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Diagnostic Performance of Extracellular Volume, Native T1, and T2 Mapping versus Lake Louise Criteria by CMR for Detection of Acute Myocarditis: A Meta-Analysis

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Abstract

Background—The Lake Louise Criteria (LLC) was established in 2009 and is the recommended cardiac magnetic resonance (CMR) imaging criterion for diagnosing patients with suspected myocarditis. Subsequently, newer parametric imaging techniques which can quantify T1, T2, and the extracellular volume (ECV) have been developed and may provide additional utility in the diagnosis of myocarditis. However, whether their diagnostic accuracy is superior to LLC remains unclear. In this meta-analysis, we compared the diagnostic performance of native T1, T2, ECV to LLC in diagnosing acute myocarditis.

Methods and Results—We searched PubMed for published studies of LLC, native T1, ECV, and T2 diagnostic criteria used to diagnose acute myocarditis. Seventeen studies were included, with a total of 867 myocarditis patients and 441 control subjects. Pooled sensitivity, specificity, and diagnostic odds ratio (DOR) of all diagnostic tests were assessed by bivariate analysis. LLC had a pooled sensitivity of 74%, specificity of 86% and DOR of 17.7. Native T1 had a significantly higher sensitivity than LLC (85% vs 74%, p = 0.025). Otherwise, there was no significant difference in sensitivity, specificity, and DOR when comparing LLC to native T1, T2, or ECV.

Conclusions—Native T1, T2, and ECV mapping provide comparable diagnostic performance to LLC. Although only native T1 had significantly better sensitivity than LLC, each technique offers distinct advantages for evaluating and characterizing myocarditis as compared to the LLC.

Keywords

CMR; Myocarditis; LLC; native T1; T2; ECV

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Introduction

Myocarditis has a significant global impact with an estimated prevalence of 22 in 100,000 patients annually[1]. Specifically, myocarditis continues to be an important cause of sudden cardiac death and non-ischemic dilated cardiomyopathy (DCM). Data suggests that up to 20–40% of sudden cardiac death of young adults is due to myocarditis[2,3]. In addition, endomyocardial biopsy (EMB) has shown that 9% of DCM is attributed to myocarditis[4]. Nevertheless, myocarditis poses as a clinically challenging diagnosis due to its heterogenous manifestations. The Lake Louise criteria (LLC) is currently the recommended diagnostic cardiac magnetic resonance (CMR) imaging criteria for patients with suspected myocarditis[5]. LLC uses tissue-based CMR markers consisting of T2-weighted (T2w) ratio, early gadolinium enhancement (EGE), and late gadolinium enhancement (LGE). These parameters assess for myocardial edema, hyperemia/capillary leak, and fibrosis/necrosis respectively. Since the inception of LLC, quantitative imaging with T1 and T2 mapping have made significant advancements in assessing diffuse myocardial injury[6–8]. Novel techniques such as native T1 and T2 mapping or extracellular volume (ECV) calculations have been shown to provide additional diagnostic information in patients with myocarditis[9–11]. While some studies have shown quantitative mapping techniques are superior to LLC[11–13], their performance across the literature remains unclear.

Methods

By email request, the data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Search Strategy and Selection

This meta-analysis was conducted according to standard guidelines from the Meta-analysis of Observational Studies in Epidemiology[14], the Preferred Reporting Items for Systematic Reviews and Meta-analyses documents[15], and the Methodological Standards for Meta-Analyses and Qualitative Systematic Reviews of Cardiac Prevention and Treatment Studies[16]. We performed a systematic search for published studies evaluating LLC, native T1, T2, and ECV diagnostic criteria for acute myocarditis using PubMed (search last updated January 2018).

Key words used were “myocarditis” AND “lake” OR “louise” OR “mapping” OR “T1” OR “T2” OR “ECV” OR “MRI” OR “MR” OR “CMR”. Abstracts were independently reviewed and selected by two investigators (JAP and YL) based on the following eligibility criteria:

1. Pertaining to LLC, native T1 mapping, T2 mapping, or ECV
2. Investigating diagnosis of acute myocarditis in human adults
3. Complete analytic study in English

LLC was defined based on the combined use of EGE, T2w, and LGE with a positive result defined as having 2 of 3 positive criteria[5]. Studies were considered eligible for inclusion if the majority of patients had suspected acute viral myocarditis. Studies pertaining to chronic or autoimmune myocarditis were excluded. Only complete analytic studies published in

peer-reviewed journals were included. Case reports, editorials, and reviews were excluded. Abstracts from meetings were excluded due to limited information regarding data.

Data Extraction

Data from each study was independently extracted by two investigators (JAP and YL). Studies were excluded if they contained: (a) overlapping subjects with other studies, (b) incomplete data, or (c) unconventional methods. Any disagreements were resolved by consensus or by consultation with a third reviewer (MS). In the case of overlapping studies, the included study was chosen based on quality of methodology, sample size, and year. Complete data consisted of sufficient information to calculate sensitivity, specificity and accuracy for acute myocarditis. Positive LLC had to be defined as showing evidence of myocarditis in two out of three criteria. Quantitative parametric tests were considered appropriate if it calculated a global mean and defined positive based on a cut-off for the global mean. Reference tests for myocarditis could be based on either clinical criteria or EMB.

Study Quality

The quality of included studies was assessed by two investigators (JAP and MS) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument[17]. It consists of a list of 14 questions with closed-ended questions (yes, no, or unclear). The items included in this instrument covered patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawal, and indeterminate results. Publication bias was assessed by visual analysis of funnel plots and using the Peter's and Egger's methods[18,19].

Statistical Analysis

Dichotomous variables are presented as percentages and continuous variables as mean ± standard deviation or median [interquartile range]. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and their 95% confidence intervals were calculated with an exact method for binomial proportions using the F-distribution method[20]. Both univariate and bivariate pooling was performed. Univariate method was performed using MetaDiSc, version 1.4 freeware package (Universidad Complutense, Madrid, Spain). Pooled estimates of sensitivity, specificity, PPV, and NPV were determined by weighting the studies by their sample sizes[21]. Likelihood ratios (LR) and diagnostic odds ratios (DOR) were pooled using a random-effects model with the DerSimonanian-Laird method[21]. Heterogeneity between studies was assessed visually from Forest plots of the individual parameters and using the Cochran's Q index and the inconsistency index (I^2). Significant statistical heterogeneity was defined based on having both p[Cochran's Q] < 0.05 and I^2 > 50%. Bivariate analysis and comparison of pooled sensitivity, specificity, and DOR estimates between the diagnostic techniques (LLC, T1, T2, and ECV) was performed as described by Reitsma et al[22] and Van Houwelingen et al[23] using SAS/STAT software, version 9.4, of the SAS System for Windows (SAS Institute Inc., Cary, North Carolina). The bivariate approach tests for significance differences between imaging parameters while incorporating possible correlation between sensitivity and specificity. Statistical significance for hypothesis testing set at the $\alpha < 0.05$, 2-tailed level. Bivariate analysis was not performed

for PPV and NPV due to their dependence on disease prevalence and the lack of well-validated bivariate pooling methods. Meta-regression and sensitivity analyses (including exclusion of 1 study at a time) were conducted to explore heterogeneity.

Results

Search Results

Our literature search identified 806 relevant abstracts; of these, 33 abstracts were considered eligible for data extraction. Sixteen studies were excluded for overlapping patient cohorts, insufficient data, or unconventional methodology. Figure 1 shows the summary of our literature search. A total of 17 studies were included for analysis (Table 1). The sequences and cut-offs used in each study can be found in Supplemental Table 1.

Clinical Characteristics

The 17 included studies had a total of 1308 subjects, of whom either had myocarditis (Table 2) or were part of the control group (Tables 3). The myocarditis group included 867 subjects with a sample-weighted mean age of 42 and 72% male. The control group included 441 subjects with a sample-weighted mean age of 39 and 67% male. The two groups had similar sample-weighted mean body mass index (26 vs 25 kg/m^2 for myocarditis and control respectively) and heart rate (72 vs 67 bpm for myocarditis and control respectively). The myocarditis group had lower sample-weighted mean ejection fraction (54 vs 62% for myocarditis and control respectively).

Diagnostic Performance

The univariate and bivariate meta-analysis results are included Table 4 and Table 5, respectively. The Forest plots of the univariate sensitivity and specificity estimates are presented in Figure 2. The bivariate comparison showed that native T1 had significantly higher sensitivity than LLC (85% vs 74%, $p = 0.025$). Otherwise, there was no significant difference in sensitivity, specificity, and DOR when comparing LLC to native T1, T2, or ECV. Native T1 had the highest point estimate DOR of 36.6 and a high point estimate specificity of 86%. T2 had a point estimate sensitivity of 76%, specificity of 82%, and DOR of 14.4. ECV had the lowest point estimate specificity of 76% and DOR of 10.5 with a moderate sensitivity of 77%.

Significant heterogeneity was seen for LLC sensitivity (p[Cochran's Q] < 0.05, $I^2 = 57.5\%$) and specificity (p[Cochran's Q] < 0.05, $I^2 = 82.0\%$), T1 sensitivity (p[Cochran's Q] < 0.05, $I^2 = 83.4\%$) and specificity (p[Cochran's Q] < 0.05, $I^2 = 74.9\%$), and T2 sensitivity (p[Cochran's Q] < 0.05, $I^2 = 78.4\%$) and specificity (p[Cochran's Q] < 0.05, I2 = 58.8%). For the meta-regression, we used publication year, age, gender, and ejection fraction as the covariates and found no significant correlation with DOR for all imaging tests. Other clinical variables were not included due to insufficient reporting. Sensitivity analysis showed that exclusion of Radunski et al[10] significantly reduced heterogeneity for T1 sensitivity (p[Cochran's Q] = 0.11, $I^2 = 41.6\%$) and T2 sensitivity (p[Cochran's Q] = 0.08, $I^2 = 51.5\%$). T1 sensitivity remained significantly higher than LLC after exclusion of Radunski et al[10] (89% vs 74%, $p < 0.001$).

Quality and Bias Assessment

The selected studies had overall high-quality scores in all the 14 items of the QUADAS questionnaire (Supplemental Table 2). Egger's test suggested presence of publication bias for LLC and ECV but Peter's test did not demonstrate evidence of significant publication bias for any of the parameters.

Discussion

In this study we demonstrate that native T1, T2, and ECV mapping are comparable to LLC with only native T1 sensitivity being significantly better. Each quantitative imaging parameter may offer unique advantages depending on the clinical question. Utilization of a single parameter such as native T1 could potentially simplify the diagnostic criteria for assessing acute myocarditis.

Lake Louise Criteria

LLC was originally designed to detect different types of injuries that occur during myocarditis[5]. Beginning with an initial insult from either direct injury or activation of the innate immune system, myocardial inflammation leads to increased membrane permeability resulting in intracellular edema, hyperemia with capillary leakage, and eventually irreversible injury[36]. In the LLC criteria, LGE imaging provides an assessment of irreversible injury whereas EGE and T2w imaging provide an assessment of inflammation and edema. However, as EGE and T2w images may be prone to artifacts and misinterpretation, generalizing the application of the LLC criteria in routine clinical practice is challenging. When using univariate pooling of LLC components (Supplemental Table 3), LGE demonstrates the highest point estimate for diagnostic accuracy, and is the main driver of LLC performance, primarily due to its high specificity in patients with irreversible injury or necrosis[5]. The low sensitivity of LGE stems from its inability to identify subtle edema and reversible injury associated with early phases of inflammation[33]. Additionally, because gadolinium contrast agents can only assess the extracellular space, LGE cannot detect intracellular edema which is also thought to occur in early stages of myocarditis[13]. The sensitivity of LGE is similar to that of EGE and the T2w ratio, and the combination of these three parameters increases the sensitivity of the LLC as compared to LGE alone. Though EGE and T2w provide some incremental improvement in performance, they present with many technical challenges. Both are susceptible to artifact, especially from respiratory motion and arrhythmias[5]. EGE is also dependent on slice orientation and segment selection[31]. T2w often has low signal-to-noise ratios and regions of signal inhomogeneities that can obscure myocardial edema[5]. Finally, in patients with underlying skeletal myositis, T2w or EGE ratios can result in false negatives when they rely on reference signal intensities from skeletal muscle. In those cases, myocarditis must be assessed based on regional changes in T2w signal intensities or global elevations of absolute EGE signal intensities.

In the MyoRacer-Trial[11] involving biventricular myocardial biopsies, LLC exhibited inferior diagnostic performance to native T1, ECV, and T2 mapping. However, it is unclear whether this holds true for other studies due to variations in methods and sample populations. In addition, many studies have opted to use only T2w and LGE for diagnosis of myocarditis as

it has shown comparable accuracy[30,32,34]. In the study by von Knobelsdorff-Brenkenhoff et al[28], they combined various parameters including native T1 mapping, T2 mapping, ECV, LGE, and T2w ratio. They found that the best combination was LGE and T2w ratio, with a diagnostic accuracy of 88.9%. The best combinations that incorporated quantitative parameters was LGE with native T1 or T2 mapping with native T1, which both had a diagnostic accuracy of 86.1%.

T2 Mapping

T2 mapping demonstrated reasonable diagnostic accuracy to other modalities. Primarily detecting free water content, T2 relaxations times are most elevated during the acute phase of myocarditis and gradually normalizes over months. This feature may be useful for staging and monitoring recovery[28]. In patients with symptoms lasting more than two weeks, T2 mapping is considered the only technique that adequately discriminates between myocarditis and non-inflammatory cardiomyopathies validated by EMB[9,11]. Other techniques such as ECV and native T1 are not specific enough to detect inflammation in patients with confounding fibrosis[11].

Extracellular Volume Mapping

Commonly used as a surrogate marker for fibrosis, ECV can also detect extracellular expansion from sustained inflammation[7]. In fact, inflammation of the myocardium has been recently shown to confound the correlation between ECV and fibrosis[37]. In this study, ECV had the lowest point estimate for specificity and DOR. At best, studies have shown that ECV is comparable to LLC[10,28]. The main advantage of ECV as compared to LGE is its ability to assess diffuse fibrosis and inflammation beyond focal areas of fibrosis. ECV measurement is relatively insensitive to field strength, as compared to native T1. In addition, Radunski et al[10] showed that ECV can be combined with LGE to improve diagnostic accuracy to 90%. Specifically, global ECV can improve the sensitivity by identifying diffuse myocardial injury in patients with negative LGE.

Native T1 Mapping

Native T1 had excellent diagnostic performance compared to the other parameters. Given that both edema and extracellular expansion contribute to T1 prolongation, native T1 mapping is capable of detecting myocarditis at various stages. Furthermore, unlike most gadolinium contrast imaging, native T1 is dependent on both intracellular and extracellular/interstitial factors[38]. During the acute phases of myocarditis in which edema is most prevalent, native T1 offers both excellent sensitivity and specificity when the optimal cut-off is chosen[13,30,31]. However, as the early inflammation subsides and subsequent fibrosis occurs, native T1 prolongation becomes less specific to myocarditis[11,28]. Therefore, native T1 struggles to discriminate between inflammatory and non-inflammatory etiologies in patients with chronic symptoms, especially given that many cardiac pathologies progress to diffuse fibrosis[9,11]. Additionally, there are a number of limitations with native T1 such as variation in sequences, different sensitivities to T2 effects, lack standardization and normal values, and partial dependence on heart rate. A recent SCMR consensus statement on CMR mapping of T1, T2, T2*, and ECV discusses these challenges and provides clinical recommendations for parametric mapping with CMR[39]. Currently, there is no consensus on

optimal cut-offs for T1 mapping when diagnosing myocarditis, especially given that absolute T1 values depend on the CMR sequence and algorithm for T1 calculation[40]. Until a cut-off is determined, T1 mapping is probably best used either with site specific reference values, or when combined with incremental thresholding, providing similar visual information as LGE without the need for gadolinium[41].

Limitations

The studies included in this meta-analysis had significant variability in duration of symptoms, severity of disease, and type of validation tests. The time from symptom onset/admission to CMR ranged from 1 to 49 days, which may impact the prevalence of edema and thus could affect test performance. In addition, some studies included patients in severe cardiac dysfunction with ejection fractions as low as 22%. Patients with such severe myocarditis or new-onset heart failure often reflect more subacute disease rather than acute myocarditis[9,10]. As a result, this subpopulation of myocarditis patients can present with less edema and more fibrosis, which can distort the diagnostic performance of parametric mapping. In particular, the study by Radunski et al[10] contributed significant heterogeneity to our study with much lower native T1 and T2 sensitivities. Their patient population represented more subacute myocarditis with a median time from onset to CMR of 14 days, which could result in partial resolution of inflammation and edema. This likely explained why heterogeneity was reduced in the sensitivity analysis when this study was removed.

There are additional factors that influence the meta-analysis results. The type of validation test can dramatically affect the study designs. Clinical criteria based on patient history, abnormal biomarkers, and absence of other causes is useful for diagnosing myocarditis but provides no definitive pathological evidence of the presence of myocarditis. EMB continues to be the gold-standard reference test for interpreting the results of these CMR studies as they accurately correlate the physiological findings. Variability in cut-off values and field strengths can also influence diagnostic performance. Of the 3 parameters, native T1 is the most field strength dependent with normal myocardium having a native T1 that is roughly 200ms longer at 3T. Another limitation of this meta-analysis is that all studies were conducted using scanners from only two vendors, largely due to the availability of parametric mapping sequences, and the results may not be generalizable to other vendors. Additionally, our meta-analysis was conducted using PubMed and does not include studies that may be exclusively found in other databases such as EMBASE, Scopus, and The Cochrane Library.

Finally, we expected typical sources of bias such as small-study effects, decline effect, and early-extreme bias to influences our results[42]. Small-study effects, which we assessed using Egger’s and Peter’s test, was most likely the largest potential source of bias in our meta-analysis given the large number of single center studies. Regarding decline effect and early-extreme bias, meta-regression showed that publication year was not a significant covariate of diagnostic performance.

Conclusion

In diagnosing patients with acute myocarditis, native T1, T2, and ECV mapping were shown to be comparable to LLC. Native T1 had significantly better sensitivity than LLC. Our results suggest that incorporation of quantitative CMR parameters may improve accuracy, provide additional disease characterization, and help guide management. Furthermore, only needing to assess a single parameter such as native T1 could simplify the diagnosis of myocarditis as compared to using the LLC. Further research is needed to investigate the optimal combinations for assessing different presentations of myocarditis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspective Summary

Established nearly a decade ago, the Lake Louise Criteria (LLC) is the recommended cardiac magnetic resonance imaging criterion for diagnosing patients with suspected myocarditis. However, advances in quantitative imaging techniques for T1, T2, and extracellular volume (ECV) have demonstrated comparable diagnostic utility in myocarditis. In the present meta-analysis, we pooled 17 studies for a total of about 13,000 subjects to compare the diagnostic performance of native T1, T2, and ECV to LLC in identifying acute myocarditis. The principle finding is that only native T1 offered a significantly better sensitivity than LLC. Otherwise, there are no other significant differences in sensitivity and specificity between quantitative imaging modalities and LLC. This study validates our hypothesis that native T1, T2, and ECV mapping provide comparable diagnostic performance to LLC. This finding implies that clinicians should carefully consider both the technical and diagnostic advantages when selecting which modalities to include in the evaluation of myocarditis.

Figure 1.
Flow diagram of the review process

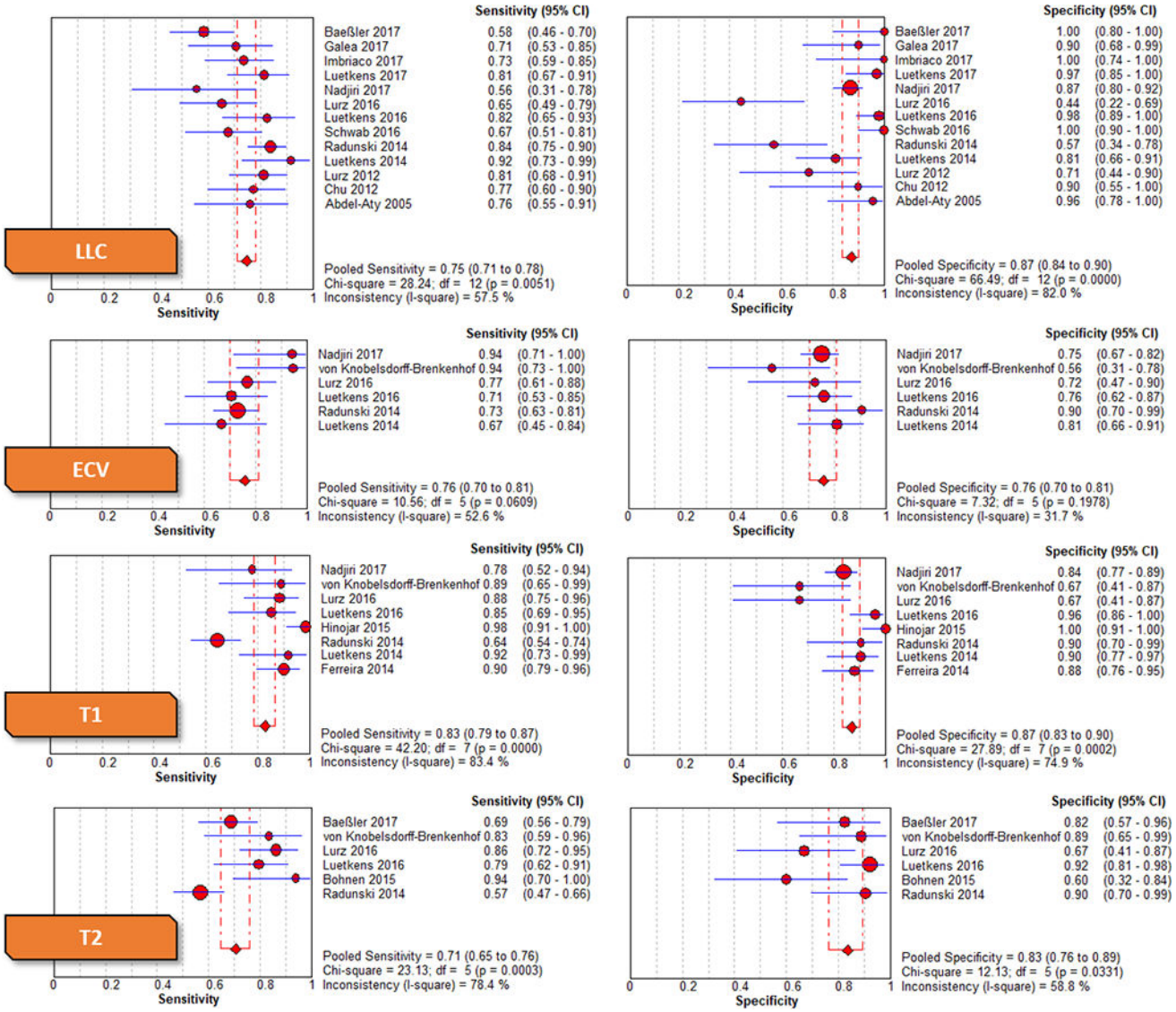

Figure 2.

Forest plots with univariate pooled sensitivities and specificities across all imaging parameters

Table 1

Characteristics of Included Studies

First Author	Year Published	Subjects (n)	Study Design	Validation	Parameters	Scanner	Vendor	Field Strength (Tesla)	Interval from Admission to CMR (days)	Interval from Onset to CMR (days)
Baeßler[12]	2017	84	Retrospective	Clinical	LLC, T2	Achieva	Philips	1.5	n/a	4.8 ± 4.4‡
Galea[24]	2017	54	Retrospective	EMB	LLC	Magnetom Avanto	Siemens	1.5	n/a	9.5 ± 5.1‡
Imbriaco[25]	2017	61	Not Reported	Clinical	LLC	Gyroscan Intera	Philips	1.5	6.8 ± 4‡	n/a
Luetkens[26]	2017	83	Prospective	Clinical	LLC	Ingenia	Philips	1.5	2.7 ± 1.9‡	n/a
Nadjiri[27]	2017	171	Retrospective	Clinical *	LLC, ECV, T1	Magnetom Avanto	Siemens	1.5	n/a	n/a
von Knobelsdorff-Brenkenhoff[28]	2017	36	Prospective	Clinical	ECV, T1, T2	Magnetom Avanto	Siemens	1.5	n/a	< 7
Lurz[11]	2016	61	Prospective	EMB	LLC, ECV, T1, T2	Intera CV	Philips	1.5	< 1.5	n/a
Luetkens[13]	2016	84	Prospective	Clinical	LLC, ECV, T1, T2	Ingenia	Philips	1.5	2.6 ± 1.9‡	n/a
Schwab[29]	2016	78	Retrospective	Clinical	LLC	Intera CV	Philips	1.5	1–17	n/a
Hinojar[30]	2015	101	Prospective	Clinical	T1	Achieva	Philips	1.5 & 3.0	n/a	2–8
Bohnen[9]	2015	31	Not Reported	EMB	T2	Achieva	Philips	1.5	3 [1–6]†	n/a
Radunski[10]	2014	125	Not Reported	Clinical	LLC, ECV, T1, T2	Achieva	Philips	1.5	n/a	14 [7–49]†
Luetkens[31]	2014	66	Prospective	Clinical	LLC, ECV, T1	Ingenia	Philips	3.0	2.6 ± 2.2‡	n/a
Ferreira[32]	2014	110	Prospective	Clinical	T1	Avanto	Siemens	1.5	3 [1–6]†	n/a
Lurz[33]	2012	70	Prospective	EMB	LLC	Intera CV	Philips	1.5	n/a	3 [1–7]†
Chu[34]	2012	45	Not Reported	Clinical	LLC	Magnetom Avanto	Siemens	1.5	n/a	7 ± 10‡
Abdel-Aty[35]	2005	48	Not Reported	EMB	LLC	Signa CV	GE	1.5	n/a	5.6 ± 4.2‡

† Expressed as median with interquartile range

‡ Expressed as mean with standard deviation

* Final diagnosis based on troponin > 10 times upper limit of normal

ECV = extracellular volume; EMB = endomyocardial biopsy; LLC = Lake Louise Criteria; n = number.

Table 2

Myocarditis Group Characteristics

First Author	Subjects (n)	Age (yrs)	Male (%)	HR (bpm)	BMI (kg/m^2)	LVEDVI (ml/m^2)	LVESVI (ml/m^2)	Troponin (T or I)	Elevated Troponin (%)	LVEF (%)
Baeßler[12]	67	37 ± 14‡	73	65	25	84	33	3 (T)	55	62 ± 7‡
Galea[24]	34	41 ± 18‡	76	n/a	n/a	87	44	n/a	44	53 ± 12‡
Imbriaco[25]	49	44 ± 16‡	75	n/a	n/a	n/a	n/a	242 (I)	43	47 ± 15‡
Luetkens[26]	48	44 ± 19‡	56	70	26	n/a	72	6.6 (I)	n/a	55 ± 11‡
Nadjiri[27]	153	47 ± 16‡	68	n/a	n/a	n/a	n/a	n/a	10	n/a
von Knobelsdorff-Brenkenhoff[28]	18	25 [23–38]†	78	n/a	n/a	90	n/a	n/a	n/a	60 [57–63]†
Lurz[11]	43	40 [29–56]†	72	n/a	n/a	n/a	n/a	0.23 (T)	77	48 [28–54]†
Luetkens[13]	34	45 ± 19‡	50	70	26	n/a	71	4.7 (I)	n/a	56 ± 12‡
Schwab[29]	43	35 ± 15‡	88	n/a	26	82	32	n/a	100	60 [54–66]†
Hinojar[30]	61	48 ± 17‡	60	70	26	94	51	n/a	95	70 ± 21‡
Bohnen[9]	16	52 [37–62]†	75	89	27	149	108	0.07 (T)	n/a	31 [22–37]†
Radunski[10]	104	44 [33–58]†	76	71	25	101	60	0.04 (T)	n/a	42 [28–57]†
Luetkens[31]	24	35 ± 33‡	75	68	27	128	n/a	7.2 (I)	n/a	60 ± 9‡
Ferreira[32]	60	41 ± 16‡	75	n/a	n/a	n/a	n/a	4.5 (I)	n/a	64 ±12‡
Lurz[33]	53	44 ± 17‡	87	n/a	n/a	n/a	n/a	n/a	52	52 [31–62]†
Chu[34]	35	40 ± 17‡	77	68	26	102	49	1.1 (T)	n/a	52 ± 11‡
Abdel-Aty[35]	25	44 ± 17‡	72	n/a	n/a	n/a	n/a	n/a	92	57 ± 13‡

†Expressed as median with interquartile range

‡Expressed as mean with standard deviation

*Data included all patients with clinical suspicion of acute myocarditis regardless validation test.

BMI = body mass index, bpm = beats per minute; HR = heart rate; I = troponin I (ng/ml); LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end diastolic index; LVESVI = left ventricular end systolic index; n = number; T = troponin T (ng/ml); yrs = years.

Table 3

Control Group Characteristics

First Author	Subjects (n)	Age (yrs)	Male (%)	HR (bpm)	BMI (kg/m^2)	LVEDVI (ml/m^2)	LVESVI (ml/m^2)	Troponin (T or I)	Elevated Troponin (%)	LVEF (%)
Baeßler[12]	17	36 ± 12‡	65	63	24	81	29	n/a	n/a	65 ± 5‡
Galea[24]	20	50 ± 15‡	65	n/a	n/a	78	38	n/a	65	52 ± 12‡
Imbriaco[25]	12	47 ± 16‡	58	n/a	n/a	n/a	n/a	1 (I)	25	54 ± 14‡
Luetkens[26]	35	41 ± 17‡	66	66	25	n/a	73	U (I)	n/a	61 ± 3‡
Nadjiri[27]	18	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
von Knobelsdorff-Brenkenhoff[28]	18	27 [24–35]†	78	n/a	n/a	90	n/a	n/a	n/a	61 [60–63]†
Lurz[11]	18	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Luetkens[13]	50	39 ± 17‡	60	66	25	n/a	73	U (I)	n/a	61 ± 13‡
Schwab[29]	35	35 ± 14‡	89	n/a	25	76	25	n/a	0	69 [58–81]†
Hinojar[30]	40	45 ± 15‡	53	68	25	74	30	n/a	0	61 ± 5‡
Bohnen[9]	15	38 [28–63]†	80	76	27	152	113	0.04 (T)	n/a	25 [18–34]†
Radunski[10]	21	34 [28–47]†	81	65	25	80	28	0.005 (T)	n/a	59 [55–66]†
Luetkens[31]	42	39 ± 10‡	64	65	25	128	n/a	U (I)	n/a	63 ± 6‡
Ferreira[32]	50	41 ± 13‡	74	n/a	n/a	n/a	n/a	n/a	n/a	72 ± 6‡
Lurz[33]	17	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Chu[34]	10	40 ± 16‡	50	66	24	82	32	n/a	n/a	61 ± 6‡
Abdel-Aty[35]	23	29 ± 10‡	57	n/a	n/a	n/a	n/a	n/a	n/a	64 ± 5‡

†Expressed as median with interquartile range

‡Expressed as mean with standard deviation

BMI = body mass index, bpm = beats per minute; HR = heart rate; I = troponin I (ng/ml); LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end diastolic index; LVESVI = left ventricular end systolic index; n = number; T = troponin T (ng/ml); U = Undetectable; yrs = years.

Table 4

Univariate Diagnostic Estimates

Parameter	Studies	Subjects	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive LR	Negative LR	Diagnostic OR
LLC	13	1022	75 [71–78]	87 [84–90]	88 [85–91]	73 [69–76]	6.2 [3.1–12.3]	0.31 [0.25–0.39]	24.0 [10.1–56.8]
ECV	6	533	76 [70–81]	76 [70–81]	72 [66–77]	79 [74–84]	3.2 [2.6–4.1]	0.32 [0.25–0.42]	11.4 [6.6–19.7]
T1	8	694	83 [79–87]	87 [83–90]	86 [81–89]	85 [81–88]	6.2 [3.4–11.0]	0.15 [0.07–0.32]	44.1 [18.4 – 105.4]
T2	6	421	71 [65–76]	84 [76–89]	90 [85–93]	58 [51–65]	4.1 [2.4–7.0]	0.29 [0.18–0.47]	18.6 [10.0–34.5]

Expressed as pooled estimate with 95% confidence interval.

ECV = extracellular volume; LLC = Lake Louise Criteria; LR = likelihood ratio; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value.

Table 5

Bivariate Diagnostic Estimates

Modality	Sensitivity	Specificity	Diagnostic OR
LLC	74 [67–80]	86 [77–92]	17.7 [9.4–33.2]
ECV	77 [66–85]	76 [60–87]	10.5 [4.6–23.6]
T1	85 [78–90]†	86 [76–93]	36.6 [17.1–78.5]‡
T2	76 [65–84]	82 [68–91]	14.4 [6.1–34.2]

Expressed as pooled estimate with 95% confidence interval.

† $p < 0.05$ vs LLC

‡ $p < 0.05$ vs ECV

ECV = extracellular volume; LLC = Lake Louise Criteria; OR = odds ratio.