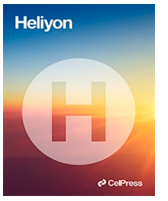
Heliyon 10 (2024) e29755

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Systematic review of cardiovascular magnetic resonance imaging T1 and T2 mapping in patients with Takotsubo syndrome

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ARTICLE INFO

Keywords:
CMR
Myocardial deformation
Prognosis
Takotsubo
T1 and T2 mapping

ABSTRACT

Background: Current imaging advancements quantify the use of cardiovascular magnetic resonance (CMR) derived T1 and T2 tissue characterization as robust indicators for cardiomyopathies, but limited literature exists on its clinical application in Takotsubo syndrome (TTS). This systematic review evaluated the T1 and T2 parametric mapping to delineate the current diagnostic and prognostic CMR imaging outcomes in TTS.

Methods: A comprehensive literature search until October 2023 was performed on ScienceDirect, PubMed, Web of Science, and Cochrane Library by two independent reviewers adhering to the PRISMA framework. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of studies.

Results: Out of 198 results, 8 studies were included in this qualitative synthesis, accounting for a total population of 399 subjects (TTS = 201, controls = 175, acute myocarditis = 14, and acute regional myocardial oedema without infarction = 9). Approximately 50.4 % were TTS patients aged between 61 and 73 years, whereof, females (n = 181, 90.0 %) and apical variants (n = 180, 89.6 %) were significantly higher, and emotional stressor (n = 42; 20.9 %) was more prevalent than physical (n = 27; 13.4 %). The NOS identified 62.5 % of studies as moderate and 37.5 % as high quality. Parametric tissue mapping revealed significantly prolonged T1 and T2 relaxation times at 1.5T and 3T respectively in TTS (1053–1164 msec, 1292–1438 msec; and 56–67 msec, 60–90 msec) with higher extracellular volume (ECV) fraction (29–36 %), compared to healthy subjects (944–1211 msec, 1189–1251 msec; and 46–54 msec, 32–68 msec; 23–29 %) and myocarditis (1058 msec, 60 msec). Other significant myocardial abnormalities included increased left ventricular (LV) end-systolic and diastolic volume and reduced global longitudinal strain.

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https://doi.org/10.1016/j.heliyon.2024.e29755
Received 14 December 2023; Received in revised form 24 March 2024; Accepted 15 April 2024
Available online 16 April 2024

Overall, myocardial oedema, altered LV mass and strain, and worse LV systolic function, with higher native T1, T2, and ECV values were consistent.
Conclusions: Future research with substantially larger clinical trials is vital to explore the CMR imaging findings in diverse TTS patient cohorts and correlate the T1 and T2 mapping outcomes with demographic/clinical covariates. CMR is a valuable imaging tool for TTS diagnosis and prognostication. T1 and T2 parametric mapping facilitates the quantification of oedema, inflammation, and myocardial injury in Takotsubo.

1. Introduction

Takotsubo syndrome (TTS), also known as stress cardiomyopathy, apical ballooning and broken heart syndrome is a non-ischemic heart failure that is acute yet reversible [1]. Takotsubo, was first described in Japan in 1990, where it acquired this distinctive title due to its close resemblance to an octopus trap [2]. Typical characteristics include transient left ventricular dysfunction, variable dyskinesia and ballooning of mid and apical segments [1]. Clinically, TTS resembles acute myocardial infarction (AMI) symptoms such as chest pain, electrocardiographic abnormalities, and troponin elevation; however, no culprit coronary artery disease (CAD) is found on coronary angiography in most cases; the condition is preceded by a severe physical or emotionally stressful trigger [3], and affects predominantly postmenopausal women [2]. During acute presentation, an echocardiogram (ECHO) is the first-line diagnostic modality to evaluate contractile dysfunction in suspected TTS patients with normal coronaries on an angiogram [1]. However, to accurately distinguish between TTS and AMI, interventionists have to identify a mismatch in myocardial perfusion and contractile function [4].

With the recent technological advancements, cardiovascular magnetic resonance (CMR) has become the preferred non-invasive imaging technique for TTS diagnosis, prognosis, and follow-up analysis [5]. The use of CMR in tissue characterization and prognostication has been remarkably transformed by longitudinal relaxation (T1), transverse relaxation (T2), extracellular volume (ECV) mappings, and threshold-based late gadolinium enhancement (LGE) measures [5]. ECV is a measurement of the extracellular matrix expansion in the heart without myocardial infarction. ECV is calculated using the T1 measurements of blood and myocardium before

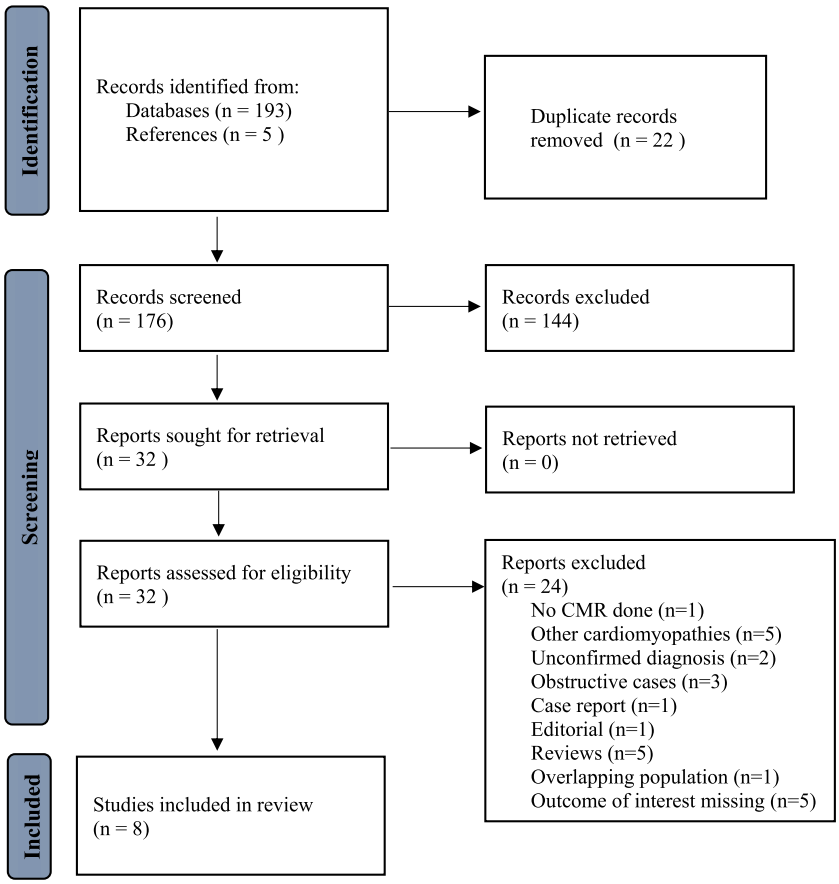

Fig. 1. Flowchart of study selection.

and after gadolinium contrast and hematocrit assessment [6]. CMR is more accurate in diagnosing TTS and helpful in ruling out other aetiologies, such as myocarditis or myocardial infarction, that may present with similar biochemical, echocardiographic, and angiographical findings [3]. Cardiac MRI parametric mapping enables myocardial assessment both visually and quantitatively by evaluating the alterations in focal and global tissue over time from initiation of disease to treatment response [7], and helps in the identification of complications that are not evident in other imaging modalities [3]. Cine-CMR can precisely evaluate the contractile function and provide a detailed depiction of the degree of apical ballooning along with an objective measurement of the wall motion anomalies and tissue strain. This is particularly meaningful in not just distinguishing TTS from similar cardiac entities but also in identifying rare TTS variants such as basal, biventricular, and midventricular ballooning patterns [8]. The reference standard for concise evaluation of the left and right ventricular volume and functions and the identification of regional wall movement abnormalities are facilitated by CMR [4]. The need to visually discern variations in signal intensities is eliminated by CMR mapping techniques. It quantifies each voxel's signal on a standardized scale and enables the direct measurement of the T1 (spin-lattice) or T2 (spin-spin) relaxation times in milliseconds (msec) [9]. Due to varying internal biochemical environments surrounding the protons, different cardiac tissues tend to have different T1 and T2 relaxation times. As a result, the signal intensity from a specific tissue is dependent upon both its proton density and T1 and T2 relaxation times in CMR [10]. Relaxation times enable additional tissue characterization based on the changes in the water content of the myocardial tissue. Notable variations in the relaxation times exist between different tissues, as well as the same tissues presenting with pathophysiological anomalies such as inflammation, ischemia, oedema, and fibrosis [9].

In current clinical practices, T1, T2, and ECV values are considered critical prognostic and therapeutic monitoring factors, and robust indicators for the diagnosis of cardiomyopathies [11]. Nevertheless, limited studies have addressed the TI and T2 tissue mapping parameters to distinguish TTS condition from other myocardial infarctions with non-obstructive coronary arteries (MINOCA) and evaluate its CMR imaging findings. Therefore, this study aims to systematically review the T1 and T2 parametric mapping application in takotsubo patients and investigate the diagnostic/prognostic outcomes detected in CMR.

2. Methods

2.1. Search strategy

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [12] as shown in Fig. 1, and it followed previous study guidelines [13–17]. The review protocol was prospectively recorded in PROSPERO registry (CRD42023471485). Four electronic databases (ScienceDirect, PubMed, Web of Science, Cochrane Library) were independently searched by two reviewers to identify relevant articles on takotsubo from inception till date. "Cardiovascular magnetic resonance imaging," "CMR," "cardiac MRI," "takotsubo syndrome," "takotsubo cardiomyopathy," "broken heart syndrome," "stress cardiomyopathy," "apical ballooning syndrome," "T1 mapping," and "T2 mapping," were searched separately and in combination using the Boolean operators ("AND/OR"). Original research articles on human subjects published in the English language with CMR intervention were considered for selection.

2.2. Inclusion and exclusion criteria

Takotsubo patients aged 18 years and above, with no signs of obstructive coronary arteries (stenosis $\geq$50 %) on clinical evaluation (echocardiogram/angiogram/ventriculogram) were selected as the target population. Healthy controls (HCs) without any abnormal CMR findings and/or positive cardiac anomalies, and patients clinically diagnosed with acute myocarditis (AM) were selected as comparator subjects. Prospective and retrospective studies, clinical trials, case-control, and cross-sectional studies were considered for selection. The PICOS criteria for study eligibility can be seen in Table 1. The diagnosis of takotsubo was confirmed/fulfilled by the European Society of Cardiology Statement [18] and/or the revised Mayo Clinic Criteria [19], as demonstrated in Fig. 2.

Exclusion criteria were patients with severe renal impairment (eGFR $<$30 mL/min/1.73m2), coronary artery disease, substance abuse, pacemakers or implanted devices, other types of cardiomyopathies (e.g., dilated, hypertrophic, peripartum, etc), valvular, hypertensive and ischaemic heart diseases, and/or individuals with contraindications to CMR. Non-English articles, conference abstracts, case reports, review articles and meta-analyses, and letters to the editor were also excluded. The detailed exclusion criteria can be found in Suppl Table 2.

Table 1
PICOS criteria for the selection of studies.

Population	• Takotsubo patients (18 years and above) with evidence of non-obstructive coronaries (no stenosis $\geq$50 %)
Intervention	• Cardiovascular magnetic resonance (CMR) imaging
Comparison	• Healthy control/acute myocarditis
Outcome of interest	• CMR T1 and T2 mapping to identify relaxation times and myocardial tissue characterization in takotsubo patients
Study design	• Prospective and retrospective cohorts, randomized controlled trials, case-control and cross-sectional studies

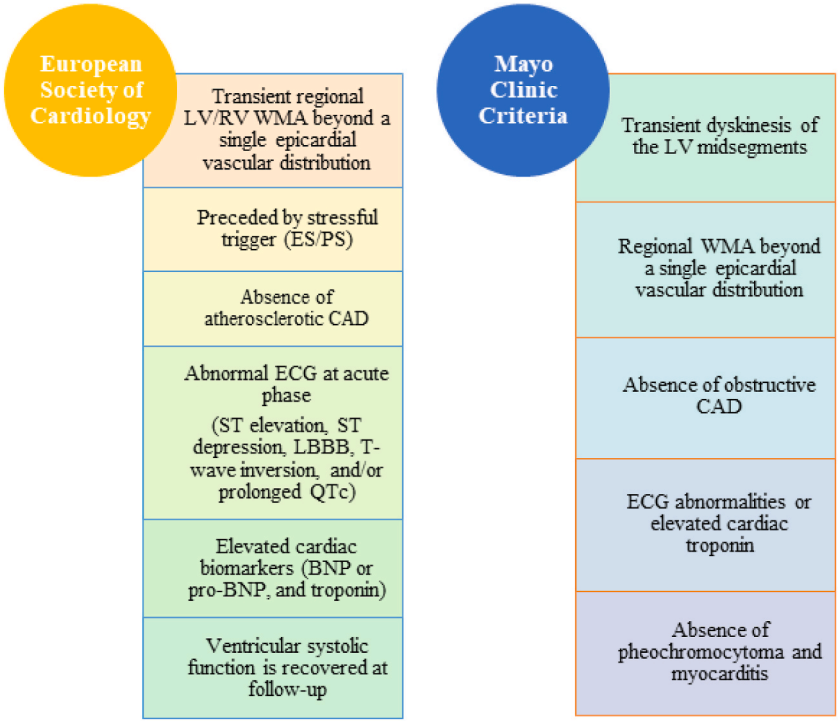

Fig. 2. Diagnostic criteria for Takotsubo syndrome.

2.3. Study selection

After the elimination of duplicates, two authors evaluated the titles and abstracts listed by the databases to determine their eligibility as shown in Fig. 1. The full-text reports of these qualifying studies were independently evaluated for final inclusion after both investigators reached a consensus through discussion with a third author. Studies reporting the CMR-derived T1 and/or T2 mapping values acquired at 1.5 T or 3 T were selected for inclusion. The reference lists were also reviewed to select any potential studies that remained unidentified in the primary search results.

2.4. Data extraction

Data were extracted from the included studies by one author and checked by a second author. The characteristics of the studies such as author, year, country, study design, sample size, study group participants, follow-up time, MRI protocol and mapping, takotsubo diagnostic criteria, and outcome measures were recorded and presented in Table 2. At the same time, relevant data regarding patient characteristics such as age, gender, symptom presentation, clinical findings, complications, and adverse events (if any) were presented in Table 3. Lastly, T1 and T2 relaxation times, CMR imaging-related information (region of interest, field strength, and sequence), presence or absence of LGE, and alterations in myocardial indexes (LV function, mass, volume, and strain) were also extracted as shown in Table 4. Data were reported either as mean ± standard deviation (SD) or as median with interquartile range. The CMR outcome data of comparator subjects (HC and AM) were extracted if available, and the main findings were summarized.

2.5. Quality assessment

The methodological assessment of studies was carried out by two independent reviewers using the Newcastle-Ottawa quality assessment scale (NOS) [28]. The quality of included studies was measured based on the three key domains of this scale: selection (4 items); comparability (1 item); and exposure/outcome (3 items). The NOS criteria for case-control studies, evaluated the definitions and representativeness of cases, the selection and definition of controls; followed by the comparability of cases and controls; the ascertainment of exposure, the method of ascertainment for cases and controls, and the non-response rate. In the case of cohort studies, the selection domain involved representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration of outcome being absent at the start of the study; followed by the comparability of cohorts; and lastly, the assessment of outcome, duration of follow-up for desired outcomes to occur, and the adequacy of follow-up. The overall study quality was measured using a star rating system, where each cohort and case-control study received a maximum quality score of nine stars, and was categorized as low-(0–3 stars), moderate-(4–6 stars), and high quality (7–9 stars).

Table 2
Summary of study characteristics.

Study, Year	Country	Study design	Sample size	Study groups	Follow-up (Days)	MRI protocol & mapping	Outcome measures	Diagnostic criteria
Arcari et al. [20]	Italy	Case-control	55	TTS = 32; HC = 23	Median = 248 (IQR = 132, 391)	CMR (T1 and T2 mapping, and scar imaging)	Cardiac volumes, function, mass, GLS, and GCS	Coronary angiogram, echocardiography, and left ventriculography
Cau et al. [21]	Italy	RC	43	TTC = 18; AM = 14; HC = 11	No follow-up	ML approach non-contrast Cine-CMR (T1 and T2 mapping)	T1 and T2 relaxation time, global and regional LV strain	Position Statement of the European Society of Cardiology Heart Failure Association
Singh et al. [2, 22]	UK	Case–control	40	TTS = 20; HC = 20	Median = 100 days (IQR = 87–368)	Manganese-enhanced CMR (native T1 and T2 mapping cine images)	T1 and T2 relaxation time, and LV function (acute vs recovery phase)	Mayo Clinic and Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology Coronary angiography and ventriculography
Vermes et al. [23]	France	PC	64	TTS = 30; HC = 34	Mean = 91 days	CMR (native and post contrast T1 and T2 mapping)	T1 and T2 relaxation time, and ECV	Coronary angiogram
Dabir et al. [24]	Germany	PC	28	TTS = 14; HC = 14	Mean = 50 days	CMR (native and post-contrast T1 and T2)	T1 and T2 relaxation time, and ECV	Heart Failure Association of the European Society of Cardiology
Aikawa et al. [25]	Japan	PC	31	TTC = 23; HC = 8	Median = 96 days	CMR (T1 and T2 mapping)	T1 and T2 relaxation time, LV function and volumes	Mayo Clinic criteria Coronary angiography Left ventriculography
Schwarz et al. [26]	Australia	PC	96	TTS = 52; HC = 44	Mean = 122 ± 5 days	Contrast-enhanced CMR (native T1 mapping)	T1 value, LV strain, twist mechanics, and myocardial structure	Takotsubo Mayo Clinic criteria Coronary angiography and left ventriculography
Ferreira et al. [27]	UK	PC	42	TTC = 12; Myocardial oedema without infarct = 9; HC = 21	No follow-up done	Pre- and post-contrast-enhanced CMR (T1 and T2 mapping)	Myocardial oedema, T1 value and T2 SI ratio	Mayo clinic criteria Coronary angiography and ventriculography

AM = acute myocarditis; CMR = cardiac magnetic resonance; ECV = extracellular volume; GCS = circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; HC = healthy control; LV = left ventricular; ML = machine learning; NR = not reported; PC = prospective cohort; RC = retrospective cohort; TTC = takotsubo cardiomyopathy; TTS = takotsubo syndrome.

3. Results

3.1. Literature search

The electronic search identified a total of 193 potential studies in ScienceDirect, PubMed, Web of Science, and Cochrane Library. In addition, 5 articles were manually included after reviewing the reference lists. Out of a total of 198 results, 176 articles were screened by titles and abstracts after the removal of 22 duplicates. After the exclusion of irrelevant records, a total of 32 studies were considered for full-text review, whereof, 24 studies were excluded due to ineligibility, and finally, 8 studies were included in the qualitative synthesis. The PRISMA flow diagram depicting the study selection process and rationale for exclusion can be seen in Fig. 1.

3.2. Study characteristics

The publication time frame existed between 2012 and 2023. Out of eight, two studies were conducted in Italy [20,21], two in the UK [22,27], one in France [23], one in Germany [24], one in Japan [25], and one in Australia [26]. The majority of the studies [23–27] were prospective cohorts, while others adopted case-control [20,22] and retrospective [21] study designs. The sample size ranged between 28 and 96 and accounted for a total population of 399 subjects (TTS = 201, controls = 175, myocarditis = 14, and myocardial oedema = 9). Most of the studies [20,22,23–26] compared two groups (TTS patient vs. control), whilst others [21,27] had three study groups. One of them compared TTS patients with HCs and AM [21], and the other one [27] compared the TTS cohort with HCs and subjects with myocardial oedema without infarction. Six out of eight studies followed up TTS subjects from baseline (acute phase/on admission) to follow-up (chronic/reversible state), whereas, two studies [21,27] did not have any follow-up data. The follow-up duration ranged from 50 to 248 days. Almost all studies presented the T1 and T2 mapping outcomes using CMR imaging protocol and evaluated the abnormal changes in myocardial tissue properties. Across all studies, the diagnosis of takotsubo was based on the

Table 3
Demographic and clinical characteristics of takotsubo patients.

Study, Year	Age (Years)	Gender n (%)	Comorbidities	Symptomatic presentation	Stress trigger	Troponin	LVEF	ECG finding	ECHO finding	Complication	Adverse event
Arcari et al. [20]	72 ± 12	M = 2 (6 %); F = 30 (94 %)	HTN = 24 (75 %); DM = 3 (9 %); DLD = 12 (37 %); Smoker = 4 (12 %)	ACP = 19 (59 %); D = 4 (12 %)	ES = 19 (59.4 %); PS = 11 (34.4 %) No trigger = 2 (6.2 %)	NR	41 ± 8 %	ST-elevation = 16 (50 %); T-wave inversion = 14 (44 %)	Apical = 26 (81 %); MV = 4 (12 %); Focal = 2 (6 %)	Pulmonary oedema = 2 (6 %); Arrhythmia = 1 (3 %)	Death = 1 (non-cardiovascular cause)
Cau et al. [21]	69 ± 10	M = 1 (5.6 %); F = 17 (94.4 %)	NR	ACP (inclusion criteria)	NR	NR	58.71 ± 8.9	NR	Apical only (inclusion criteria)	NR	NR
Singh et al. [2, 22]	63 ± 12	M = 2 (10 %); F = 18 (90 %)	HTN = 8 (40 %); HCL = 5 (25 %); DM = 2 (10 %) Psychiatric disorder = 14 (70 %)	Chest pain = 14 (70 %); Dyspnea = 6 (30 %);	Emotional = 13 (65 %); physical = 4 (20 %); No specific trigger = 3 (15 %)	6981 ng/L	36%–49 % = 9 (45 %); <35 % = 7 (35 %)	ST-elevation = 8 (40 %); T-wave inversion = 10 (50 %)	Apical = 17 (85 %); Basal = 1 (5 %); Focal = 2 (10 %)	NR	Cerebrovascular event = 1 (5 %); Reoccurrence = 1 (5 %)
Vermes et al. [23]	Median = 73	M = 4 (13.3 %) F = 26 (86.7 %)	NR	NR	NR	NR	48 %	NR	Apical = 21 (70 %)	NR	NR
Dabir et al. [24]	67 ± 18	M = 2 (14.3 %); F = 12 (85.7 %)	NR	Chest pain = 11; Dyspnea = 8	ES = 5 (35.7 %); PS = 9 (64.3 %)	Max = 5.42 ng/mL	46 ± 10 %	ST-elevation = 1; ST-depression = 4; LQTS = 7	Apical = 13 (93 %) MV = 1 (7 %)	NR	NR
Aikawa et al. [25]	63 ± 11	M = 2 (8.7 %); F = 21 (91.3 %)	HTN = 17 (74 %); HLD = 13 (57 %); DM = 6 (26)	Chest pain and/or dyspnea = 21 (91 %)	NR	Elevated troponin = 19 (83 %)	46 ± 8 %	ST-elevation = 17 (74); T-wave inversion = 4 (17 %)	Apical only	NR	Oozing cardiac rupture = 1, LV thrombus = 1, and cardiac tamponade = 1
Schwarz et al. [26]	66 ± 11	M = 5 (8); F = 47 (92 %)	HTN = 15 (28 %); Diabetes = 5 (9 %); Mental health disease 17 (34 %)	Chest pain = 41 (79 %); Syncope = 9 (17 %)	ES only (inclusion criteria)	3.81 (1.2–8.8	45 ± 13 %	ST-segment elevation = 41 (79 %)	Apical only	Pulmonary oedema = 2 (4 %)	Death = 4 (cardiogenic shock = 2, arrhythmic cardiac arrest = 1, and suicide = 1)
Ferreira et al. [27]	61 ± 10	M = 2 (16.7 %); F = 10 (83.3 %)	NR	ACP = 11 (91.7 %); D = 1 (8.3 %)	ES = 5 (41.7 %); PS = 3 (25 %); No clear trigger = 4 (33.3 %)	8.26 μg/L (0.84–36.80 μg/L)	61 ± 10 %	ST-elevation/ T-wave inversion (inclusion criteria)	Apical = 10 (83.3 %); MV = 2 (16.7 %)	NR	NR

ACP = acute chest pain; D = dyspnea; DLD = dyslipidaemia; DM = diabetes mellitus; ES = emotional stressor; F = female; HCL = hypercholesterolemia; HLD = hyperlipidemia; HTN = hypertension; LQTS = long QT syndrome; M = male; MV = midventricular; PS = physical stressor.

Table 4
Cardiac MRI outcomes in takotsubo patients to highlight myocardial deformation.

Study, Year	ROI	Field strength and Sequence	Cardiac MRI outcomes (TTS subjects/Comparator groups)											Main findings
			Myocardial tissue mapping			LVEF (%)	LV mass (g/m^2)	Cardiac volumes (mL/m^2)		LV strain (%)			LGE	
			T1 relaxation time (msec)	**T2 relaxation time (msec)**	**ECV (%)**			**LVEDV**	**LVESV**	**GLS**	**GCS**	**GRS**		
Arcari et al. [20]	Basal septal segment	1.5T STIR	Native T1 = 1116 ± 73/ 970 ± 23	T2 = 56 ± 5/ 46 ± 2	32 ± 5/24 ± 1	49 ± 12 61 ± 5	55 ± 11 46 ± 8	76 ± 18/74 ± 13 (ns)	39 ± 15/ 29 ± 8	−17 ± 4/-24 ± 4	−16 ± 4/-22 ± 3	NR	Absent	Takotsubo patients had significantly higher LV mass and strain, worse systolic function, higher septal native T1, T2 and ECV values CMR T1 and T2 mapping demonstrated increased myocardial oedema in acute TTS which can be a potential prognostic marker and therapeutic target
Cau et al. [21]	Apical, mid-ventricular, and basal segments	1.5T MOLLI STIR	Global T1 = 1141.78 ± 67.45/ 1058.3 ± 95.58/ 1031.26 ±76.59	T2 = 63.85 ± 4.47/ 60.08 ± 5.92/54.82 ± 3.9	NR	58.71 ± 8.9/ 58.11 ± 5.03/ 59.24 ± 4.88 (ns)	NR	72.37 ± 16.03/ 90.42 ± 18.14/ 78.84 ± 12.49	29.86 ± 9.63/ 38.57 ± 11.85/ 32.12 ± 6.13 (ns)	−12.91 ± 2.62/-12.45 ± 2.24/-17.76 ± 1.82	−16.02 ± 9.13 −18.46 ± 2.61 −20.56 ± 2.17 (ns)	30.31 ± 7.35 28.44 ± 7.32 36.14 ± 6.59	–	CMR using a ML model identified TTC subjects with increased T1 and T2 relaxation time with abnormal GLS and GRS
Vermes et al. [23]	Basal, mid and apical	1.5T NR	Native T1 = 1053 ± 75/ 960 ± 61	T2 = 59 ± 8/ 51 ± 4	29 ± 5/23 ± 3 %	48 %/NR	NR	NR	NR	NR	NR	NR	No patients had LGE visually assessed	Native T1 value and T2 relaxation time, and ECV were significantly higher in the TTS group T2 and native T1 mapping have the ability to detect acute myocardial injury with a high diagnostic accuracy
Dabir et al. [24]	Apical, mid, basal	1.5T MOLLI GraSE STIR	Native T1 = 1132 ± 82/ 956 ± 27	T2 = 67 ± 7/ 52 ± 2	36 ± 9/28 ± 4	46 ± 10 %/62 ± 2 %	NR	117.4/158	NR	NR	NR	NR	Absent	TTS patients had significantly impaired LVEF and acute wall motion abnormalities.

(*continued on next page*)

Table 4 (*continued*)

Study, Year	ROI	Field strength and Sequence	Cardiac MRI outcomes (TTS subjects/Comparator groups)											Main findings
			Myocardial tissue mapping			LVEF (%)	LV mass (g/m^2)	Cardiac volumes (mL/m^2)		LV strain (%)			LGE	
			T1 relaxation time (msec)	**T2 relaxation time (msec)**	**ECV (%)**			**LVEDV**	**LVESV**	**GLS**	**GCS**	**GRS**		
														Native T1 and T2 values, and ECV fraction were significantly higher Native T1 and T2 mapping, and ECV fraction, discriminate between visually affected vs. unaffected segments in takotsubo and reveal significant T1 and T2 tissue changes
Ferreira et al. [27]	–	1.5T ShMOLLI STIR	Native T1 = 1064 ± 51/ 1051 ± 98/ 944 ± 17	NR	NR	61 ± 10/66 ± 9/75 ± 6	NR	NR	NR	NR	NR	NR	Absent	T1 value significantly increased in patient segments with abnormal and normal wall motion compared to controls T1-mapping may serve as a complementary technique to T2W imaging for assessing myocardial oedema in heart diseases
Singh et al. [2, 22]	Mid-ventricular/ basal	3T MOLLI	Native T1 = 1358 ± 49/ 1211 ± 28	T2 = 60 ± 7/ 38 ± 3	34 ± 5/26 ± 3	51 ± 11/67 ± 8 %	86 ± 11/57 ± 14	71 ± 20/79 ± 15 (ns)	36 ± 11/ 27 ± 7	−12 ± 6/−18 ± 1	NR	NR	Present	Manganese-enhanced CMR recognized TTS cohort with significantly higher T1, T2, and ECV fraction and increased LV mass, ESV and GLS
Aikawa et al. [25]	Base, mid-ventricle, and apex	3T HASTE MOLLI MESE	Native T1 = 1438 ± 162/ 1251 ± 90	T2 = 90 ± 34/68 ± 12	35 ± 5/29 ± 4	46 ± 8/62 ± 2	NR	73 ± 23/78 ± 12 (ns)	39 ± 16/ 31 ± 6 (ns)	NR	NR	NR	Absent	TTC patients relatively have higher native T1, ECV, and T2 relaxation time Native T1 mapping offers high diagnostic performance, detection of myocardial oedema, and prediction of LV

(*continued on next page*)

Table 4 (*continued*)

Study, Year	ROI	Field strength and Sequence	Cardiac MRI outcomes (TTS subjects/Comparator groups)											
			Myocardial tissue mapping			LVEF (%)	LV mass (g/m^2)	Cardiac volumes (mL/m^2)		LV strain (%)			LGE	Main findings
			T1 relaxation time (msec)	**T2 relaxation time (msec)**	**ECV (%)**			**LVEDV**	**LVESV**	**GLS**	**GCS**	**GRS**		
														wall motion restoration in TTC
Schwarz et al. [26]	Basal and apical	3T MOLLI	Native T1 = 1292 ± 80.6/1189 ± 16	NR	33 ± 4/27 ± 5	53 ± 15/66 ± 4 (ns)	139 (114–154)/ 106 ± 21	132 (110–152)/ 118 ± 16 (ns)	56 (46–83)/ 41 ± 9 (ns)	−10 ± 3/-19 ± 1	NR	NR	NR	Native T1 and ECV values in TTS were significantly higher in both normally contracting and dysfunctional segments Regional LV systolic and diastolic deformation abnormalities persisted beyond the acute event, despite normalization of global LV EF and size

ECV = extracellular volume; GraSE = gradient echo spin echo; HASTE = half fourier Single-shot Turbo spin-Echo; MESE = multi echo spin echo; MOLLI = modified look-locker inversion recovery; msec = milliseconds; NR = not reported; ShMOLLI = shortened modified look-locker inversion recovery; STIR = short tau inversion recovery.

Position Statement of the European Society of Cardiology Heart Failure Association and/or the Takotsubo Mayo Clinic Criteria; except for two studies [20,23] that did not report the diagnostic criteria but they performed imaging modalities for confirmed diagnosis. The study characteristics of the CMR imaging protocol and mapping of the included studies are detailed in Table 2.

3.3. Study quality

The NOS quality assessment revealed that 87.5 % of the included studies earned 3 stars and above for the NOS selection item, 62.5 % earned 1 star for the NOS comparability item, 50.0 % of the case-control studies earned 3 stars for the NOS exposure item, and 67.7 % of the cohort studies earned 2 stars for the NOS outcome item. Only one of the included studies received the maximum NOS quality score. The definitions of patients and controls were adequately described across all studies; however, the selection of non-exposed cohort/controls (community/hospital-based and derived from same/different source) was not mentioned in four studies, and one study did not specify the representativeness of the exposed cohort/cases. In terms of comparability between patients and controls, almost all included studies adjusted an important confounding factor (age/sex) and three studies matched control groups with additional comorbid/cardiovascular factors. The ascertainment of exposure for controls and cases was adequately presented. Although the ascertainment of CMR mapping outcomes was adequate, the independent blinding assessment was not carried out in most cases. At the same time, there was inadequacy in reporting the clinical characteristics and follow-up information. Nevertheless, the overall quality of included studies was between moderate to high according to the NOS criteria. A summary of the quality assessment is shown in Supp Table 3.

3.4. Demographic and clinical characteristics

Among 201 TTS patients aged between 61 and 73 years, 181 (90.0 %) were females and 20 (10.0 %) were males. Four out of eight studies did not report the comorbid status of the patients, while the others presented hypertensive (n = 64, 31.8 %) and diabetic patients (n = 16, 8.0 %), and two studies [22,26] had individuals with psychiatric or mental health conditions (n = 31, 15.4 %). Symptomatically, acute chest pain (ACP) (n = 135, 67.2 %) and dyspnoea (n = 40, 20.0 %) were prevalent across the studies. However, one study [23] did not report the symptomatic presentation in patients, and another study [21] had ACP as an inclusion criterion. During, the acute phase, the majority of patients demonstrated increased emotional stressor (ES) (n = 42; 20.9 %) compared to the physical stressor (PS) (n = 27; 13.4 %). However, three studies [21,23,25] did not report the TTS stressful trigger, and one study [26] had ES as an inclusion criterion. In addition, some TTS patients (n = 9; 4.5 %) showed no clear trigger on examination. Elevated cardiac troponin was reported in most of the studies, except three articles [20,21,23], which did not report the troponin values. Left ventricular ejection fraction (LVEF) values ranged between 35 % and 61 %. ECG findings demonstrated an ST-segment elevation in five studies among 83 (41.3 %) TTS patients and T-wave inversion in 28 (14.0 %) patients. Whereas, ST-depression and long QT syndrome were observed in one study only [24], accounting for one case and seven cases respectively. An apical variant was the most prevalent form of TTS presented among patients (n = 180, 89.6 %), in comparison to other forms such as mid-ventricular (n = 7, 3.5 %), basal (n = 1, 0.5 %), and focal (n = 4. 2.0 %). On follow-up, only two studies reported complications, whereof, pulmonary oedema was present in both [20,26]. Mortality was reported in two studies [20,26] and constituted a total of 5 deaths, majorly due to cardiovascular causes. Other adverse events included cerebrovascular events and recurrence of TTS [22], oozing cardiac rupture, LV thrombus, and cardiac tamponade [25].

3.5. Cardiac MRI outcomes in takotsubo

The primary outcome measures were the CMR mapping parameters (T1/T2/ECV values), and the secondary outcomes were the myocardial deformation markers (LVEF/LV mass/LVEDV/LVESV/GLS/GCS/GRS). Five studies used the 1.5 T field strength [20,21,23,24,27], and three studies used a 3T scanner for high-field imaging evaluation [22,25,26]. Apical, mid, and basal segments were the most commonly reported ROIs in CMR imaging. The modified look-locker inversion recovery (MOLLI) and the short tau inversion recovery (T2 STIR) were predominantly used measurement sequences for T1 and T2 CMR mapping.

In 1.5 T field strength, the native T1 relaxation times among TTS patients ranged between 1053 and 1164 msec, and in 3 T, from 1292 to 1438 msec. In controls, the T1 (1.5 T) values ranged between 944 and 1211 msec, and 1189–1251 msec (3 T). In terms of comparator groups, patients with AM had 1058 msec T1 timing [21] and the group with acute regional myocardial oedema without infarction had 1051 msec at 1.5 T [27]. In TTS, the highest T1 relaxation time at 1.5 T was reported in Ferreira et al. [27] and at 3 T in Aikawa et al. [25]. The T2 values in takotsubo ranged between 56 and 67 msec at 1.5 T, and 60–90 msec at 3 T CMR scan. The highest values were recorded in Dabir et al. [24] and Aikawa et al. [25] respectively. Healthy subjects showed T2 values between 46 and 54 msec (1.5 T) and 32–68 msec (3 T). In AM group, the T2 value was 60 msec at 1.5 T [21]. Two studies [27,26] did not report the T2 relaxation times. The ECV fraction ranged between 23 and 29 % in HCs, and 29–36 % in TTS, whereof, the highest value was observed in Dabir et al. [24]. Overall, the study results indicated that the T1 and T2 prolongation times and ECV values were significantly higher in TTS patients than the comparator groups.

Simultaneously, it was also found that the LVEF (46–61 % vs. 59–75 %) was significantly lower [20,22,27,24,25] and LV mass (55–139 g/m^2 vs. 46–106 g/m^2) was remarkably higher in TTS subjects compared to controls [20,22,26]. Although myocardial oedema was consistent across six studies, nevertheless, two studies [25,26] did not report any significant changes in the cardiac volumes (LV end-systolic and diastolic volume). On the other hand, two studies revealed significantly increased LVEDV in TTS subjects compared to others (72.37 ± 16.03 mL/m^2 vs. 90.42 ± 18.14 mL/m^2 vs. 78.84 ± 12.49 mL/m^2; 117 vs. 158 mL/m^2; $p < 0.05$) [21,24].

While, the remaining two studies found a significant rise in the LVESV (39 ± 15 mL/m^2 vs. 29 ± 8 mL/m^2; 36 ± 11 mL/m^2 vs. 27 ± 7 mL/m^2; $p < 0.05$) among TTS groups [20,22]. Myocardial strain analysis was performed in four studies [20–22,26], and it revealed significantly reduced global longitudinal strain (GLS) (-17 ± 4 % vs. -24 ± 4 %; -12.91 ± 2.62 % vs. -12.45 ± 2.24 % vs. -17.76 ± 1.82 %; -12 ± 6 % vs. -18 ± 1 %; -10 ± 3 % vs. -19 ± 1 %), and global circumferential strain (GCS) (-16 ± 4 %, -22 ± 3 %) [20] among the TTS patients. In addition, significant differences in global radial strain (GRS) was also observed in one study (30.31 ± 7.35 % vs. 28.44 ± 7.32 % vs. 36.14 ± 6.59 %) [21], although diminished GLS was more prevalent than GCS and GRS. Lastly, the presence of LGE was noted in one study only, in which, the two TTS subjects presented with AMI as well [22].

4. Discussion

Previously, several literature reviews [4,5,29–33] highlighted the clinical significance of CMR in takotsubo; nevertheless, the systematic representation of the tissue mapping characteristics and follow-up prognostic outcomes in this target population was found to be limited. Recently, few studies [8,34,35] evaluated the diagnostic role of CMR imaging modality in MINOCA but focused more on the classification of non-ischemic entities, such as myocarditis, TTS, and cardiomyopathies, in general. In contrast, the current systematic review integrated the existing literature on CMR-based parametric mapping, and found that the TTS patients have significantly higher native T1, T2, and ECV values, which can be used to reach precise diagnostic consensus in clinical practice by comparing the reference cut-off values of healthy and AM subjects. Secondly, the exploration of myocardial deformation markers and follow-up prognostication in this study may shed further light on the TTS disease progression and promote its effective management.

The parametric quantitative sequences in CMR T1 and T2 mappings yield tissue-specific T1 and T2 values. It enables the comparison of measured myocardial parameters with normal reference values, under standardized scanning conditions (e.g., scanner type, contrast agent, and scan time) [11]. The differentiation between abnormal and healthy myocardium is based on quantitative analysis of factors such as myocardial scarring, oedema, and paramagnetic iron-containing depositions since they tend to modulate the myocardial T1, T2 and T2* time constants [36]. According to previous clinical applications among healthy individuals, the normal native T1 reference values using MOLLI have been reported to be 930 ± 21 msec at 1.5 T and 1052 ± 23 msec at 3T; while the normal T2 values using steady-state free precision (SSFP) have been reported to be 52.18 ± 3.4 ms at 1.5T and 45.1 ms at 3T, considering that normal values largely vary between scanners, sequences and local post-processing softwares and even between similar MOLLI sequences [37]. Myocardial ECVs in HCs were similar at field strengths of 1.5T (0.25 ± 0.04) and 3T (0.26 ± 0.04) [11]. A previous study investigating the T1 and T2 relaxation times in myocarditis reported significant differences between AM and HCs at baseline (T1 = 986.5 ± 44.4 msec vs. 965.1 ± 28.1 ms; T2 = 55.5 ± 3.2 msec versus 52.6 ± 2.6 msec), and on last follow-up (T2 = 54.9 ± 3.0 msec vs. 52.6 ± 2.6 msec) [38]. In the present review, T1 (1.5 T: 1053–1164 msec; 3 T: 1292–1438 msec) and T2 relaxation times (1.5 T: 56–67 msec; 3 T: 60–90 msec) in patients with takotsubo were significantly prolonged, and showed increased ECV fraction (29–36 %). While, the T1/T2/ECV values in healthy subjects (1.5 T: 944–1211 msec; 3 T: 1189–1251 msec/1.5 T: 46–54 msec; 3 T: 32–68 msec/23–29 %) and AM patients (1.5 T: 1058 msec/1.5 T: 60 msec) [38] ranged almost within the reference cut-off values from previous literature [11,38].

Cumulatively, takotsubo patients showed increased LV mass and strain, worse systolic function, higher native T1, T2 and ECV values. The majority of TTS patients exhibited myocardial oedema in areas with abnormal systolic function. This is possibly due to inflammation, elevated wall stress, or transient ischemia, and it is suggestive of the degree and kind of tissue damage [39]. Between the acute-subacute phase, the majority of the CMR parameters were significantly elevated in the TTS group compared to others, thus indicating prominent inflammatory alterations of the myocardium. Furthermore, studies that compared the baseline and follow-up CMR data, found a significant and consistent decrease in the CMR parameters (T1 and T2 relaxation times, ECV, and myocardial deformation indexes) in TTS subjects. In addition, native T1 and ECV values in TTS were significantly higher in both normally contracting and dysfunctional segments. Regional LV systolic and diastolic deformation abnormalities persisted beyond the acute event, despite normalization of global left ventricular size and function. Due to the inflammatory changes in myocardial tissue, CMR recognized TTS cohort with significantly reduced GLS and GRS, and increased ESV index. Basal RS and apical tissue mapping analysis can be stated as the most advanced CMR parameters in differentiating TTS from AM. In summary, high diagnostic accuracy can be achieved by detecting acute myocardial injury and oedema through the implementation of native T1 and T2 mapping, which can also predict the restoration of LV wall motion in takotsubo.

Prolongation in T2 relaxation times are primarily caused by increased myocardial water content and serves as an accurate indicator of myocardial oedema [40]. Oedema caused by an increase in intra- and extracellular fluid is typically diffuse in nature, and it disappears along with the restoration of myocardial contractility in a few weeks. Therefore, oedema is a hallmark diagnostic characteristic for identifying the degree and extent of myocardial stunning in TTS patients [4]. A recent meta-analysis validated that higher T2 mapping values can help in distinguishing patients with myocardial infarction, dilated cardiomyopathy, myocarditis, and heart transplantation [36]. In TTS cases, the oedema patterns can be typically distinguished from other cardiac pathologies as they frequently exhibit diffuse transmural oedema, which differs greatly from the sub-epicardial or mid-myocardial oedema in myocarditis. Furthermore, no specific vascular area limits the degree of oedema involvement in TTS unlike AMI, where oedema is only limited to the corresponding damaged vessel [8]. Conversely, alterations in the T1 relaxation times are often linked to typical cardiac pathologies including diffuse myocardial fibrosis, oedema, inflammation, and infiltrative diseases [11]. In the presence of myocardial oedema, ECV is a metric which is sensitive to myocardial water [41]. Whereas, an increased ECV is most typically attributable to excessive collagen deposition as a result of adverse myocardial structural remodelling in non-ischemic cardiomyopathies (NICM), which could be a strong indicator of myocardial fibrosis in TTS [42].

CMR is superior to ECHO in several ways, especially, in terms of identifying right ventricular (RV) involvement in isolated RV TTS

since it has a detrimental impact on cardiac outcomes [39]. Although initially RV involvement in TTS was thought to be rare, recently, with the increasing use of CMR, it has been noted in some cases, hence a higher resolution may provide better visibility of regional dysfunction and restoration of myocardium [3]. Crucially, the lack of LGE in areas of the heart that are dysfunctional enables the differentiation of TTS from other disorders, such as acute coronary syndrome [39]. Although cardiac MRI offers better contrast compared to computed tomography, however, in the clinical setting, contrast agent (Gadolinium) is usually needed in suspected cases of Takotsubo and during follow-up [43]. Myocardial injury can be diagnosed, staged, and tracked with quantitative CMR parametric mapping, and the limitations of T2-weighted imaging for a reliable assessment of diffuse myocardial oedema are well ensured [40].

Despite the numerous advantages of CMR, the parametric mapping methods still require further research for validation on the standardization of sequences and cut-off values in clinical practice guidelines [4]. Previous studies associated prolonged T2 relaxation time with increasing age, female gender, and apical segments [40], and T1 relaxation time was correlated with blood pressure, heart rate (HR), and EF [43]. Another study also reported similar alterations showing higher T1 and T2 values in healthy females, with prolonged T1 and shortened T2 in increased HR [9]. In addition, the strength of the magnetic field also affects the tissue relaxation characteristics, as higher fields are predicted to result in longer T1 and shorter T2 values [44]. The differences in mapping values among studies make it more difficult to compare results with external values; for this reason, local healthy reference values are necessary to evaluate quantitative data in a clinical context [36]. Additionally, given that most cardiomyopathies exhibit similar variations in T2 and T2* levels, disease distinction based on T1 and T2 mapping alone are restricted, and require evaluation of other cardiac MRI parameters for accurate TTS diagnosis [36].

5. Limitations and future directions

In the majority of the studies, males were underrepresented compared to females. There were notable differences in CMR imaging time, field strength, and sequence. Since the T1 and T2 relaxation times may vary due to physiological factors and differences in CMR protocols [9], these could be potential limitations. Due to missing/incomplete data on study outcomes and overlapping populations, some studies had to be excluded. The scarce number of studies compromised the data availability for qualitative analysis. At the same time, reporting of the myocardial outcomes and clinical characteristics was varied, inconsistent, or unreported. Additionally, the HR was not reported in most of the studies which may have influenced the CMR outcomes. Although the majority of the included studies adjusted the confounding effects of age and sex, the cardiovascular risk factors, comorbid status, and psychological well-being were not uniformly justified. Moreover, few studies had apical TTS and ES in higher proportion, which may have contributed to possible differences in study outcomes as well. Most of the studies were single-centered, and the selection of participants was both hospital and community-based. This could give rise to possible discrepancies in demographic/clinical factors among study participants. Nevertheless, the cumulative effects of these differences are likely to be small in magnitude since most of the participants were recruited from international health registries and thus may have had greater representativeness of the general population. Despite this fact, participant/patient-related differences may have still contributed to some heterogeneity across studies. Overall, the amount of variability seen across the studies, mostly owing to the different patient groups and CMR protocols led to some notable heterogeneity; therefore, it was not possible to conduct a sensitivity analysis or quantify the pooled data through a meta-analysis.

In NICM including TTS, native T1 measures were significantly predictive of adverse cardiovascular events and all-cause mortality [9]. In addition, GLS normalization at follow-up was greater predictor of event-free survival than LVEF normalization [45]. Hence parametric tissue mapping can be used to detect acute and chronic myocardial changes to target baseline vs. follow-up events [9], facilitating better diagnostic performance and disease prognostication. However, disease prognostication and myocardial deformation indexes were not comprehensively quantified in this review since most of the included studies did not compare the baseline and follow-up CMR outcomes, and there were some inconsistencies in the follow-up period and/or CMR image performing time. The RV involvement in TTS was not explored in this study since majority were LV dominant. In future, larger clinical trials from multi-centered healthcare settings are necessitated to investigate a wider range of CMR outcomes in diverse TTS patient cohorts, and correlate the mapping outcomes with demographic/clinical covariates. In addition, since the updated Heart Failure Association diagnostic criteria for Takotsubo no longer supports the existence of an obstructive coronary lesion as an exclusion, as TTS and CAD may coexist in some cases [46], future researchers should implement these latest changes during patient selection and incorporate them effectively in clinical/research practices. Simultaneously, to ensure greater accuracy and reproducibility in mapping, future studies should follow standardized CMR mapping protocol, sequence parameters, and cut-off values in accordance with the Society for Cardiovascular Magnetic Resonance guidelines, and recruit controls with similar HCs with similar demographic and clinical traits as TTS patients.

6. Conclusion

CMR helps in the quantification of oedema, inflammation, and myocardial injury in TTS patients by using T1 and T2 parametric mapping. The presence of increased myocardial oedema in acute TTS can be a potential prognostic marker and therapeutic target. In summary, the qualitative synthesis of CMR imaging analysis in Takotsubo revealed a positive relationship between increasing T1/T2/ECV values and myocardial deformation markers.

Data availability statement

No data was used for the research described in the article. All secondary data from included studies to support the conclusions of this review have been provided within the manuscript.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

This article does not need informed consent.

Consent to publish

Not applicable.

CRediT authorship contribution statement

Syeda Humayra: Writing – review & editing, Writing – original draft, Conceptualization. **Noorazrul Yahya:** Writing – review & editing. **Chai Jia Ning:** Writing – review & editing. **Imtiyaz Ali Mir:** Writing – review & editing. **Abdul Latiff Mohamed:** Writing – review & editing. **Hanani Abdul Manan:** Writing – review & editing, Supervision, Conceptualization.

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.

Acknowledgement

This work was supported by the RIA2 Modal Insan Penyelidikan (Incentive Grant for Postdoctoral Researchers) under Universiti Kebangsaan Malaysia (UKM) RIA2-MIP-2023, Geran Fundamental Fakulti Perubatan (GFFP) FF-2024-024, Dana Fundamental Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) (PPUKM Fundamental Fund) FF-2020-013 and Publication Incentive Fund GP-2020-K021856.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29755.

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