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Diagnostic Accuracy of Cardiovascular Magnetic Resonance in Acute Myocarditis

A Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVES The purpose of this systematic review was to explore the diagnostic accuracy of various cardiovascular magnetic resonance (CMR) index tests for the diagnosis of acute myocarditis in adult patients.

BACKGROUND Acute myocarditis remains one of the most challenging diagnoses in cardiology. CMR has emerged as the diagnostic tool of choice to detect acute myocardial injury and necrosis in patients with suspected myocarditis.

METHODS We considered all diagnostic cohort and case-control studies. We searched MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science up to April 21, 2017. We used the Quality Assessment of Diagnostic Accuracy Studies-2 tool to assess the quality of included studies. PROSPERO registration number CRD42017055778 was used.

RESULTS Twenty-two studies were included in the systematic review. Because significant heterogeneity exists among the studies, we only present hierarchical receiver operator curves. The areas under the curve (AUC) for each index test were for T1 mapping 0.95 (95% confidence interval [CI]: 0.93 to 0.97), for T2 mapping 0.88 (95% CI: 0.85 to 0.91), for extracellular volume fraction (ECV) 0.81 (95% CI: 0.78 to 0.85), for increased T2 ratio/signal 0.80 (95% CI: 0.76 to 0.83), for late gadolinium enhancement (LGE) 0.87 (95% CI: 0.84 to 0.90), for early gadolinium enhancement (EGE) 0.78 (95% CI: 0.74 to 0.81), and for the Lake Louise criteria (LLC) 0.81 (95% CI: 0.77 to 0.84). Native T1 mapping had superior diagnostic accuracy across all index tests. The AUC of T2 mapping was greater than the AUC of increased T2 ratio/signal and EGE, whereas ECV showed no superiority compared with other index tests. LGE had better diagnostic accuracy compared with the classic CMR index tests, similar accuracy with T2 mapping and ECV, and only T1 mapping surpassed it.

CONCLUSIONS Novel CMR mapping techniques provide high diagnostic accuracies for the diagnosis of acute myocarditis and constitute promising successors of the classic elements of the LLC for routine diagnostic protocols. (J Am Coll Cardiol Img 2018;11:1583–90) © 2018 by the American College of Cardiology Foundation.

Acute myocarditis is defined as an inflammatory disease of the myocardium that can result from a wide variety of infectious agents (viruses, bacteria, and others), systemic diseases, drugs, and toxins (1). The variable clinical presentation of patients with acute myocarditis (2) makes its diagnosis a challenge. Although endomyocardial biopsy is considered the gold standard for the diagnosis of acute myocarditis (3), several limitations restrict its widespread application. Therefore, it is only recommended in a limited number of clinical scenarios such as patients with evidence of heart failure in combination with acute disease (<2 weeks, Class I) or left ventricular dilation (<3 months, Class I) or specific other cases of heart failure (Class IIa) (4).

Cardiovascular magnetic resonance (CMR) is currently considered the most comprehensive and accurate diagnostic tool in patients with suspected

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CMR = cardiovascular magnetic resonance

ECV = extracellular volume fraction

EGE = early gadolinium enhancement

HSROC = hierarchical summary receiver-operator curve

LGE = late gadolinium enhancement

LLC = Lake Louise criteria

MOLLI = modified Look-Locker inversion recovery sequence

QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2

ShMOLLI = shortened modified Look-Locker inversion recovery sequence

myocarditis (5). The Lake Louise criteria (LLC) recommend combining different CMR techniques in patients with suspected myocarditis to determine myocardial edema (T2-weighted imaging), hyperemia (T1-weighted imaging), and fibrosis (late gadolinium enhancement [LGE]) (5). The LLC use a semiquantitative approach and allow detection of myocardial inflammation and necrosis. However, several technical limitations exist. T1-weighted spin-echo sequences during free breathing frequently suffer from poor image quality, whereas T2-weighted spin-echo images have a low signal-to-noise ratio (5). Furthermore, LGE alone may fail to characterize acute myocarditis, as some patients only present with acute myocardial inflammation/edema. T1 and T2 mapping are novel CMR techniques for quantitative tissue characterization with tight normal ranges, which allow a more objective assessment of myocardial tissue properties. Importantly, parametric mapping techniques appear to overcome some of the aforementioned technical limitations of the LLC (5) and enable the assessment of diffuse myocardial injury, because they have been shown to be highly sensitive to increased free water content rendering them ideal for detecting acute myocardial inflammation/edema (6).

The aim of this systematic review was to explore the diagnostic accuracy of classic and novel CMR index tests for the diagnosis of acute myocarditis in adult patients. Secondary aims were to investigate potential sources of heterogeneity and provide preliminary comparisons of the diagnostic accuracy across studied index tests.

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METHODS

The methods and results of this review are being presented according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) (7). The review protocol was previously registered on PROSPERO (International Prospective Register of Systematic Reviews) with the CRD (Centre of Reviews and Dissemination) report number CRD42017055778.

ELIGIBILITY CRITERIA. We considered all diagnostic cohort and case-control studies that used either endomyocardial biopsy or clinical criteria for the diagnosis of acute myocarditis. We excluded studies in which we were not able to reconstruct a 2×2 diagnostic table.

SEARCH STRATEGY. We searched MEDLINE (via PubMed), EMBASE (via Ovid), Cochrane Library, SCOPUS, and Web of Science by using both free-text terms and Medical Subject Headings (MeSH) terms, without any date or language restrictions. We also used manual searches of hand-searched trial registries and reference lists of the included studies. The detailed search strategy that was used and a list of literature sources searched are listed in the Online Appendix. The last search was performed on April 21, 2017.

STUDY SELECTION AND DATA EXTRACTION. Two authors (C.K. and M.A.B.) independently screened the records retrieved from the search after deduplication by title and abstract. Selected records were further screened for eligibility in full text independently by the same investigators (C.K. and M.A.B.). Data collection was initially piloted using a pre-designed extraction form on 3 manuscripts, as proposed by literature (8). After necessary adjustments, 2 independent reviewers (C.K. and M.A.B.) extracted data using a customized extraction form. Discrepancies at each stage of selection were arbitrated by a third reviewer (T.D.K.) and resolved by consensus. We contacted the authors of included studies to obtain additional data.

ASSESSMENT OF METHODOLOGIC QUALITY. We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to assess the quality of included studies (9). Two review authors adjusted both the signaling questions and the assessment questions to form a review-specific version of the tool. The tool was subsequently piloted, and when good agreement was achieved, it was used to assess risk of bias and applicability of all included studies independently by the same authors. Disagreements were resolved by consensus.

DATA SYNTHESIS. Initially, for each index test, the derived estimates of sensitivity and specificity were plotted in receiver operating characteristic (ROC) curves and forest plots for preliminary investigation. We expected that studies would use different thresholds to dichotomize test results measured on a continuous scale and therefore planned to perform meta-analyses using hierarchical models to produce summary ROC (HSROC) curves and 95% prediction regions, in Stata version 13 (Stata Corp., College Station, Texas) (10,11). We also estimated summary sensitivities and specificities, in separate analyses, where studies reported common thresholds. After visual inspection of the forest plots and the summary ROC curves, we investigated the presence of heterogeneity between studies, by performing appropriate meta-regression models and wherever possible,

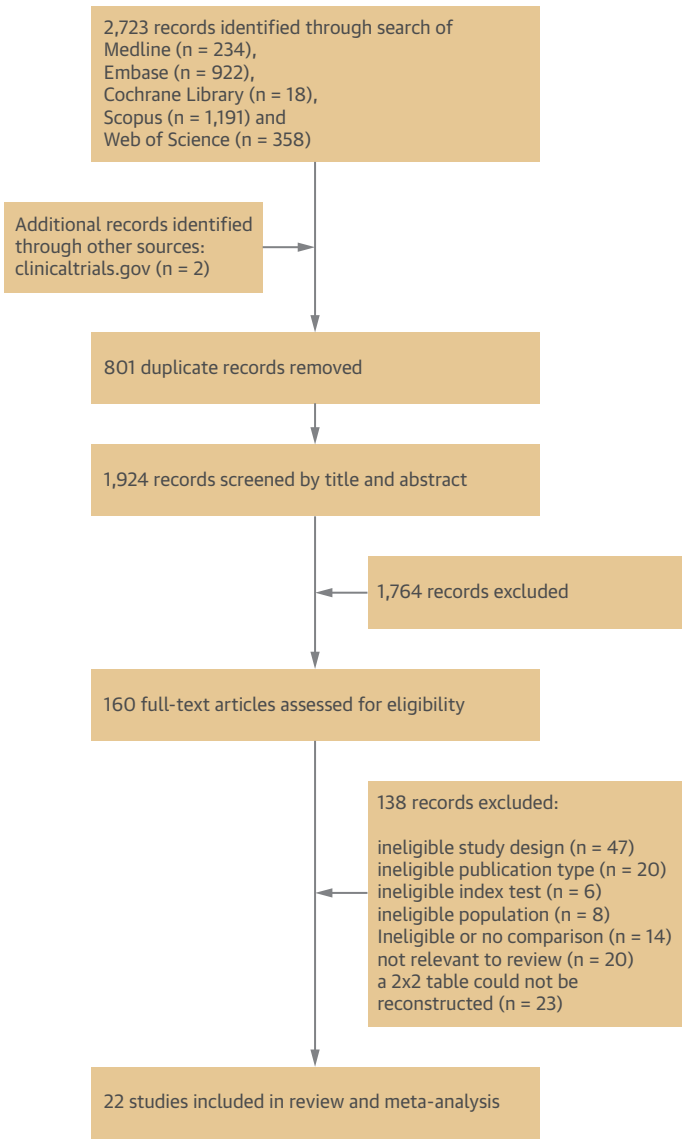
subgroup analyses according to study type (cohort/case-control) and CMR field strength. We also performed sensitivity analyses, if the number of available studies was enough, by restricting analyses to studies at low risk of bias. We used the Bonferroni correction to compensate for the Type I error increase that occurs with multiple comparisons (12).

RESULTS

SEARCH RESULTS. Our search yielded 2,725 results from the various literature sources. After removing duplicates, we screened 1,924 records by title and abstract, 1,764 records were excluded, and the remaining 160 records were screened by full-text for eligibility. Finally, 22 studies were included in our systematic review. A detailed flow diagram with the study selection process and various reasons for exclusion is shown in **Figure 1**.

NATIVE T1 MAPPING. Seven studies provided data regarding the diagnostic accuracy of native T1 mapping (13-19). All studies except for 1 were considered to be at high risk of bias (Online Figure 1). Consequently, it was impossible to perform a sensitivity analysis based on methodological quality. Details pertaining to study characteristics (Online Table 1) and methodologic quality assessment are available in the Online Appendix. In the main analysis, sensitivity ranged from 0.64 to 0.98 and specificity ranged from 0.67 to 1.00 (Online Figure 2). We observed heterogeneity between included studies, which could be attributed to the use of different CMR field strengths and variable positivity thresholds. Hence, we only present an HSROC curve (**Figure 2**) with an area under the curve (AUC) of 0.95 (95% confidence interval [CI]: 0.93 to 0.97). We performed subgroup analysis (Online Figure 3) excluding the 2 studies that used field strengths other than 1.5-T (15,17), with the AUC retreating to 0.92 (95% CI: 0.89 to 0.94). In the appendix, we depicted the conditional probability plot (Online Figure 5) and Fagan nomogram (Online Figure 4) to support decision-making and interpretation of the clinical utility of the index test for detecting patients with acute myocarditis. For example, in an average-risk population with a pretest probability (prevalence) equal to 25%, native T1 mapping increased the probability of acute myocarditis to 75% when the test result is positive and decreased the probability to 4% when the test result was negative. We found no publication bias (Online Figure 6) in the regression test for funnel plot asymmetry ($p = 0.19$). To explore the potential effect of publication year and sample size on heterogeneity, we conducted a meta-regression analysis. Neither one proved to affect sensitivity/specificity values.

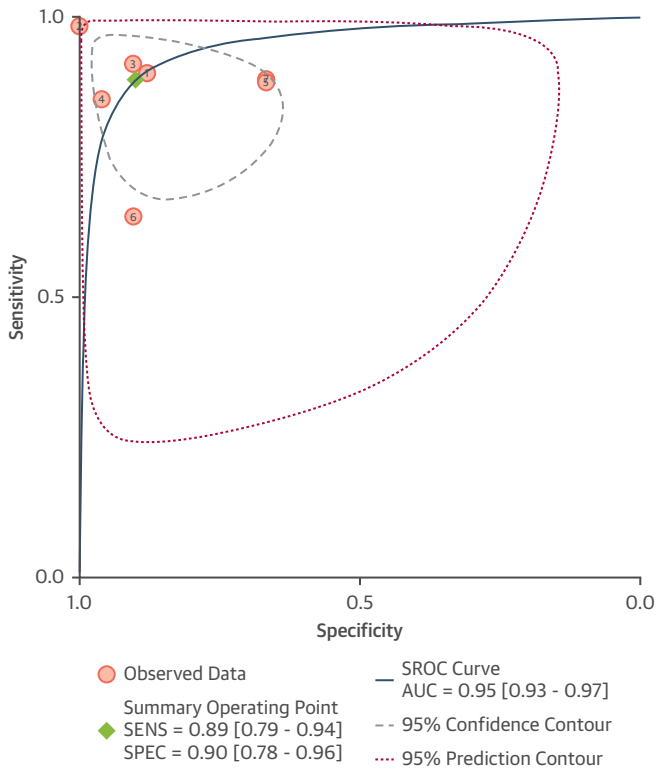
FIGURE 1 PRISMA Flow Diagram



The flow diagram depicts the flow of information through the different phases of the systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions. PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.

T2 MAPPING. Six of the included studies (13,14,18-21) provided data regarding the diagnostic accuracy of T2 mapping. Details about study characteristics (Online Table 2) and methodologic quality are available in the appendix. Four of the studies included were considered to be at high risk of bias (Online Figure 9). The forest plot depicting sensitivities and specificities of

FIGURE 2 HSROC Plot of Sensitivity Versus Specificity of Native T1 Mapping



Each **circle** represents a study. The **curve** represents the summary receiver operating characteristic curve for native T1 mapping. The **green rhombus** represents the summary estimate of test performance. The zone outlines represent the 95% confidence and 95% prediction regions of the summary estimate, respectively. HSROC = hierarchical summary receiver operating curve.

the 6 included studies in the main analysis is available in Online Figure 7. Sensitivity ranged from 0.57 to 0.94 and specificity from 0.60 to 0.92. Because of variable cutoff values being used across the studies, we avoided presenting summary sensitivity and specificity points and chose to present an HSROC curve (**Figure 3**). We found no publication bias in the regression test for funnel plot asymmetry ($p = 0.19$). All studies used 1.5-T field strength, so we solely sought to perform subgroup analysis based on study design. Only 2 studies used the 1-gated prospective cohort design, and we were unable to fit proper meta-analytical models because those required a minimum of 4 studies (22). Sample size proved to affect sensitivity/specificity values ($p = 0.04$) with small studies presenting higher values of test performance, contrary to publication year.

EXTRACELLULAR VOLUME FRACTION. Data for the diagnostic accuracy of extracellular volume fraction (ECV) was available in 5 studies (13-15,18,19). Four of the studies included were considered to be at high risk of bias (Online Figure 10). Only 1 study used a cohort design (19), and therefore sensitivity analysis was not possible. A detail of study characteristics (Online Table 3) as well as information about methodologic quality assessment are available in the Online Appendix. Online Figure 8 presents the forest plot depicting sensitivities and specificities of the 5 studies. Sensitivity ranged from 0.67 to 0.94 and specificity from 0.56 to 0.90. Because of variable cutoff values being used across the studies, we only present an HSROC curve (**Figure 4**) with an AUC of 0.81 (95% CI: 0.78 to 0.85) and not summary sensitivity or specificity points.

CLASSIC CMR TECHNIQUES. In this section, we present the core findings of our review regarding the diagnostic accuracy of increased T2 signal, LGE, early gadolinium enhancement (EGE), and their combination, the LLC. A more detailed presentation with information about methodologic quality assessment and data synthesis is available in the Online Appendix (Online Figures 11 to 29). In total, 15 of the included studies provided data on the diagnostic accuracy of increased intensity in T2-weighted images (13-18,23-31). Sensitivity ranged from 0.45 to 1.00 and specificity from 0.43 to 1.00. Fitting the HSROC curve yielded an AUC equal to 0.80 (95% CI: 0.76 to 0.83). The diagnostic accuracy of LGE was examined in 17 of the included studies (13-19,23,25-30,32-34) with a summary sensitivity point of 0.68, a summary specificity point of 0.96, and an AUC of 0.87 (95% CI: 0.84 to 0.90). Ten studies (14,15,18,23,25-27,30,31,35) provided data for the diagnostic accuracy of early enhancement. Sensitivity ranged from 0.49 to 0.85, specificity from 0.43 to 1.00, and the AUC was equal to 0.78 (95% CI: 0.74 to 0.81). The diagnostic accuracy of the LLC was investigated in 8 studies (14,15,18,19,25-27,30). Sensitivity was 0.78, specificity 0.88, and AUC 0.83 (95% CI: 0.79 to 0.86).

COMPARISON OF THE DIAGNOSTIC ACCURACY OF INDEX TESTS. In order to compare the diagnostic accuracy of index tests analyzed in the preceding paragraphs, we compared the AUC values derived from fitting summary ROC curves to the individual study data for each index test (36). Overall results from all meta-analyses conducted with details on accuracy can be found in **Table 1**. Online Table 8 presents the comparison matrix, with corresponding p values. Native T1 mapping proved to be superior in terms of diagnostic accuracy across all index tests, including the comparison with T2 mapping or LGE. The AUC of T2 mapping was significantly greater than

the AUC of increased T2 ratio/signal and EGE, whereas ECV showed no superiority compared with other index tests. LGE proved to have better diagnostic accuracy compared with both T2-weighted imaging and EGE, similar accuracy with T2 mapping and ECV, and only T1 mapping managed to surpass it.

DISCUSSION

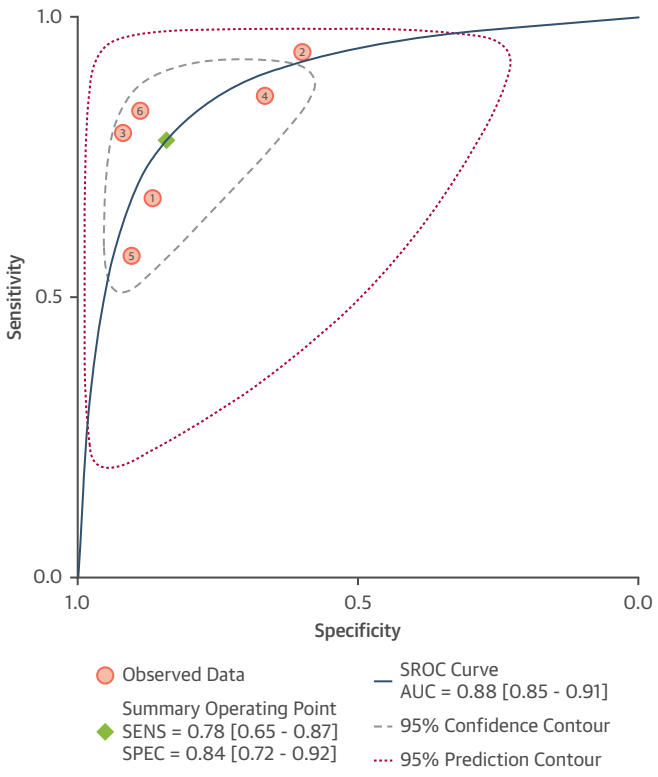
This meta-analysis showed that the accuracy of standard CMR techniques for the diagnosis of acute myocarditis (LLC: edema on T2-weighted imaging, hyperemia on T1-weighted imaging, and fibrosis on LGE imaging) is good but can be further improved with the addition of novel parametric mapping techniques. In an acute clinical setting, imaging of myocardial edema by T2-weighed sequences could be replaced by native T2 mapping, and similarly, imaging of myocardial hyperemia using T1-weighted sequences could be replaced by native T1 mapping. LGE has high diagnostic accuracy and can constitute the third component of the revised CMR criteria for acute myocarditis. It should be noted, however, that we observed significant heterogeneity between studies, which arise from the different sequences, imaging protocols, and field strengths used.

The diagnostic value of native T1 relaxation times in subjects with acute myocarditis has been reported in numerous studies, achieving an accuracy of 61% to 99% (13,15–17). Different T1 thresholds but within a tight range of 990 to 1,000 ms have been used at 1.5-T. A cutoff value of 992 ms used by Hinojar et al. (17) yielded the highest sensitivity of 98% and specificity of 100%. Of note, 6 of 7 studies (13–15,17–19) used a modified Look-Locker inversion recovery sequence (MOLLI), whereas Ferreira et al. (16) used a shortened version of MOLLI (ShMOLLI), which yielded a sensitivity and specificity of 90% and 88%, respectively. Apart from MOLLI-based inversion sequences, which are the most commonly used and validated, several other T1 mapping sequences exist. The plethora of different T1 mapping methods generates some uncertainty as to whether results of one study can be confirmed on a similar patient population with a different T1 mapping methodology. Additionally, there was a variation in the days that CMR was performed. Although in most studies, CMR was performed shortly after presentation, Radunski et al. (18) report a median interval between onset of symptoms and CMR of 2 weeks. This resulted in a significantly lower sensitivity of 64% but a high specificity of 90%.

Studies using T2 mapping at 1.5-T reported sensitivity that ranged from 57% to 94%, whereas specificity ranged from 60% to 92%. Bohnen et al. (21), in a study with 1-gated design found the highest sensitivity of 94% with a cutoff of 60 ms, whereas Radunski et al. (18) using a similar cutoff of 61 ms found a significantly lower sensitivity of 57%. Once again, this discrepancy is probably due to the more subacute clinical presentation (2 weeks after onset of symptoms) in the study by Radunski et al. (18). Luetkens et al. (14) reported an equivalent diagnostic performance of T2 mapping when compared with T1 mapping and increased diagnostic accuracy when compared with T2-weighed imaging, confirming the improved detection of diffuse inflammation by T2 mapping compared with standard T2-weighed images. Several T2 mapping sequences exist (although fewer than T1 mapping), which may affect diagnostic thresholds for detecting disease.

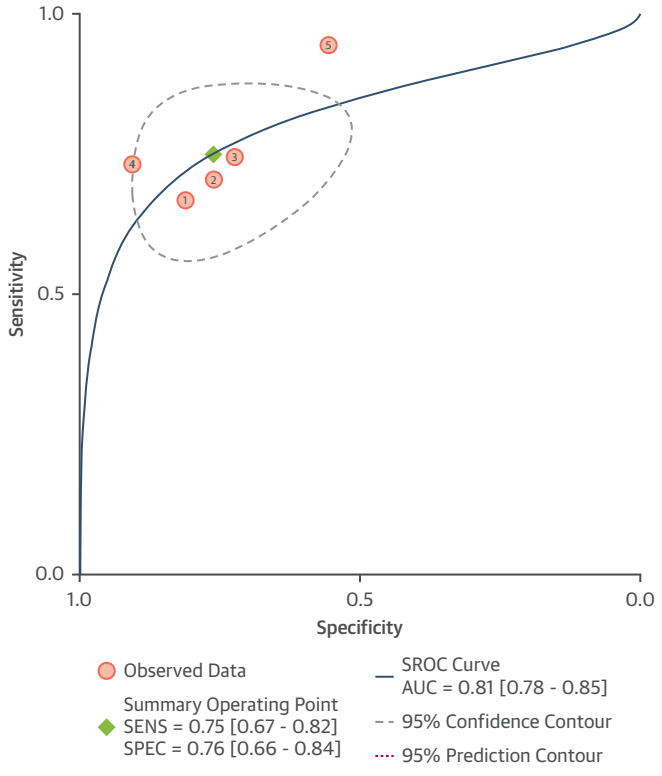
In the 5 studies that used ECV in acute myocarditis, sensitivity ranged from 67% to 94%, and specificity

FIGURE 3 HSROC Plot of Sensitivity Versus Specificity of T2 Mapping



Each **circle** represents a study. The **curve** represents the summary receiver operating characteristic curve for T2 mapping. The **green rhombus** represents the summary estimate of test performance. The zone outlines represent the 95% confidence and 95% prediction regions of the summary estimate, respectively. Abbreviations as in Figure 2.

FIGURE 4 HSROC Plot of Sensitivity Versus Specificity of ECV



Each **circle** represents a study. The **curve** represents the summary receiver operating characteristic curve for ECV. The **green rhombus** represents the summary estimate of test performance. The zone outlines represent the 95% confidence and 95% prediction regions of the summary estimate, respectively. ECV = extracellular volume fraction.

ranged from 56% to 90%. Von Knobelsdorff-Brenkenhoff et al. (13) reported lower ECV values compared to those of Luetkens et al. (14) and Radunski et al. (18). This discrepancy may be explained by the focal nature of disease, the number of slices used to cover the heart, and whether rudimentary or advanced image analysis (ECV maps) was performed. Furthermore, some differences in T1 techniques, timing of post-contrast T1 maps, and disease severity in the various patient populations could also have affected ECV values. Luetkens et al. (14) showed that the diagnostic accuracy of ECV is inferior to native T1 mapping. The diagnostic performance of ECV might have been hampered in the early course of the disease when ECV might still have be normal. In addition, ECV values may vary depending on the CMR sequence used, but they are not affected by field strength, unlike native T1 and T2 mapping (14).

We identified 15 studies regarding the diagnostic accuracy of T2-weighed imaging on acute myocarditis. Sensitivity ranged from 45% to 100%, and specificity ranged from 43% to 100%, whereas the AUC derived was 0.80 (95% CI: 0.76 to 0.83). Field strength did not appear to affect accuracy. LGE was investigated in 17 studies. Diagnostic accuracy was variable between studies, with sensitivity ranging from 30% to 95% and specificity from 39% to 100%. For the main analysis, LGE appeared to have moderate sensitivity and excellent specificity, 68% and 96%, respectively, in diagnosing acute myocarditis. Many studies presented a specificity of 100% for LGE (13-15,17,18,25,30). However, the 6 studies that were considered at low risk of bias did not confirm this finding, with Lurz et al. (19) reporting a specificity of 39% and Rieker et al. (28) presenting a specificity of 60% for LGE. As expected, sensitivity analysis of high quality studies yielded a specificity of 77%, suggesting that the summary specificity point may have been overestimated in the main analysis. This highlights the problematic design of case-control studies, which include healthy individuals in order to estimate the specificity of a diagnostic test. EGE's

TABLE 1 Overall Results of Meta-Analyses Conducted

Index Test	No. of Studies	N	TP	TN	Sensitivity	Specificity	Area Under the Curve	Diagnostic Odds Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio
Native T1 mapping	7	583	286	213	0.89 (0.79-0.94)	0.90 (0.78-0.96)	0.95 (0.93-0.97)	71.31 (17.70-287.22)	8.87 (3.69-21.34)	0.12 (0.06-0.26)
T2 mapping	6	381	165	128	0.78 (0.65-0.87)	0.84 (0.72-0.92)	0.88 (0.85-0.91)	19.19 (10.37-35.46)	4.97 (2.92-8.44)	0.26 (0.16-0.41)
Extracellular volume fraction	5	372	165	114	0.75 (0.67-0.82)	0.76 (0.66-0.84)	0.81 (0.78-0.85)	9.62 (5.62-16.48)	3.15 (2.19-4.53)	0.33 (0.25-0.43)
Increased T2 ratio/signal	15	1056	428	332	0.68 (0.59-0.75)	0.91 (0.75-0.97)	0.80 (0.76-0.83)	20.44 (6.65-62.87)	7.33 (2.61-20.60)	0.36 (0.28-0.46)
Late gadolinium enhancement	17	1308	531	444	0.68 (0.56-0.77)	0.96 (0.87-0.99)	0.87 (0.84-0.90)	54.26 (12.38-237.78)	18.64 (4.93-70.43)	0.34 (0.24-0.47)
Early gadolinium Enhancement	10	710	289	189	0.70 (0.61-0.78)	0.74 (0.61-0.84)	0.78 (0.74-0.81)	6.77 (3.65-12.55)	2.73 (1.77-4.23)	0.40 (0.31-0.53)
Lake Louise criteria	8	577	283	181	0.78 (0.72-0.83)	0.88 (0.68-0.96)	0.83 (0.79-0.86)	26.78 (7.65-93.76)	6.64 (2.20-20.10)	0.25 (0.19-0.32)

TN = true negative; TP = true positive.

sensitivity ranged from 49% to 85% and specificity from 43% to 100%, while the pooled analysis yielded an AUC of 0.78, with moderate positive and negative likelihood ratios. Sample size and publication year proved to have an effect on the estimates. The accuracy of the presence of at least 2 of 3 LLC was identified in 7 studies. Summary sensitivity was 78% and specificity 88%, with an AUC of 0.83.

Apart from reviewing and presenting in a systematic fashion the diagnostic performance of CMR in acute myocarditis, a secondary aim of our review was to compare novel parametric mapping techniques with the standard components of the LLC. We found that the diagnostic accuracy of mapping techniques is at least equal, and in some cases even superior, to older techniques. One of the most striking findings is that native T1 mapping has a significantly higher diagnostic accuracy than all other index tests, both classic and novel. This is in agreement with results presented in several studies (13,14,16,17,19) that showed superior diagnostic performance of T1 mapping compared with LLC. Notably, T1 mapping appears to have superior diagnostic performance compared with T2 mapping or ECV. T2 mapping also has higher diagnostic accuracy than either T2-weighted signal/ratio or EGE. In contrast, ECV offers no additional value in diagnosing acute myocarditis than the standard components of the LLC, alone or combined.

STUDY LIMITATIONS. As depicted in the QUADAS-2 summary figures of all separate meta-analyses, the majority of included studies were at high risk of bias, mainly because of design issues. A sensitivity analysis requiring at least 4 studies could only be conducted for LGE and resulted in an alteration of the specificity estimate and a significant mitigation of the diagnostic accuracy, as portrayed by the decrease of the AUC from 0.87 to 0.78. We must acknowledge that endomyocardial biopsy is rarely used as the reference standard in diagnostic accuracy studies because of complications and lack of proper setting. This led researchers to use clinical evaluation as the reference standard and adopt a case-control design. We compare the AUCs derived from the meta-analyses, in order to provide insights into the diagnostic value of each CMR test. However, we acknowledge that mapping techniques are relatively new and studies performing direct comparisons across all available CMR index tests are scarce. Therefore, more studies are needed to test mapping methods in different patient cohorts and clinical settings in order to establish accuracy variations. For more precise and systematic comparative purposes, a diagnostic network meta-analysis is perhaps a better fit, but models are currently still being developed. Importantly, the streamlining of mapping protocols (sequences and post-processing analysis) and the development of a unified approach to T1 mapping is one of the most important challenges for the CMR community. Finally, although CMR is an excellent test to detect acute myocarditis compared with normal controls, the situation is often different in clinical practice where acute myocarditis should be differentiated from other pathologies with similar clinical presentation.

CONCLUSIONS

Acute myocarditis remains one of the most challenging diagnoses in cardiology. This is the first meta-analysis presenting data on the diagnostic accuracy of all available CMR techniques, novel and standard, for the diagnosis of acute myocarditis. Novel CMR mapping techniques provide high diagnostic accuracies for the diagnosis of acute myocarditis and may become promising successors of the classic elements of the LLC for routine diagnostic protocols.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CMR based on the Lake Louise criteria (edema on T2-weighted imaging, hyperemia on T1-weighted imaging, fibrosis on late gadolinium enhancement imaging) has significant clinical application for the diagnosis of acute myocarditis. Novel parametric mapping techniques (T1 and T2 mapping) allow a quantitative and more objective assessment of myocardial inflammation.

TRANSLATIONAL OUTLOOK: T1 and T2 mapping further improve the diagnostic performance of CMR in acute myocarditis. An update of the Lake Louise criteria is necessary to include recent developments in myocarditis imaging by CMR.

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KEY WORDS acute myocarditis, CMR, Lake Louise criteria, meta-analysis, T1 mapping, T2 mapping

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.