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ORIGINAL PAPER

Diagnostic and prognostic value of cardiac magnetic resonance in acute myocarditis: a systematic review and meta-analysis

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Abstract

While diagnostic criteria were elaborated for acute myocarditis using cardiac magnetic resonance (CMR) in 2009, studies have since examined the yield of traditional and novel CMR parameters to achieve greater accuracy and to predict clinical outcomes. The purpose of this systematic review and meta-analysis was to determine the diagnostic and prognostic value of CMR parameters for acute myocarditis. MEDLINE and EMBASE were systematically searched for original studies that reported CMR parameters in adult patients suspected of acute myocarditis. Each CMR parameter's binary prevalence, mean value and standard deviation were extracted. Parameters were meta-analyzed using a random-effects model to generate standardized mean differences. After screening 1492 abstracts, 53 studies were included encompassing 2823 myocarditis patients and 803 controls. Pooled standardized mean differences between myocarditis patients and controls were: T2 mapping time 2.26 (95% CI 1.50–3.02), extracellular volume 1.64 (95% CI 0.87–2.42), LGE percentage 1.30 (95% CI 0.95–1.64), T1 mapping time 1.18 (95% CI 0.35–2.01), T2 ratio 1.17 (95% CI 0.80–1.54), and EGE ratio 0.93 (95% CI 0.66–1.19). Prolonged T1 mapping time had the highest sensitivity (82%), pericardial effusion had the highest specificity (99%). Baseline LV dysfunction and the presence of LGE were predictive of major adverse cardiac events. The results support integration of parametric mapping criteria in the diagnostic criteria for myocarditis. The presence of baseline LV dysfunction and LGE predict patients at higher risk of adverse events.

Keywords Acute myocarditis · Cardiac magnetic resonance · Lake Louise criteria · Parametric mapping · Meta-analysis

Introduction

Acute myocarditis is a commonly-encountered cause of myocardial injury [1], sudden cardiac death [2] and non-ischemic cardiomyopathy [3]. Cardiac magnetic resonance imaging (CMR) is the recommended noninvasive test to visualize the myocardial inflammation and fibrosis typical of acute myocarditis [4, 5]. CMR-based diagnostic criteria for acute myocarditis were elaborated in 2009 and became known as the Lake Louise criteria (LLC). The presence of 2 out of 3 of these criteria was said to be diagnostic [4]: (1) T2 ratio of myocardium in relation to skeletal muscle (global or focal) > 1.9 (2) early gadolinium enhancement ratio of myocardium in relation to skeletal muscle (EGE) > 4 or an absolute myocardial enhancement of > 45%, and (3) non-ischemic late gadolinium enhancement (LGE). At the time these criteria were published, their pooled specificity of 91% supported their use, albeit with a modest sensitivity of 67% [4].

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Since the original LLC were defined, new techniques including mapping of T1, T2 and extracellular volume (ECV) have emerged as potentially useful parameters for the diagnosis of acute myocarditis. Despite the theoretical advantages of these newer parameters to precisely evaluate myocardial inflammation and interstitial fibrosis, their incremental diagnostic value remains unclear in individual published studies that have had relatively small sample sizes and conflicting results. For example, three independent studies differently concluded that the optimal parameter to diagnose myocarditis was T1 mapping time [6], T2 mapping time [7] and ECV [8]; while all of these studies agreed that the parametric maps provided superior diagnostic value when compared to the traditional LLC.

The prognostic value of CMR parameters has similarly been a source of debate, with no consensus on how to best discriminate between low-risk and high-risk subsets of patients. The clinical implications are substantial since a minority of acute myocarditis patients—many of them young in age—go on to develop major adverse cardiac events that could potentially be prevented by more intensive treatment and surveillance.

Therefore, we undertook a systematic review and meta-analysis of the available body of evidence to characterize and compare the diagnostic and prognostic yield of traditional and novel CMR-derived parameters in acute myocarditis. The results of this meta-analysis could be considered to inform future guideline statements and best clinical practice for patients undergoing CMR for suspected acute myocarditis.

Materials and methods

Design

A systematic review and meta-analysis were conducted using the published literature of original studies that reported CMR parameters in patients with suspected acute myocarditis. The manuscript was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [9].

Data sources and search strategy

MEDLINE and EMBASE were systematically searched for retrospective and prospective studies published between 2000 and 2017. The MeSH headings *myocarditis* and *magnetic resonance imaging* were used to search MEDLINE and the Emtree headings *myocarditis, cardiovascular magnetic resonance* and *nuclear magnetic resonance* were used to search EMBASE in addition to the keywords "myocarditis", "perimyocarditis", "MRI", "magnetic", "CMR", and "multimodality". The search strategy is documented in Supplementary Fig. 1. Search results were imported into the Rayyan web-based software platform [10] for screening and classification. Additionally, references from retrieved studies and guideline documents were hand-searched. Study investigators were contacted to provide missing data and clarifications when necessary.

Study selection

Two independent reviewers screened search results for articles that met the pre-determined inclusion criteria: (1) human patients with clinically suspected acute myocarditis (< 14 days); (2) CMR at 1.0 T, 1.5 T or 3 T field strength; (3) Qualitative or quantitative reporting of at least one CMR parameter of interest, namely T2 ratio, EGE, LGE, T1 mapping time, T2 mapping time, or ECV. Certain studies also reported on CMR parameters in control subjects without myocarditis, although this was not required for inclusion. Reviews, case reports and non-English language articles were excluded. The reviewers were blinded to each other's selections for inclusion or exclusion, and disagreements were resolved by a third referee.

Data collection

The extracted CMR parameters were: T2 ratio, EGE, LGE, pericardial effusion, T1 mapping time, T2 mapping time and ECV. T2 ratio was reported as a ratio of myocardial-to-skeletal muscle signal intensity > 1.9 or > 2.0. EGE was defined either as a ratio of myocardial-to-skeletal muscle signal intensity after gadolinium divided by before gadolinium > 4 or as the absolute myocardial enhancement. LGE was defined by qualitative or quantitative analysis using a threshold of either 2 or 5 standard deviations above of the myocardial signal intensity. The extracted clinical variables were: mean age of patients, proportion of females, image acquisition parameters, magnet strength, reference standard for the diagnosis of myocarditis and incident major adverse cardiac events.

Study quality

A quality assessment of all included studies was carried out using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies [11]. A maximum of 8 points were assigned based on the selection criteria (presence and robustness of an accepted reference definition for diagnosing acute myocarditis and presence of a methodology for determining that control subjects were free of cardiac disease and did not have a preceding diagnosis of myocarditis), comparability (similarity of affected and control subjects in terms of age, sex and demographic characteristics; and exposure (patients

underwent CMR at 1.5 or 3 T using a standardized acquisition and analysis protocol).

Statistical analysis

After study-level data were extracted and verified, random-effects meta-analysis was performed using the *metan* and *metanprop* commands in STATA version 15 (College Station, TX). Each CMR parameter was assessed in its continuous format (e.g. % of LGE) and dichotomous format (e.g. presence or absence of LGE) to calculate the pooled mean value and the pooled proportion of myocarditis patients exhibiting the given criteria, with the accompanying 95% confidence intervals. For studies that included control subjects, each CMR parameter was compared in its continuous and dichotomous formats between myocarditis patients and controls to calculate the pooled sensitivity and specificity and the pooled standardized mean difference. The standardized mean difference describes differences between patients and controls for continuous variables across multiple studies. The standardized mean difference was calculated for each study by subtracting the difference between a given CMR parameter in myocarditis patients and controls and then dividing by the standard deviation before pooling in a random-effects model to calculate the pooled standardized mean difference. A large standardized mean difference is generally considered to be >0.8 [12]. Heterogeneity was assessed using the I^2 statistic, with high heterogeneity generally considered to be $>50\%$. Findings not amenable to statistical pooling (e.g. distribution of LGE) were narratively summarized.

Results

Study characteristics

After screening 1492 unique search results, 78 articles were potentially eligible based on their title and abstract. After full-text review, 53 articles [6, 7, 13–62] met the inclusion criteria (Fig. 1) encompassing a total of 2823 myocarditis patients and 803 controls (Table 1). Twenty-three studies (43%) performed CMR in control subjects, and 11 studies (21%) performed myocardial biopsies to confirm the diagnosis of acute myocarditis. The majority of studies (85%) were performed using 1.5 T magnet strength. The weighted mean age of patients was 41.8 years with 25% females.

Meta-analysis of diagnostic value of CMR parameters

The CMR parameters reported in the included studies were, in descending order of frequency: LGE in 52 studies (98%), T2 ratio in 33 studies (62%), EGE ratio in 23 studies (43%), pericardial effusion in 17 studies (32%), T1 mapping time in 9 studies (17%), T2 mapping time in 8 studies (15%), and ECV in 7 studies (13%). Notably, all studies including parametric mapping on patients with suspected myocarditis and controls were performed at 1.5 T. EGE was predominantly reported as the EGE ratio rather than as the percentage of myocardial enhancement, limiting pooling of the latter definition of positive EGE for analysis. The pooled mean value and standardized mean difference for continuous parameters, and pooled prevalence and sensitivity–specificity for dichotomous parameters are presented in Tables 2 and 3. Forest plots are available in Supplementary Figs. 2, 3, 4, 5, 6, and 7.

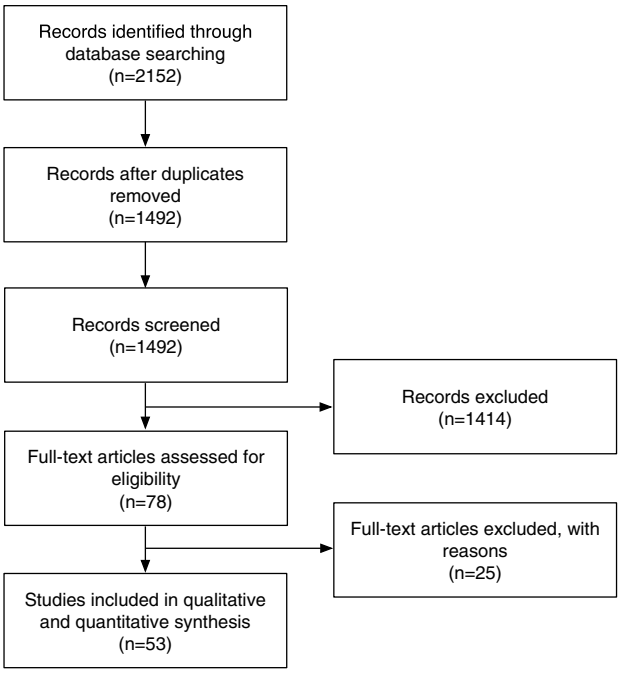

Fig. 1 Study flow diagram

Other CMR parameters

Eight studies [19, 23, 25, 27, 48, 50, 54, 60] totaling 589 patients reported data on wall motion, with 147 (25%) having at least one wall motion abnormality. Five studies [25, 31, 36, 42, 48] reported the distribution of LGE, with subepicardial LGE being the most common location (57%), followed by midwall LGE (15%), the combination of midwall and subepicardial LGE (4%), transmural LGE (2%), and subendocardial LGE (0.2%). A minority of patients (21%) did not have LGE present. Three studies [15, 45, 59] totaling 100 patients reported data on strain, with the peak global longitudinal strain being significantly lower in myocarditis patients than controls, even when the LVEF was within normal limits. Whereas one study suggested that strain had

Table 1 Characteristics of included studies

Study	Validation of myocarditis	Magnet strength	Myocarditis (N)	Controls (N)	Females (N)	Mean age (Years)	LGE	EGE	T2 Ratio	T2map	T1map	ECV	Pericardial Effusion	Study Quality Points *
Abdel-Aty 2005 [13]	Clinical (2 biopsied)	1.5	25	23	7	44	✔	✔	✔	NR	NR	NR	NR	5
Ammirati 2017 [14]	Clinical (13 biopsied)	1.5	76	0	10	33	✔	NR	✔	NR	NR	NR	NR	6
Andre 2016 [15]	Clinical	1.5	36	36	5	41	✔	NR	NR	NR	NR	NR	NR	7
Baebler 2015 [16]	Clinical	1.5	45	20	6	41	✔	✔	✔	NR	NR	NR	NR	5
Barone-Rochette 2014 [17]	Clinical	3	28	0	9	33	✔	NR	✔	NR	NR	NR	✔	5
Bohnen 2015 [7]	Biopsy	1.5	16	11	4	52	✔	✔	✔	✔	✔	✔	NR	4
Camastra 2007 [18]	Clinical	1.5	13	0	2	32	✔	NR	NR	NR	NR	NR	✔	4
Chopra 2016 [19]	Clinical	1.5 or 3	88	0	18	39	✔	NR	NR	NR	NR	NR	✔	2
Chu 2013 [20]	Clinical	1.5	35	10	8	40	✔	✔	✔	NR	NR	NR	NR	7
Cocker 2009 (females) [21]	Clinical	1.5	24	0	24	NR	✔	✔	✔	NR	NR	NR	NR	4
Cocker 2009 (males) [21]	Clinical	1.5	41	0	0	NR	✔	✔	✔	NR	NR	NR	NR	4
Danti 2009 [22]	Clinical	1.5	21	0	1	30	✔	NR	NR	NR	NR	NR	NR	5
De Lazarri 2016 [23]	Clinical	1.5	76	0	10	34	✔	✔	✔	NR	NR	NR	NR	5
Deux 2011 [24]	Clinical	1.5	18	0	3	38	✔	NR	NR	NR	NR	NR	NR	6
Ferreira 2013 [6]	Clinical	1.5	50	45	11	42	✔	NR	✔	NR	✔	NR	NR	7
Florian 2015 [25]	Clinical	1.5	89	0	10	28	✔	NR	✔	NR	NR	NR	✔	4
Francone 2014 [26]	Clinical	1.5	57	0	16	49	✔	✔	✔	NR	NR	NR	NR	4
Gahide 2010 [27]	Clinical	1.5	50	0	NR	NR	✔	NR	NR	NR	NR	NR	✔	5
Goitein 2009 [28]	Clinical	1.5	23	0	0	33	✔	NR	NR	NR	NR	NR	NR	6
Grun 2012 [29]	Biopsy	1.5	203	0	63	52	✔	NR	NR	NR	NR	NR	NR	5
Hinojar 2015 [30]	Clinical	1.5 and 3	61	40	32	48	✔	NR	✔	NR	✔	NR	✔	3
Ingkanisorn 2006 [31]	Clinical	1.5	21	0	4	40	✔	NR	NR	NR	NR	NR	✔	5
Jeserich 2009 [32]	Clinical	1.5	36	21	11	49.8	✔	NR	✔	NR	NR	NR	✔	4
Jeserich 2014 [33]	Clinical	1.5	92	0	28	52	✔	NR	✔	NR	NR	NR	NR	0
Laissy 2002 [34]	Clinical	1	20	7	5	43	NR	✔	✔	NR	NR	NR	✔	8
Luetkens 2016 [35]	Clinical	1.5	24	45	9	41	✔	✔	NR	✔	✔	✔	NR	8
Lurz 2012 [36]	Biopsy	1.5	70	0	9	44	✔	✔	✔	NR	NR	NR	NR	4
Lurz 2016 [37]	Biopsy	1.5	61	0	17	40	✔	✔	✔	✔	✔	✔	NR	6
Mahrholdt 2006 [38]	Biopsy	1.5	102	0	26	41	✔	NR	NR	NR	NR	NR	NR	5
Mavrogeni 2011 [39]	Clinical (50 biopsed)	1.5	71	20	NR	42	✔	✔	✔	NR	NR	NR	NR	8
Melendez-Ramirez 2014 [40]	Clinical	1.5	32	0	3	29	✔	NR	NR	NR	NR	NR	NR	5
Mewton 2015 [41]	Clinical	1.5	41	0	9	39	✔	NR	NR	NR	NR	NR	✔	5
Natale 2012 [42]	Biopsy	1.5	56	0	10	45	✔	NR	NR	NR	NR	NR	NR	4
Ong 2011 [43]	Biopsy	1.5	35	0	14	49	✔	NR	✔	NR	NR	NR	✔	5
Perfetti 2014 [44]	Clinical	1.5	39	20	11	34	✔	NR	NR	NR	NR	NR	NR	6
Puntmann 2010 [45]	Clinical	1.5	36	34	24	41	✔	NR	✔	NR	NR	NR	NR	6
Radunski 2014 [8]	Clinical	1.5	104	21	25	44	✔	✔	✔	✔	✔	✔	NR	8
Radunski 2017 [46]	Clinical	1.5	20	20	4	38	✔	NR	NR	✔	✔	✔	NR	7
Rottgen 2011 [47]	Biopsy	1.5	131	0	46	45	✔	✔	✔	NR	NR	NR	NR	3
Sanguineti 2015 [48]	Clinical	1.5	203	0	48	43	✔	✔	✔	NR	NR	NR	✔	6
Schumm 2014 [50]	Clinical	1.5	180	225	55	50	✔	NR	NR	NR	NR	NR	✔	4
Schwab 2015 [50]	Clinical	1.5	43	35	5	35	✔	✔	✔	NR	NR	NR	✔	7
Spieker 2017 [51]	Biopsy	1.5	46	60	13	41	✔	NR	✔	✔	NR	NR	NR	8
Sramko 2013 [52]	Biopsy	1.5	15	0	4	42	✔	✔	✔	NR	NR	NR	✔	2
Stensaeth 2012 [53]	Clinical	1.5	42	0	3	37	✔	✔	✔	NR	NR	NR	✔	5
Thavendiranathan 2012 [54]	Clinical	1.5	20	30	11	38	✔	NR	NR	✔	NR	NR	NR	5
Toussaint 2015 [55]	Clinical	3	6	0	0	32	✔	NR	NR	NR	✔	✔	NR	5
Vermes 2014 [56]	Clinical	1.5	37	0	8	43	✔	✔	✔	NR	NR	NR	NR	6
von Knobelsdorff-Brenkenhoff 2017 [57]	Clinical	1.5	18	18	4	25	✔	✔	✔	✔	✔	✔	NR	7
Wagner 2003 [58]	Clinical	1	16	26	NR	26	NR	✔	NR	NR	NR	NR	NR	7
Weigand 2016 [59]	Clinical	1.5 or 3	28	20	2	18	✔	NR	NR	NR	NR	NR	NR	6
Yelgec 2007 [60]	Biopsy	1.5	20	0	6	40	✔	NR	✔	NR	NR	NR	✔	5
Zagrosek 2009 [61]	Clinical	1.5	36	0	5	33	✔	✔	✔	NR	NR	NR	NR	6
Zarka 2016 [62]	Clinical	1.5 or 3	47	16	12	42	✔	NR	✔	NR	NR	NR	NR	7

ECV extracellular volume, *EGE* early gadolinium enhancement, *LGE* late gadolinium enhancement, *NR* not reported

*Points on the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies (with the highest quality denoted by a score of 8 points)

the highest C-statistic for detecting LGE [59] another study suggested that strain was not correlated with the extent of LGE [15].

Meta-analysis of prognostic value of CMR parameters

The prognostic yield of CMR parameters is summarized in Table 4.

Prolonged T2 mapping time, EGE, LGE, baseline LVEF and RVEF were associated with adverse clinical events in unadjusted analyses (Supplementary Fig. 8). After controlling for confounding, only LGE and baseline LVEF remained independent predictors of adverse clinical events in adjusted analyses (Supplementary Fig. 9). Beyond the presence of LGE, two studies [19, 41] provided quantitative thresholds for the extent of LGE to stratify patients at higher risk. The LGE cut-off was similar in these two studies, > 17 grams [19] or > 13% of the myocardial mass [41] with the hazard ratio ranging from 1.4 to 3.4 at approximately 2 years. Notably, in a study of 203 patients with biopsy-proven acute myocarditis, no patient without LGE

Table 2 Pooled mean and standardized difference for CMR parameters in continuous form

	Myocarditis patients			Myocarditis patients vs. controls		
	Pooled mean (95% CI)	N	I^2	Standardized mean difference (95% CI)	N	I^2
LGE[a](% of LV mass)	13.2 (10.7–15.7)	18	97	1.30 (0.95–1.64)	2	0
T2 ratio	2.1 (2.0–2.3)	17	95	1.17 (0.80–1.54)	9	76
EGE ratio	5.9 (5.0–6.7)	10	84	0.93 (0.66–1.19)	5	0
T2 time (ms)	62 (60–65)	9	95	2.26 (1.50–3.02)	5	83
T1 time (ms)	1071 (1038–1113)	7	96	1.18 (0.35–2.01)	4	89
ECV (%)	31.8 (28.7–34.9)	6	97	1.64 (0.87–2.42)	4	83

ECV extracellular volume, *EGE* early gadolinium enhancement, *LGE* late gadolinium enhancement

[a]For LGE, the pooled mean number segments affected was 3.9 (3.2–4.7) in ten studies with I^2 of 99%

Table 3 Pooled prevalence, sensitivity & specificity for CMR parameters in dichotomous form

	Myocarditis patients			Myocarditis patients vs. controls	
	Pooled prevalence (95% CI)	N	I^2	Sensitivity (%)	Specificity (%)
LGE	77% (69–84%)	93	40	69	95
T2 ratio	52% (43– 61%)	90	22	56	77
EGE ratio	66% (57–74%)	82	14	62	74
T2 time	N/A			75	84
T1 time	N/A			82	87
ECV	N/A			77	79
Pericardial effusion	35% (26–44%)	88	18	36	99
Lake Louise Criteria	78% (62–91%)	71	3	78	74

ECV extracellular volume, *EGE* early gadolinium enhancement, *LGE* late gadolinium enhancement, *NA* not applicable (due to absence of a validated dichotomous cutoff for these parameters)

experienced sudden cardiac death, even if the left ventricle was dilated or dysfunctional [29].

Discussion

This systematic review and meta-analysis has consolidated the current body of knowledge on the diagnostic and prognostic yield of CMR parameters for acute myocarditis. The CMR parameters found to have the greatest diagnostic yield were T2 mapping time, ECV and LGE – only one of which is included in the current iteration of the LLC. Additionally, in the context of suspected acute myocarditis, the mere presence of a pericardial effusion was found to have high diagnostic specificity. The CMR parameters found to have the greatest prognostic yield were LVEF and LGE—both of which were robust independent predictors of major adverse cardiac events after adjustment for clinical confounders.

Our results align with the inclusion of parametric mapping, pericardial effusion and wall motion abnormalities in the recently-published Updated LLC [63], where patients must fulfill 2 of 2 criteria for acute myocarditis: (1) T2-based imaging (regionally high T2 signal intensity or globally elevated T2 ratio, or regional or global increase in T2 time) and (2) T1-based imaging (regional or global increase in T1 time/ECV or areas with high signal intensity in a non-ischemic pattern on LGE images). Supportive features include CMR-evidence of pericarditis (pericardial effusion, abnormal LGE, T2 or T1 signal) and wall motion abnormalities [63].

While our review of 53 studies is consistent with a recent review of 22 studies, our review differs and adds to that of Kotanidis et al. [64]. The meta-analysis by Kotanidis et al. [64] similarly concluded that LGE and parametric mapping offered the highest discriminatory value for the diagnosis of acute myocarditis. Ours included 32 additional studies that they had excluded mostly because a "2 × 2 table could not be reconstructed" from the published data. This exclusion criteria was not related to the quality or content of the studies, but rather to the meta-analysis technique that they had chosen, which required the raw data to be extracted in this specific dichotomous format. By opting for a standardized mean difference meta-analysis technique, our review captured a more comprehensive portfolio of studies, and decreased the emphasis on dichotomous cut-offs.

Our review furthers our understanding of the clinical utility of MRI in patients with acute myocarditis by summarizing the prognostic value of CMR parameters. Inclusion of prognostic information derived from MRI is a novel aspect of our review, which was not addressed in the meta-analysis by Kotanidis et al. [64]. To our knowledge, this represents the first systematic attempt to summarize the prognostic information afforded by a CMR examination in acute myocarditis. Prognostication of patients with acute myocarditis is a challenging yet critical endeavor. Although all LLC demonstrated some measure of association with incident clinical events, only CMR-derived LVEF and LGE demonstrated

Table 4 Association of CMR parameters with clinical outcomes

	Composite mortality or major morbidity	Mortality	Follow-up LVEF
Baseline LVEF	Chopra 2016 [19][a] Spieker 2017 [51][b] **Sanguineti 2015** [48][c] **Schum 2014** [49][d]	Schum 2014 [49]	Spiker 2017 [51] **De Lazzari 2016** [23]
Baseline LGE	Mewton 2015 [41][e] **Chopra 2016*** [19][a]	**Grun 2012** [29]	Mavrogeni 2011 [39] Natale 2012 [42] **Mahrholdt 2006** [38]
EGE	Sanguineti 2015 [48][c]		Mavrogeni 2011 [39]
T2 time	Spieker 2017 [51][b]		
Baseline RVEF	Chopra 2016 [19][a]		

Bolded studies denote those in which the CMR predictor was found to be statistically significant in a multivariable analysis adjusting for other covariates. Superscript symbols denote the definition of the composite endpoint of mortality or major morbidity, as follows

EGE early gadolinium enhancement, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *RVEF* right ventricular ejection fraction

[a]All-cause mortality, recurrent myocarditis, heart failure, or sustained ventricular tachycardia

[b]All-cause mortality, cardiac death, cardiac transplantation, ventricular assist device implantation, or hospitalization for heart failure

[c]Cardiac mortality, cardiac transplantation, sustained ventricular tachycardia, hospitalization for heart failure or other cardiac cause, or recurrent myocarditis

[d]Cardiac mortality, aborted sudden cardiac death, appropriate implantable cardiac defibrillator discharge, or hospitalization for heart failure

[e]All-cause mortality, cardiac transplantation, repeat hospitalization for heart failure or other cardiac cause

independent predictive value for LV recovery and adverse events in adjusted analyses. There is an unmet need for risk models that integrate these CMR parameters along with clinical risk factors to generate predictive risk estimates for myocarditis patients. Given the young age of many myocarditis patients, these risk models should capture a sufficiently long follow-up period and consider combinations of findings such that could herald a low likelihood of recovery. Further research is needed to validate the LGE cut-offs of > 17 g or > 13% of the myocardial mass derived by Chopra et al. [19] and Mewton et al. [41], respectively, before being implemented in clinical practice for therapeutic decision making (for example, to guide decisions on implantable cardiac defibrillators).

The value of parametric mapping is consistent with a recommendation from the joint SCMR/EACVI consensus statement to incorporate myocardial mapping in potential cases of acute myocarditis [5] and the Updated LLC [63]. These mapping techniques highlight the potential for non-contrast enhanced CMR to diagnose acute myocarditis when gadolinium-based contrast agents are contraindicated. However, one caveat must be addressed before mapping techniques can be applied in clinically-oriented diagnostic criteria—substantial variability in measured values depending on the type of CMR scanner (vendor, magnet strength) and the mapping sequence used [5]. While our meta-analysis computed standardized values to overcome this issue, clinical criteria would ideally have to specify scanner- and sequence-specific cut-offs for the T1 and T2 mapping values or require institutions to derive their own local cut-offs.

There are limitations that merit discussion. First, only 43% of studies included a healthy control group, 22% of studies required a histopathological confirmation of acute myocarditis, few studies captured all of the CMR parameters of interest, and few studies captured long-term clinical outcomes. Second, inter-observer reliability of CMR parameters was not routinely reported, and the measurements made by few experienced observers in research studies are likely to be more reliable than those made by multiple diverse observers in clinical practice. Third, the results of published studies are likely to be more positive than those of unpublished studies. Lastly, the well-documented variation in normative values across vendors and institutions precludes the generalizable use of cut-offs for parametric sequences. Accordingly, the specific values presented in Table 2 are provided to highlight the magnitude of difference between patients with myocarditis and controls rather than to provide specific cut-off values. In overcoming the limitations, studies could consider reporting all of the aforementioned CMR parameters and including a control group, particularly to provide local reference values for parametric sequences.

Conclusions

The comprehensive CMR examination contains several parameters that are useful to establish the diagnosis of acute myocarditis, among which LGE and parametric mapping were found to be especially valuable. The majority of acute myocarditis cases present with preserved LV systolic function and without regional wall motional abnormalities, thus reaffirming the value of CMR for tissue characterization in this context. Within the realm of tissue characterization, LGE distribution and extent has both diagnostic and prognostic value, with clinical outcomes being highly favorable when LGE is absent.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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