cardiac magnetic resonance, Heart Fail. Rev. 22 (4) (2017) 465–476, https://doi.org/10.1007/s10741-017-9621-8.

[28] T. Stiermaier, K. Busch, T. Lange, et al., Prognostic value of different CMR-based techniques to assess left ventricular myocardial strain in Takotsubo syndrome, J. Clin. Med. 9 (12) (2020) 3882, https://doi.org/10.3390/jcm9123882.

[29] D. Haghi, A. Athanasiadis, T. Papavassiliu, et al., Right ventricular involvement in Takotsubo cardiomyopathy, Eur. Heart J. 27 (20) (2006) 2433–2439, https://doi.org/10.1093/eurheartj/ehl274.
[30] I. El-Battrawy, F. Santoro, T. Stiermaier, et al., Incidence and clinical impact of right ventricular involvement (Biventricular Ballooning) in Takotsubo syndrome: Results from the GEIST registry, Chest 160 (4) (2021) 1433–1441, https://doi.org/10.1016/j.chest.2021.04.072.
[31] N. Kagiyama, H. Okura, T. Tamada, et al., Impact of right ventricular involvement on the prognosis of takotsubo cardiomyopathy, Eur. Hear. J. Cardiovasc. Imaging 17 (2) (2016) 210–216, https://doi.org/10.1093/ehjci/jev145.
[32] E. Surkova, B. Cosyns, B. Gerber, A. Gimelli, A. La Gerche, M.N. Ajmone, The dysfunctional right ventricle: the importance of multi-modality imaging, Eur. Hear. J. - Cardiovasc. Imaging 23 (7) (2022) 885–897, https://doi.org/10.1093/ehjci/jeac037.
[33] C. Scally, T. Ahearn, A. Rudd, et al., Right ventricular involvement and recovery after acute stress-induced (Tako-tsubo) cardiomyopathy, Am. J. Cardiol. 117 (5) (2016) 775–780, https://doi.org/10.1016/j.amjcard.2015.11.057.
[34] F. Scudiero, L. Arcari, L. Cacciotti, et al., Prognostic relevance of GRACE risk score in Takotsubo syndrome, Eur. Hear. J. Acute Cardiovasc. Care 9 (7) (2020) 721–728, https://doi.org/10.1177/2048872619882363.
[35] J.R. Ghadri, V.L. Cammann, S. Jurisic, et al., A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry, Eur. J. Heart Fail. 19 (8) (2017) 1036–1042, https://doi.org/10.1002/ejhf.683.
[36] Cau R, Muscogiuri G, Pisu F, et al. Exploring the EVolution in PrognOstic CapabiLity of MUltisequence Cardiac MagneTIc ResOnance in PatieNts Affected by Takotsubo Cardiomyopathy Based on Machine Learning Analysis Design and Rationale of the EVOLUTION Study. 2023;00(00):1-8. doi:10.1097/RTI.0000000000000709.
[37] T. Polidori, D. De Santis, C. Rucci, et al., Radiomics applications in cardiac imaging: a comprehensive review, Radiol. Med. 128 (8) (2023) 922–933, https://doi.org/10.1007/s11547-023-01658-x.
[38] Cau R, Pisu F, Suri JS, et al. Artificial Intelligence in the Differential Diagnosis of Cardiomyopathy Phenotypes. *Diagnostics (Basel, Switzerland)*. 2024;14(2). doi: 10.3390/diagnostics14020156.
[39] I. Eitel, F. von Knobelsdorff-Brenkenhoff, P. Bernhardt, et al., Clinical characteristics and cardiovascular magnetic resonance findings in stress (Takotsubo) cardiomyopathy, J. Am. Med. Assoc. 306 (3) (2011), https://doi.org/10.1001/jama.2011.992.
[40] Y. Naruse, A. Sato, K. Kasahara, et al., The clinical impact of late gadolinium enhancement in Takotsubo cardiomyopathy: Serial analysis of cardiovascular magnetic resonance images, J. Cardiovasc. Magn. Reson. 13 (1) (2011) 67, https://doi.org/10.1186/1532-429X-13-67.
[41] S. Nakamori, K. Matsuoka, K. Onishi, et al., Prevalence and signal characteristics of late gadolinium enhancement on contrast-enhanced magnetic resonance imaging in patients with takotsubo cardiomyopathy, Circ. J. 76 (4) (2012) 914–921.
[42] A. Rolf, H.M. Nef, H. Möllmann, et al., Immunohistological basis of the late gadolinium enhancement phenomenon in tako-tsubo cardiomyopathy, Eur. Heart J. 30 (13) (2009) 1635–1642, https://doi.org/10.1093/eurheartj/ehp140.
[43] R. Cau, P. Bassareo, F. Cademartiri, et al., Epicardial fat volume assessed with cardiac magnetic resonance imaging in patients with Takotsubo cardiomyopathy, Eur. J. Radiol. 160 (2023) 110706, https://doi.org/10.1016/j.ejrad.2023.110706.
[44] M.N. Bellera, J.T. Ortiz, M.T. Caralt, et al., Magnetic resonance reveals long-term sequelae of apical ballooning syndrome, Int. J. Cardiol. 139 (1) (2010) 25–31, https://doi.org/10.1016/j.ijcard.2008.08.023.
[45] S. Thomas, E. Charlotte, D. Stefanie, et al., Prevalence and clinical significance of life-threatening arrhythmias in Takotsubo cardiomyopathy, J. Am. Coll. Cardiol. 65 (19) (2015) 2148–2150, https://doi.org/10.1016/j.jacc.2015.02.062.
[46] R.J. Perea, J.T. Ortiz-Perez, M. Sole, et al., T1 mapping: Characterisation of myocardial interstitial space, Insights Imaging 6 (2) (2015) 189–202, https://doi.org/10.1007/s13244-014-0366-9.
[47] 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. 24 (1) (2022) 33, https://doi.org/10.1186/s12968-022-00866-0.
[48] C. Scally, A. Rudd, A. Mezincescu, et al., Persistent long-term structural, functional, and metabolic changes after stress-induced (Takotsubo) cardiomyopathy, Circulation 137 (10) (2018) 1039–1048, https://doi.org/10.1161/CIRCULATIONAHA.117.031841.
[49] Y. Aikawa, T. Noguchi, Y. Morita, et al., Clinical impact of native T1 mapping for detecting myocardial impairment in takotsubo cardiomyopathy, Eur. Hear. J - Cardiovasc. Imaging 20 (10) (2019) 1147–1155, https://doi.org/10.1093/ehjci/jez034.
[50] L. Arcari, G. Camastra, F. Ciolina, 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. Hear. J. - Cardiovasc. Imaging 24 (8) (2023) 1082–1091, https://doi.org/10.1093/ehjci/jead035.
[51] L. Arcari, L.R. Limite, C. Adduci, et al., Novel imaging and genetic risk markers in Takotsubo syndrome, Front. Cardiovasc. Med. 8 (2021) 703418, https://doi.org/10.3389/fcvm.2021.703418.
[52] Humayra S, Yahya N, Ning CJ, Mir IA, Mohamed AL, Manan HA. Systematic review of cardiovascular magnetic resonance imaging T1 and T2 mapping in patients with Takotsubo syndrome. Heliyon. 2024 Apr 16;10(9):e29755. doi: 10.1016/j.heliyon.2024.e29755. PMID: 38707280; PMCID: PMC11068528.
[53] Jensch PJ, Stiermaier T, Eitel I. Takotsubo Syndrome-Is There a Need for CMR? Curr Heart Fail Rep. 2021 Aug;18(4):200-210. doi: 10.1007/s11897-021-00518-x. Epub 2021 Jun 20. PMID: 34148183; PMCID: PMC8214719.