The Detection Rate of Late Gadolinium Enhancement in Takotsubo Syndrome: a Systematic Review and Meta-analysis

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Absence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) is commonly used to distinguish takotsubo syndrome (TTS) from other myocardial diseases. However, case series have reported the presence of LGE in TTS. The present study aimed to summarize the evidence on the frequency of LGE in TTS and identify potential variables that may influence the detection of LGE. Electronic databases were systematically searched for studies reporting LGE frequency in TTS patients. The overall frequency was estimated using the inverse variance method and a random-effect model for single proportion. Factors influencing LGE detection were analyzed. Among 490 studies screened, 21 were included (703 patients, 90% female). The estimated overall frequency of LGE was 22.4% (95% CI 8.7-39.6%). Among TTS patients who underwent CMR within three days of symptom occurrence, the frequency of LGE was 40.7% (95% CI 18.8-64.5%), significantly higher than among those who performed CMR after three days (3.9%, $p<0.010$). The sensitivity threshold used in the imaging protocols had a statistically significant impact on the frequency of LGE detection ($p=0.030$). Ten studies performed a follow-up CMR after at least three months, reporting a frequency of LGE of 1.7 % (95% CI 0.0-8.9%). In conclusion, published studies report the presence of LGE in TTS at presentation among a significant proportion of patients. However, its detection is strongly influenced by the duration between symptom onset and CMR acquisition, and by the sensitivity threshold used for the imaging protocol. LGE is rarely present at follow-up.

Introduction

According to the international takotsubo (InterTAK) and Mayo Clinic diagnostic criteria, takotsubo syndrome (TTS) is defined by transient left ventricular dysfunction with regional wall motion abnormalities that extend beyond a single epicardial vascular distribution combined with new electrocardiographic (ECG) abnormalities and elevated biomarker of myocardial necrosis (1-3). Approximately 90% of TTS cases occur in females, typically postmenopausal (4-6), and account for 1-6% of women initially suspected of an acute ST-segment elevation myocardial infarction (7-10). The underlying pathophysiological and mechanistic pathways that cause TTS remain elusive. The most widely accepted hypothesis involves microvascular dysfunction due to an excess of catecholamines, often triggered by physical or emotional stress (11).

The diagnostic criteria require that coronary angiography be performed to exclude significant coronary artery stenosis (1, 2, 12). However, differentiating between other causes of myocardial infarction with non-obstructive coronary arteries (MINOCA) can be challenging. Cardiac magnetic resonance (CMR) is a useful non-invasive imaging tool for this purpose. Specifically, the morphological characterization of TTS in CMR involves the identification of myocardial edema on T2 sequences without documentation of fibrosis, as assessed by late gadolinium enhancement (LGE) sequences. Although, based on clinical experience and general consensus, the absence of LGE is often used to support the diagnosis of TTS, several studies have reported cases with LGE (13-15). However, the frequency of LGE in this scenario and its clinical significance remain unclear. The aim of the present systematic review and meta-analysis was therefore to summarize the available evidence on the frequency of LGE in TTS and to identify clinical and technical variables associated with its presence.

Methods

The present study was conducted in accordance with the principles of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (16).

Studies selection

Two reviewers systematically searched PubMed-MEDLINE and SCOPUS electronic databases up to January 31st, 2024, for studies reporting the frequency of LGE detected by CMR in patients with a diagnosis of TTS. The relevant terms used were "late gadolinium enhancement", "stress cardiomyopathy", "takotsubo syndrome" and "takotsubo cardiomyopathy" (detailed search strategy in the Supplementary appendix).

The literature obtained from the searches was independently filtered by two authors, L.F. and M.F., using titles, abstracts, and full text when deemed appropriate; discrepancies were resolved by consensus. Moreover, the references of recent systematic reviews were screened to identify relevant studies. We included studies enrolling patients diagnosed with stress cardiomyopathy or TTS, undergoing a CMR assessment within 3 months from the index event, and reporting the number of patients who presented LGE at CMR. We excluded studies that applied the absence of LGE as a diagnostic criterion for TTS. Additionally, case reports, non-English language papers, and papers with irrelevant titles or abstracts were excluded.

Data extraction

Once two authors (L.F. and M.F.) selected the included papers, one author (L.F.) extracted data from the identified literature. The extracted data were collected in a dedicated electronic database and were assessed for completeness and accuracy by a second author. The name of the first author, publication year, number of patients with TTS, age, gender, number of patients with LGE, sensitivity LGE CMR threshold (standard deviations (SD) above the mean signal intensity), timing of CMR performing, and magnetic field intensity (i.e. Tesla) of the CMR were collected.

Whenever reported, the timing of CMR at follow-up and the presence of LGE at follow-up were collected.

Objective

The primary aim of our study was to determine the frequency of LGE detection in a population affected by TTS who underwent CMR within 3 months of the initial symptom onset. Frequency of detection was defined as the proportion of patients in whom the presence of LGE was documented among the total of TTS patients studied with CMR. Additionally, we sought to analyze factors potentially influencing LGE detection. Despite limited follow-up data in most studies, we also aimed to describe the dynamic nature of LGE in TTS and its frequency during follow-up.

Statistical analysis

The extracted data were analyzed using the "meta" package in the statistical software environment R (17). The overall frequency of LGE in patients affected by TTS was estimated using the inverse variance method and a random-effect model for a single proportion (i.e. DerSimonian and Laird method) (18). To address the skewness in the distribution of observed proportions, the variance-stabilizing double arcsine transformation was applied to the proportions collected (19). The heterogeneity across studies was evaluated by using the Tau^2, I^2, and Q-statistics. The I^2 index describes the percentage of total variation across the studies that is due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75%, were attributed to small, moderate, and large amounts of heterogeneity (20). Two subgroup analyses were performed in order to stratify outcomes based on the timing of CMR performing (i.e. within or after 3 days from TTS diagnosis) and the LGE sensitivity threshold (i.e. threshold 1÷ 5 SD, or > 5 SD above the

mean signal intensity [SI]). Some studies reported data for both thresholds and were considered separate studies for the purposes of this subgroup analysis. A leave-out-one sensitivity analysis was performed to evaluate the influence of each study on the pooled results. A univariate meta-regression was conducted to examine the impact of age, female gender, sample size, and year of publication on the LGE frequency estimation. Moreover, in order to prevent the potential risk of misleading conclusions for the Freeman-Tukey double arcsine transformation reported by some authors (21), a sensitivity analysis was conducted using the logit transformation instead of the Freeman-Tukey transformation.

Results

Literature selection

The literature selection flowchart is displayed in **Figure 1**. From 167 results identified on PubMed and 319 results on SCOPUS, 21 studies were included in the final analysis. The included studies with their main features are reported in **Table 1**. While 14 studies exclusively included patients with TTS, 7 studies included patients with MINOCA among whom we selected only patients with TTS for inclusion.

Patient and study characteristics

Overall, 703 patients were included. The mean age was 69.2 years (95% CI 67.8-70.6), and 90% were females. The time between symptom onset to CMR imaging was reported to be within 3 days or within a median time of ≤3 days in 12 studies. The LGE sensitivity protocol was not described in 12 studies. Three studies used a threshold greater than 5 SD above the mean SI, while two studies applied 2 to 5 SD above the mean SI (i.e. a more sensitive protocol for LGE detection), and four studies reported data using both thresholds. Further details on the TTS diagnostic criteria and LGE protocols are provided in the supplementary materials.

LGE frequency

At the time of the initial CMR, 132 patients exhibited LGE, corresponding to an estimated LGE frequency of 22.4% (95% CI 8.7-39.6%) (**Figure 2)**. We observed high heterogeneity among studies, and it was computed by I^2=92%, tau^2 0.1493, Q-statistic p<0.0001.

Subgroup analyses, meta-regressions, and sensitivity analyses

Studies in which CMR was performed within three days of symptoms onset showed a statistically significant higher estimated LGE frequency as compared with studies that performed CMR after three days [40.7% (95%CI 18.8-64.5%) vs 3.9% (95% CI 0.0-16.7%), p for subgroup differences=0.004)] **(Figure 3)**. Moreover, a statistically significant impact of different LGE threshold protocols on the frequency of LGE detection has been identified. Studies that used a threshold greater than 5 SD above the mean SI had a lower overall estimated frequency of LGE detection (6.7%; 95%CI 0.0-21.6%) than studies that used a threshold between 2 and 5 SD above the mean SI (28.3%; 95%CI 15.7-42.7% - p for subgroup difference 0.0288) **(Figure 4)**. Both subgroup analyses still showed significant heterogeneity. The meta-regression analyses failed to identify any potential interaction of age, gender, sample size, or publication year on the estimated frequency of LGE (supplementary). The reported results were globally consistent throughout the sensitivity analyses performed (supplementary). Despite a clear trend, the subgroup sensitivity analysis studying the impact of using different LGE thresholds conducted using the logit transformation failed to show a statistically significant difference between the studied groups (p for subgroups difference 0.0537).

Follow-up

Among the studies included, 10 conducted CMR examinations with LGE assessment during follow-up **(Table 2).** The mean follow-up duration was 4.4±3.4 months. Interestingly, only

three studies reported patients with LGE during follow-up. Specifically, 9 patients exhibited LGE during follow-up, with one patient identified in the Eitel I et al. study and three patients in the Naruse Y et al. study. It's worth noting that the remaining patients were from the Kato K et al. study, which reported a notably higher frequency of LGE during follow-up compared to other studies (5 patients with LGE among the 12 who underwent CMR). Overall, the estimated frequency of LGE during follow-up was 1.7% (95% CI 0.0-8.9% - Figure S4 in the supplementary).

Discussion

The major findings of the present study into CMR imaging in TTS are that the presence of LGE: 1) at presentation has been reported with a frequency of 22.4% (95% CI 8.7-39.6%), 2) varies depending on the duration between symptom onset and imaging, 3) is impacted markedly by the imaging sensitivity protocol used, and 4) is rarely seen during follow-up (Graphical abstract).

The unexpectedly high frequency of LGE in the literature appears to be mainly driven by studies that performed CMR within the first three days from the onset of symptoms. This observation provides caution for using the absence of LGE on CMR as a firm diagnostic criterion for TTS, but rather as supportive evidence (22, 23). We recommend that the diagnosis of TTS should be based on the published diagnostic criteria and exclusion of other acute cardiac diagnoses that mimic acute myocardial infarction (1-3). Additionally, our results prompt consideration of whether the resolution of LGE during follow-up could serve as a potential diagnostic criterion for TTS.

A marked heterogeneity was present among the studies. The timing of CMR imaging during the acute presentation appears to determine the likelihood of finding LGE. Imaging at >3

days was associated with a very low frequency of LGE. This might be one explanation for the low incidence of LGE in clinical practice among contemporary cohorts.

Several methods have been proposed to differentiate the presence and extent of LGE, including qualitative and quantitative methods. The first is based on visual assessment, categorizing the area of myocardial enhancement dichotomously as absent or present. In contrast, quantitative methods involve operators manually segmenting the endocardium and epicardium to semi-automatically obtain the quantitative percentage of LGE (24, 25). As reported in the literature, and confirmed in our study, the various LGE sensitivity protocols used across different studies may influence the frequency of LGE. Indeed, lower SD cutoff thresholds may overestimate the presence of LGE. From this perspective, it is worth mentioning that three studies observed LGE with 2-5 SD while they did not detect any patients with LGE when using a higher detection threshold (>5 SD) (13, 15, 26). This observation highlights the importance of using optimal imaging protocols and another explanation for the discordance with the contemporary understanding of LGE in TTS.

Since TTS is characterized by recovery of global systolic function, we speculate that the pathological mechanisms underlying LGE in TTS may differ from those observed with acute coronary syndromes and myocarditis. LGE reflects changes in relative intracellular and extracellular volumes, thus any increase in the extracellular volume (i.e. edema or fibrosis), may lead to LGE (27, 28). Additionally, myocardial necrosis results in intracellular gadolinium accumulation, expanding the distribution of LGE (29). LGE has been extensively documented in many cardiac conditions that are characterized by edema, necrosis, and fibrosis, and carries prognostic significance (30-35). In the case of edema, LGE is due to increased extracellular volume and the accumulation of inflammatory cells, contributing to LGE in CMR. Unlike ischemic injury

and myocarditis, which exhibit specific patterns of LGE, subendocardial/transmural and subepicardial/intramyocardial, respectively, that are easily detectable (with a less sensitive LGE protocol >5 SD), LGE in TTS demonstrates a lower signal intensity and volume likely presenting with either transmural or patchy pattern (36, 37). The clinical utility of detecting the low-intensity signal in TTS reported, predominantly by older studies, is uncertain and merits further research. Given the identified impact of CMR acquisition timing on LGE detection, the very low frequency of LGE at follow-up, and hence the decreasing radiological signal intensity over time, it is likely that LGE in TTS is a marker of edema rather than fibrosis (36). Indeed, studies that reported LGE in TTS described the pattern to be transmural and colocalizing to the segments with ventricular akinesis/hypokinesis and edema (13-15, 36, 38-40).

LGE at follow-up

The extent of LGE in myocarditis and ischemic heart disease is known to be a dynamic phenomenon, often diminishing over time, and associated with adverse prognosis (41-43). In TTS, the fact that LGE is rarely present at follow-up further supports the notion that it is predominantly determined by edema, which tends to resolve within a few weeks. Only nine patients exhibited LGE at follow-up. We speculate that the occasional presence of LGE at follow-up may either be due to preexisting myocardial injury or potentially related to coexistent myocardial infarction (44, 45). Kato et al., observed an LGE frequency out of the ordinary underscoring the potential inter-observer variability and the need for further LGE characterization in future follow-up studies (46). LGE's association with adverse prognosis has been well-established in non-ischemic cardiomyopathies and myocarditis (30-35), however, its clinical implication in TTS is unknown. Some of the studies included in the present meta-analysis attempted to address this issue. Eitel et al. explored the clinical correlates of the presence of LGE, evaluated with both thresholds, showing

no relationship to clinical presentation, mortality, ECG pattern, and type of trigger (13). Likewise, Naruse et al. did not report any differences based on LGE presence and occurrence of heart failure, ejection fraction, ECG abnormalities, or peak creatinine kinase. Ananthakrishna et al. showed no correlation between LGE and major adverse cardiovascular events (15, 47). These observations, associated with the low frequency of LGE during follow-up, suggest that LGE in TTS may not be associated with an adverse prognosis. Nonetheless, prospective studies are needed to better elucidate this issue (48).

Limitations

Our systematic review and meta-analysis have several limitations. First, we did not have access to the individual patient-level data and therefore conducted a study-level analysis. Second, some of the studies included TTS patients exclusively, while others enrolled patients with MINOCA from which we selected the TTS subset for inclusion. This could have led to a selection bias, mainly enrolling patients with a myocardial infarction-like presentation. However, this risk is mitigated by the fact that all patients underwent CMR which facilitated the exclusion of non-TTS cases. Third, only nine studies described the LGE sensitivity protocol used. Beyond the LGE sensitivity protocol, even the specific LGE image sequences might impact its detection. Although most of the studies used magnitude sequences, the detailed image sequence was not systematically reported (the available protocol details are reported in Supplementary Table 2). Additionally, concerning LGE detection, the assessment and quantification of LGE still lack standardized protocols, limiting the comparability of results across studies and centers. Various methods for delineating LGE extent are described in the literature, but there is still no clear consensus on which technique is the most reliable and reproducible (49), and these should be considered potential sources of bias. Fourth, despite the LGE detection rate heterogeneity among studies being the

reason that prompted us to perform several subgroup analyses and meta-regressions, high heterogeneity was still reported in these analyses. Finally, only ten studies reported follow-up CMR data, therefore our conclusion on rates of LGE at follow-up is limited by the low numbers of patients. The introduction of standardized protocols and post-processing methods for delineating LGE extent is warranted in clinical consensus guidelines to guide future multicenter studies to identify the most reproducible technique for quantifying LGE and evaluating its clinical significance in TTS patients.

Conclusion

Approximately one in five TTS patients in our meta-analysis had LGE during acute imaging. The frequency was higher in those who underwent CMR within three days of symptom onset, and the sensitivity protocol used impacted the likelihood of detecting LGE. Thus, we propose that optimal CMR imaging techniques be deployed and that the absence of LGE should be used as a supportive finding but not a firm diagnostic criterion for TTS. The prognostic implication of LGE remains unclear as it is rarely present at follow-up. Available evidence suggests that the presence of LGE does not portend adverse long-term outcomes in TTS.

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Figure Legend

Figure 1. Study selection flow-chart.

Figure 2. Forest plot of overall late gadolinium enhancement (LGE) frequency among takotsubo syndrome (TTS).

Figure 3. Forest plot of subgroup analysis according to cardiac magnetic resonance (CMR) timing after symptom onset.

Figure 4. Forest plot of subgroup analysis according to LGE sensitivity protocol.

Table Legend

Table 1. Characteristics of included studies.

Table 2. Follow-up data among studies that documented a follow-up CMR.

Table 1.

Study	Inclusion diagnosis	Age (years)*	Female, %	Size (n=TTS)	CMR timing (days after symptom) $	CMR LGE sensitivity threshold (SD)	TTS with LGE, n (%)
Abanador-Kamper N., 2017 (50)	TTS	68.8 ± 17.5	93	72	2 (IQR 1-3.5)	>5	0 (0)
Aikawa Y., 2019 (51)	TTS	63 ± 11	91	23	7 (IQR 5-8.5)	N/A	0 (0)
Alter P., 2014 (52)	TTS	69.9 ± 11.3	100	8	Within 1	N/A	3 (37.5)
Ananthakrishna R., 2022 (47)	MINOCA	70 ± 12	93	45	6 (IQR 2-8)	N/A	20 (44)
Avegliano G., 2011 (38)	TTS	57.5 (IQR 53-73)	100	8	Within 3	N/A	8 (100)
Cau R., 2023 (39)	TTS	70.6 ± 9.4	90	30	1 (1-10)	>5	9 (30)
Collste O., 2013 (53)	MINOCA	N/A	N/A	33	12 (IQR 6-28)	N/A	0 (0)
Dabir D., 2019 (54)	TTS	67 ± 18	86	14	4 (IQR 1-8)	N/A	0 (0)
Eitel I., 2011 (13)	TTS	69 ± 12	89	239	3 (IQR 2-4)	2-5	22 (9)
Emrich T., 2015 (55)	MINOCA	75 (IQR 65-78)	75	12	3 (IQR 1-5)	N/A	12 (100)
Emrich T., 2021 (56)	MINOCA	79 (IQR 67-84)	90	14	3 (IQR 1-5)	N/A	11 (75)
Gaikwad N., 2016 (40)	TTS	66 (IQR 41-87)	91	44	2.4 (mean)^	2-5	18 (41)
Gerbaud E., 2012 (57)	MINOCA	70.8 ± 10.8	96	28	4 (IQR 2-6)	N/A	0 (0)
Kato K., 2022 (46)	TTS	71 ± 5	100	14	2 (IQR 1-2)	>5	3 (21)
Mavrogeni S., 2017 (58)	MINOCA	N/A	88	8	Within 12%	N/A	0 (0)
Nakamori S., 2012 (14)	TTS	72 ± 10	78	23	Within 3	2-5	5 (22)
Naruse Y., 2011 (15)	TTS	77 (IQR 65-82)	90	20	5 (IQR 3-6)	2-5	8 (40)
Perazzolo Marra M., 2013 (26)	TTS	65 ± 10	95	20	3 ± 0.3^	2-5	8 (40)

Reynolds H. R., 2011 (59)	MINOCA	N/A	100	3	6 (IQR 4-8)	N/A	0 (0)
Rolf A., 2009 (36)	TTS	63 (IQR 57-72)	80	15	0.9 (0.8-1.1)	2-5	5 (33)
Vermes E., 2020 **(60)**	TTS	73 (median)	87	30	5 (mean)^	**N/A**	0 (0)

*: Some of the studies reported age as a mean with standard deviation. Six of them reported age as median with interquartile range.
$: Most of the studies reported timing between symptom onset and CMR performing as a median with interquartile range. Some of them reported the day within the CMR was performed. Three of them reported the mean days (marked with ^).
%: Between 8 and 12 days after symptom onset.
CMR: cardiac magnetic resonance, IQR: interquartile range, LGE: late gadolinium enhancement, MINOCA: myocardial infarction with no obstructive contrary artery, TTS: takotsubo syndrome.

Table 2.

Study	CMR follow-up timing (months)	LGE at diagnosis, n (%)	Patients with CMR at follow-up, n	TTS with LGE at follow-up, n (%)
Abanador-Kamper N., 2017 (50)	2.3 (IQR 1.3-2.9)	0 (0)	63	0 (0)
Avegliano G., 2011 (38)	3	8 (100)	8	0 (0)
Eitel I., 2011 (13)	3.2 (IQR 1.2-4.1)	22 (9)	158	1 (0.6)
Gaikwad N., 2016 (40)	8 (IQR 2-27)	18 (41)	16	0 (0)
Gerbaud E., 2012 (57)	3	0 (0)	-	0 (-)
Kato K., 2022 (46)	3	3 (21)	12	5 (42)
Nakamori S., 2012 (14)	12	5 (22)	5	0 (0)
Naruse Y., 2011 (15)	6	8 (40)	19	3 (16)
Perazzolo Marra M., 2013 (26)	3	8 (40)	20	0
Rolf A., 2009 (36)	0.47 (14 days)	5 (33)	15	0

CMR: cardiac magnetic resonance, IQR: interquartile range, LGE: late gadolinium enhancement, TTS: takotsubo syndrome