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Risk Stratification in Nonischemic Dilated Cardiomyopathy Using CMR Imaging
A Systematic Review and Meta-Analysis

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IMPORTANCE Accurate risk stratification of nonischemic dilated cardiomyopathy (NIDCM) remains challenging.

OBJECTIVE To evaluate the association of cardiac magnetic resonance (CMR) imaging–derived measurements with clinical outcomes in NIDCM.

DATA SOURCES MEDLINE, Embase, Cochrane Library, and Web of Science Core Collection databases were systematically searched for articles from January 2005 to April 2023.

STUDY SELECTION Prospective and retrospective nonrandomized diagnostic studies reporting on the association between CMR imaging–derived measurements and adverse clinical outcomes in NIDCM were deemed eligible.

DATA EXTRACTION AND SYNTHESIS Prespecified items related to patient population, CMR imaging measurements, and clinical outcomes were extracted at the study level by 2 independent reviewers. Random-effects models were fitted using restricted maximum likelihood estimation and the method of Hartung, Knapp, Sidik, and Jonkman.

MAIN OUTCOMES AND MEASURES All-cause mortality, cardiovascular mortality, arrhythmic events, heart failure events, and major adverse cardiac events (MACE).

RESULTS A total of 103 studies including 29 687 patients with NIDCM were analyzed. Late gadolinium enhancement (LGE) presence and extent (per 1%) were associated with higher all-cause mortality (hazard ratio [HR], 1.81 [95% CI, 1.60-2.04]; $P < .001$ and HR, 1.07 [95% CI, 1.02-1.12]; $P = .02$, respectively), cardiovascular mortality (HR, 2.43 [95% CI, 2.13-2.78]; $P < .001$ and HR, 1.15 [95% CI, 1.07-1.24]; $P = .01$), arrhythmic events (HR, 2.69 [95% CI, 2.20-3.30]; $P < .001$ and HR, 1.07 [95% CI, 1.03-1.12]; $P = .004$) and heart failure events (HR, 1.98 [95% CI, 1.73-2.27]; $P < .001$ and HR, 1.06 [95% CI, 1.01-1.10]; $P = .02$). Left ventricular ejection fraction (LVEF) (per 1%) was not associated with all-cause mortality (HR, 0.99 [95% CI, 0.97-1.02]; $P = .47$), cardiovascular mortality (HR, 0.97 [95% CI, 0.94-1.00]; $P = .05$), or arrhythmic outcomes (HR, 0.99 [95% CI, 0.97-1.01]; $P = .34$). Lower risks for heart failure events (HR, 0.97 [95% CI, 0.95-0.98]; $P = .002$) and MACE (HR, 0.98 [95% CI, 0.96-0.99]; $P < .001$) were observed with higher LVEF. Higher native T1 relaxation times (per 10 ms) were associated with arrhythmic events (HR, 1.07 [95% CI, 1.01-1.14]; $P = .04$) and MACE (HR, 1.06 [95% CI, 1.01-1.11]; $P = .03$). Global longitudinal strain (GLS) (per 1%) was not associated with heart failure events (HR, 1.06 [95% CI, 0.95-1.18]; $P = .15$) or MACE (HR, 1.03 [95% CI, 0.94-1.14]; $P = .43$). Limited data precluded definitive analysis for native T1 relaxation times, GLS, and extracellular volume fraction (ECV) with respect to mortality outcomes.

CONCLUSION The presence and extent of LGE were associated with various adverse clinical outcomes, whereas LVEF was not significantly associated with mortality and arrhythmic end points in NIDCM. Risk stratification using native T1 relaxation times, extracellular volume fraction, and global longitudinal strain requires further evaluation.

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Supplemental content

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Nonischemic dilated cardiomyopathy (NIDCM) is characterized by left-ventricular or biventricular dilatation and contractile dysfunction in the absence of significant coronary artery disease and abnormal loading conditions, such as those presented by hypertensive, valvular, congenital, infiltrative, and acute inflammatory pathologies.[1-3] NIDCM represents the most common indication for heart transplantation globally, with 5-year mortality reaching up to 20% because of progressive heart failure or sudden cardiac death (SCD).[4,5] With an annual incidence of 2% to 3%, NIDCM accounts for considerable proportions of SCD, particularly among people of working age. To mitigate the risk of SCD, approximately 100 000 implantable cardioverter-defibrillators (ICDs)[6] are placed prophylactically in patients with NIDCM in the US each year, generating a lifetime cost of approximately $230 000 per device.[7,8] Yet landmark trials have repeatedly failed to demonstrate long-term survival benefits of prophylactic ICD implantation under current selection criteria,[9-12] which are based on a left ventricular ejection fraction (LVEF) at or below 35% as the sole imaging criterion at the core of risk stratification algorithms. Of note, the majority of patients with NIDCM receiving ICDs under this convention did not experience a single defibrillator shock after a mean follow-up duration of 5.3 years,[13] whereas patients with only mild to moderate contractile impairment continue to remain at disproportionate risk of SCD.[14,15] These circumstances illustrate that precise risk assessment for guiding surveillance, resource allocation, and therapeutic decision-making remain a major unmet clinical need for patients with this complex, heterogeneous disease.

Cardiac magnetic resonance (CMR) imaging has unique potential for optimizing risk stratification in NIDCM given its increasing accessibility in clinical practice and its potency in providing noninvasive, multiparametric assessment of myocardial function, morphology, and tissue characteristics. Late gadolinium enhancement (LGE) represents the reference standard for noninvasive assessment of focal replacement fibrosis. Measurement of T1 relaxation times enables voxel-by-voxel tissue characterization while extracellular volume fraction (ECV) quantification offers a physiologically intuitive estimation of myocardial collagen content, both serving as measures of diffuse interstitial fibrosis.[16-18] Further, myocardial strain has been suggested to detect even subtle contractile dysfunction.[19] Previous meta-analyses focused on the evaluation of singular CMR imaging–based measurements in predicting a narrow spectrum of clinical and nonclinical outcomes in NIDCM, thereby limiting their applicability to clinical practice. Against this background, this analysis aimed to summarize the association of CMR imaging–derived LVEF, LGE presence, LGE extent, native T1 relaxation times, ECV, and global longitudinal strain (GLS) with adverse clinical outcomes in individuals with NIDCM.

Key Points

Question Are cardiac magnetic resonance imaging–derived measurements associated with adverse outcomes in nonischemic dilated cardiomyopathy (NIDCM)?

Findings In this meta-analysis of 103 studies comprising 29 687 patients with NIDCM, late gadolinium enhancement (LGE) presence and extent were consistently associated with arrhythmic, nonarrhythmic, and mortality end points, whereas left ventricular ejection fraction (LVEF) was not significantly associated with mortality and arrhythmia. Higher native T1 relaxation times were associated with arrhythmic end points and major adverse cardiac events. Due to insufficient data, a pooled analysis could not be conducted for the measurements of native T1 relaxation times, extracellular volume fraction, and global longitudinal strain concerning mortality end points.

Meaning The presence and extent of LGE were associated with adverse clinical outcomes, whereas LVEF was not associated with mortality and arrhythmic end points in NIDCM.

Methods

This meta-analysis is reported in line with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE)[20] guidance (supporting checklist) and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[21] statements and was registered on the international Prospective Register of Systematic Reviews (PROSPERO, CRD42022335477).[22] Additional methods are described in eAppendix 1 in Supplement 1.

Search Strategy

The electronic databases MEDLINE, Embase, Cochrane Library, and Web of Science Core Collection were comprehensively searched by a librarian (B.C.) for English-language papers from January 2005 through April 2023. The search syntax was designed by combining keywords and Medical Subject Headings around the concepts of CMR imaging, cardiomyopathy, and clinical outcomes (eAppendix 2 in Supplement 1). The references of included studies were searched for additional eligible studies. Conference abstracts and Cochrane Library ongoing trial registry records were excluded. Following deletion of duplicate records, abstract screening was conducted in a blinded manner by 2 independent reviewers (C.E., D.K.).

Study Selection

We deemed eligible any prospective or retrospective nonrandomized diagnostic study fulfilling the following inclusion criteria: (1) the study population consisted entirely of patients with NIDCM (as defined by World Health Organization, European Society of Cardiology, or American Heart Association criteria,[1-3] including ventricular dilatation and contractile dysfunction, absence of abnormal loading conditions, infiltrative or acute inflammatory pathologies), NIDCM subgroup data were provided separately, or cardiomyopathies other than NIDCM represented a minor proportion (<10%) of the study population; (2) the prognostic value of 1 or more CMR imaging–derived measurements of LVEF, LGE presence, LGE extent, native T1 relaxation times, ECV, or GLS was explored; (3) 1 of the clinical outcomes of interest was reported; and (4) the study provided quantitative information (either an estimate of association or data for constructing 2 × 2 tables) for at least 1 CMR imaging measurement and its corresponding outcome(s) of interest, which could be used for the quantitative synthesis.

Potential overlap between study cohorts was investigated for each measurement and outcome using study centers and recruitment periods as overlap indicators. In case of suspected overlap, only data from the report with the largest study size, longest follow-up duration, and/or highest statistical robustness, in that order of priority, was extracted.

Data Extraction and Quality Assessment

Full-text review, data extraction, and quality assessment were performed by 2 investigators (C.E., D.K.) independently. Interreviewer discrepancies were resolved by consensus or discussion with other investigators (G.C.M.S., C.G.). Study-level characteristics, including year of publication, number of included patients, study design, recruitment and follow-up period, primary recruitment center, recruitment countries, inclusion criteria, primary and secondary outcomes, CMR field strength, age, gender (male), body mass index, comorbidities (hypertension, dyslipidemia, smoking history, atrial fibrillation, diabetes), LVEF, left ventricular end-diastolic volume (LVEDV), and LVEDV index were extracted. Quality assessment was performed using the Quality In Prognosis Studies (QUIPS) tool.[23]

Outcomes

The outcomes of interest were all-cause mortality, cardiovascular mortality, arrhythmic events, heart failure events, and major adverse cardiac events (MACE). Cardiovascular mortality was defined as cardiovascular death or heart transplant. Arrhythmic events were defined as any combination of SCD, aborted SCD, appropriate ICD therapy, and sustained ventricular arrhythmias. Heart failure events were defined as any combination of heart failure mortality, heart transplant, left ventricular assist device implantation, or hospitalization for heart failure. Outcomes were classified as MACE if they were composed of end points from multiple outcome categories (mortality, arrhythmia, or heart failure).

Statistical Analysis

Hazard ratios (HRs) with corresponding 95% CIs were chosen as the primary summary metric because they are most appropriate for summarizing time to event data.[24] Where different HRs were available for the same measurement at the study level, estimates with the highest level of adjustment were preferred over those adjusted for fewer covariates or unadjusted estimates. For dichotomous measurements (eg, LGE presence), relative risks and 95% CIs were derived from crude event numbers and 2 × 2 tables if HRs were not available. Primary meta-analyses for continuous measurements were based on the most commonly reported increment (per 1% for LVEF, LGE extent, ECV, and GLS; per 10 ms for native T1 relaxation times). We fitted random-effects meta-analysis models using restricted maximum likelihood estimation and the method of Hartung, Knapp, Sidik, and Jonkman to synthesize estimates from different studies for each CMR imaging–derived measurement and outcome of interest.[25,26] Heterogeneity was quantified using the I^2 statistic, which describes the proportion of the variability in measures of association that is due to heterogeneity rather than chance. Additionally, *P* values were calculated from a χ^2 test. Strict thresholds for interpretation are not recommended, but in general, an I^2 statistic at or above 50% and a χ^2 test *P* value <.10 may be considered representative of substantial or considerable heterogeneity.[27,28] To explore the impact of study and patient characteristics on associations of CMR imaging–derived measurements with clinical outcomes, random-effects meta-regression was performed for those end points with 10 or more studies available. The effect of baseline age, gender, LVEF, study design (prospective vs retrospective), analytical method (unadjusted vs adjusted analysis), and study centers (single-center vs multicenter) on outcomes was tested. Assessment of small-study effects, encompassing publication bias, outcome reporting bias, and clinical heterogeneity, was conducted graphically using funnel plots and statistically using the Egger test if at least 10 studies were included in the meta-analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied to assess the quality of the evidence base (eTable 1 in Supplement 1).[29] All analyses were performed in the statistical programming environment R version 4.3.1 using the meta package (RStudio).

Results

Following the screening of 10 479 abstracts and the full-text review of 176 reports, 103 studies[30-133] comprising 29 687 patients were included (PRISMA flowchart in eAppendix 3 in Supplement 1). Details about included studies, outcomes, and technical information can be found in eAppendix 4 in Supplement 1. The majority of included studies were prospective (51%) and single-center (77%). The median (IQR) follow-up duration was 37.8 (26.5-47.9) months. Patients were a median (IQR) age of 55.0 (51.6-58.5) years, were predominantly male (71.1% [64.7%-75.7%]), displayed severely reduced systolic function (LVEF, 29.5% [25.0%-36.4%]), and increased left ventricular end-diastolic volume indices (130.6 mL/m^2 [119.7-146.3]). Baseline study/patient characteristics are summarized and stratified by CMR imaging–derived measurements in the **Table**. Study quality (QUIPS) is included in eAppendix 5 in Supplement 1. Results from primary meta-analyses, including pooled estimates, are represented visually in **Figure 1** and are summarized, including statistical heterogeneity and small-study effects assessment, in eTable 1 in Supplement 1. Funnel plots are found in eAppendix 6 in Supplement 1, and GRADE ratings are outlined in eTable 1 in Supplement 1. eTable 3 in Supplement 1 summarizes relevant additional studies for each parameter and end point that could not be incorporated into quantitative analysis due to discrepancies in units or increments of reported measurements.

LGE Presence

Ninety-six studies[30-125] (n = 27 590) reported the association between LGE presence and clinical outcomes in NIDCM, all of which were incorporated into the primary meta-analysis. Data on all-cause mortality, cardiovascular mortality, arrhythmic events, heart failure events, and MACE in relation to LGE presence were presented by 23 (n = 9738), 19 (n = 5228), 40 (n = 13 791), 32 (n = 9464), and 54 (n = 12 040) studies,

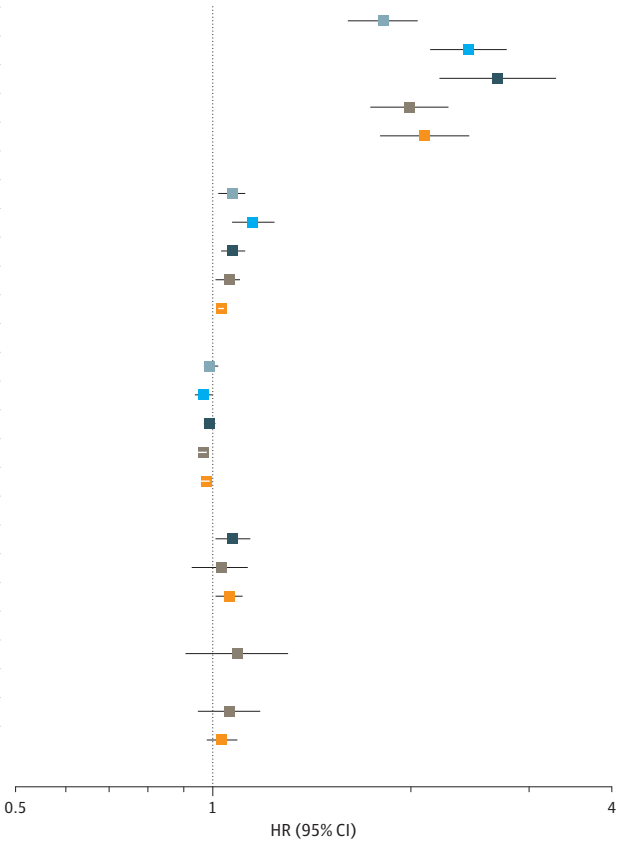
Table. Study and Participant Characteristics

Study characteristic	Total population	Late gadolinium enhancement presence	Late gadolinium enhancement extent	LVEF	Native T1 mapping relaxation times	Extracellular volume fraction	Global longitudinal strain
No. of studies	103	96	28	47	7	3	9
No. of patients	29 687	27 590	7344	14 180	2461	1372	2226
Design, No. (%)							
Prospective	53 (51)	50 (51)	14 (50)	24 (51)	7 (100)	3 (100)	3 (33)
Retrospective	49 (48)	45 (47)	14 (50)	23 (49)	0	0	6 (67)
Mixed	1 (1)	1 (1)	0	0	0	0	0
Single-center	79 (77)	73 (76)	21 (75)	35 (74)	5 (71)	2 (67)	8 (89)
Multicenter	24 (23)	23 (24)	7 (25)	12 (26)	2 (29)	1 (33)	1 (11)
Location, No. (%)							
Europe	37 (35)	34 (35)	8 (29)	17 (36)	3 (43)	1 (33)	3 (33)
North America	15 (15)	15 (16)	4 (14)	6 (13)	1 (14)	0	0
Asia	43 (42)	39 (41)	14 (50)	20 (43)	2 (29)	1 (33)	6 (66)
Australia	4 (4)	4 (4)	0	1 (2)	0	0	0
Multiple	4 (4)	4 (4)	2 (7)	3 (6)	1 (14)	1 (33)	0
Sample size, No. (%)							
≤100	31 (30)	29 (30)	3 (11)	8 (17)	3 (43)	0	1 (11)
>100 to ≤500	54 (52)	51 (53)	21 (75)	30 (64)	1 (14)	1 (33)	7 (78)
>500	18 (17)	16 (17)	4 (14)	9 (19)	3 (43)	2 (66)	1 (11)
Follow-up, median (IQR), mo	37.8 (26.5-47.9)	37.6 (26.5-47.6)	38.4 (20.9-50.2)	38.0 (26.6-47.7)	25.0 (22.0-31.0)	22.0 (13.6-23.3)	42.7 (20.5-47.3)
CMR field strength, No. (%)							
1.5 T	58 (59)	55 (60)	12 (46)	19 (42)	3 (43)	0	3 (33)
3.0 T	15 (15)	13 (14)	7 (27)	12 (27)	2 (29)	1 (33)	3 (33)
Both	25 (26)	24 (26)	7 (27)	14 (31)	2 (29)	2 (66)	3 (33)
Studies investigating outcome, No. (total No.)							
All-cause death	NA	23 (9738)	4 (1852)	5 (3220)	0	0	0
Cardiovascular death	NA	19 (5228)	3 (1323)	7 (3522)	0	0	0
Arrhythmic events	NA	40 (13 791)	9 (2086)	12 (5055)	5 (1778)	0	0
Heart failure events	NA	32 (9464)	6 (1686)	10 (4576)	3 (2198)	3 (1372)	3 (1001)
MACE	NA	54 (12 040)	13 (3004)	24 (5446)	3 (962)	0	7 (1397)
Patient characteristics							
Age, median (IQR), y	55.0 (51.6-58.5)	55.0 (51.8-58.5)	53.0 (49.0-57.0)	54.3 (50.0-57.0)	54.3 (48.0-58.6)	54.3 (51.9-58.7)	53.6 (47.0-59.2)
Male sex, median (IQR), %	71.1 (64.7-75.7)	71.0 (64.3-75.9)	69.8 (62.7-74.3)	70.7 (64.7-75.6)	72.0 (66.0-77.3)	62.0 (60.7-66.0)	70.0 (66.7-75.0)
BMI, median (IQR)	26.0 (24.2-27.0)	26.0 (24.3-27.0)	24.7 (24.1-27.2)	24.7 (24.1-26.7)	25.5 (24.1-27.8)	NA	24.4 (23.9-25.3)
Comorbidities, median (IQR), %							
Hypertension	37.0 (30.7-47.7)	37.0 (31.4-48.0)	38.5 (31.3-45.5)	39.0 (31.7-44.8)	33.2 (23.0-35.0)	NA	37.4 (20.1-51.4)
Dyslipidemia	30.1 (26.2-38.5)	31.0 (26.4-39.0)	30.0 (24.0-38.0)	30.5 (25.4-38.0)	30.0 (30.0-31.0)	NA	26.0 (14.7-29.4)
Smoking history	30.6 (19.9-41.0)	31.3 (22.0-41.0)	26.8 (18.8-32.3)	30.5 (20.3-39.5)	30.0 (19.0-37.5)	NA	32.6 (28.5-41.0)
Atrial fibrillation	20.0 (15.4-28.2)	20.0 (15.0-28.2)	16.2 (11.5-20.6)	18.4 (14.6-27.0)	20.0 (15.0-31.8)	NA	NA
Diabetes	16.5 (12.0-22.0)	17.0 (12.0-22.6)	15.1 (10.0-24.0)	15.1 (12.0-23.6)	14.3 (13.0-17.0)	NA	19.5 (14.2-28.3)
Cardiac function, median (IQR)							
LVEF, %	29.5 (25.0-36.4)	29.5 (25.0-36.3)	28.4 (24.1-35.7)	28.0 (25.0-36.4)	30.7 (23.4-41.4)	40.7 (24.9-42.0)	23.7 (21.0-36.7)
LVEDVi, mL/m^2	130.6 (119.7-146.3)	129.3 (119.7-145.1)	138.4 (122.0-159.1)	136.8 (120.6-158.9)	142.1 (111.0-188.8)	112.0 (110.0-159.1)	136.8 (123.0-167.9)
LVEDV, mL	243.3 (211.5-272.6)	241.1 (210.0-270.0)	277.0 (259.1-284.3)	270.0 (244.6-286.8)	NA	NA	NA

Abbreviations: BMI, body mass index; CMR, cardiac magnetic resonance; LVEDV, left ventricular end-diastolic volume (as measured by CMR, where available); LVEDVi, left ventricular end-diastolic volume index (as measured by CMR, where available); LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NA, not applicable.

Figure 1. Cardiac Magnetic Resonance (CMR) Imaging Parameters and Clinical Outcomes

Parameter	Studies/ patients, No.	HR (95% CI)
Late gadolinium enhancement presence (yes/no)		
All-cause mortality	23/9738	1.81 (1.60-2.04)
Cardiovascular mortality	19/5228	2.43 (2.13-2.78)
Arrhythmia	40/13791	2.69 (2.20-3.30)
Heart failure	32/9464	1.98 (1.73-2.27)
MACE	54/12040	2.09 (1.79-2.44)
Late gadolinium enhancement extent (per 1%)		
All-cause mortality	4/1852	1.07 (1.02-1.12)
Cardiovascular mortality	3/1323	1.15 (1.07-1.24)
Arrhythmia	9/2086	1.07 (1.03-1.12)
Heart failure	6/1686	1.06 (1.01-1.10)
MACE	13/3004	1.03 (1.02-1.04)
Left ventricular ejection fraction (per 1%)		
All-cause mortality	5/3220	0.99 (0.97-1.02)
Cardiovascular mortality	7/3522	0.97 (0.94-1.00)
Arrhythmia	12/5055	0.99 (0.97-1.01)
Heart failure	10/4576	0.97 (0.95-0.98)
MACE	24/5446	0.98 (0.96-0.99)
T1 relaxation time (per 10 ms)		
Arrhythmia	5/1778	1.07 (1.01-1.14)
Heart failure	3/2198	1.03 (0.93-1.13)
MACE	3/962	1.06 (1.01-1.11)
Extracellular volume (per 1%)		
Heart failure	3/1372	1.09 (0.91-1.30)
Global longitudinal strain (per 1%)		
Heart failure	3/1001	1.06 (0.95-1.18)
MACE	7/1397	1.03 (0.94-1.14)



Pooled hazard ratios (HRs) for the association between CMR imaging–derived measurements of late gadolinium enhancement (LGE) presence, LGE extent, left ventricular ejection fraction, native T1 relaxation times, extracellular volume fraction, and global longitudinal strain and clinical outcomes when 3 or more studies were available for meta-analysis. MACE indicates major adverse cardiovascular events.

respectively. Statistically significantly higher risks of all-cause mortality (HR, 1.81 [95% CI, 1.60-2.04]; $P < .001$) (**Figure 2**A), cardiovascular mortality (HR, 2.43 [95% CI, 2.13-2.78]; $P < .001$) (Figure 2B), arrhythmic events (HR, 2.69 [95% CI, 2.20-3.30]; $P < .001$) (eFigure 1A in Supplement 1), heart failure events (HR, 1.98 [95% CI, 1.73-2.27]; $P < .001$) (eFigure 1C in Supplement 1), and MACE (HR, 2.09 [95% CI, 1.79-2.44]; $P < .001$) (eFigure 1E in Supplement 1) were observed in the presence of LGE.

LGE Extent

The association of LGE extent with clinical outcomes in NIDCM was evaluated by 28 studies[34,41,44,51,52,55,57,62,76,86,91,92,94-96,98,99,102,105,110,113,121,124,126-130] (n = 7344) within the meta-analysis. All-cause mortality, cardiovascular mortality, arrhythmic events, heart failure events, and MACE per 1% higher LGE extent were reported by 4 (n = 1852), 3 (n = 1323), 9 (n = 2086), 6 (n = 1686), and 13 (n = 3004) studies, respectively. Statistically significantly higher risks of all-cause mortality (HR, 1.07 [95% CI, 1.02-1.12]; $P = .02$) (**Figure 3**A), cardiovascular mortality (HR, 1.15 [95% CI, 1.07-1.24]; $P = .01$) (Figure 3B), arrhythmic events (HR, 1.07 [95% CI, 1.03-1.12]; $P = .004$) (eFigure 1B in Supplement 1), heart failure events (HR, 1.06 [95% CI, 1.01-1.10]; $P = .02$) (eFigure 1D in Supplement 1), and MACE (HR, 1.03 [95% CI, 1.02-1.04]; $P < .001$) (eFigure 1F in Supplement 1) were observed with every 1% higher LGE extent.

LVEF

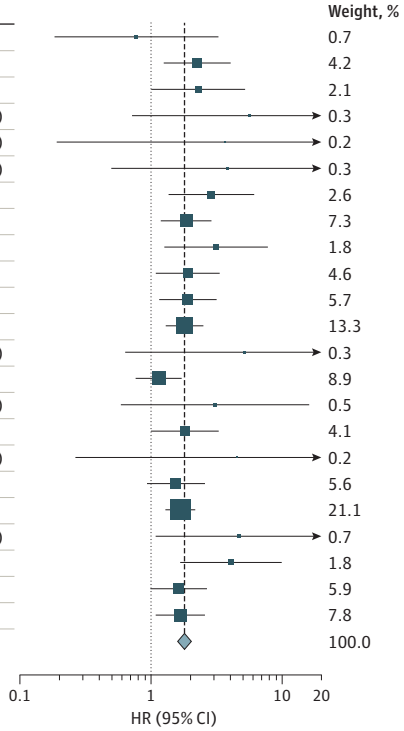
The association between LVEF and adverse outcomes in NIDCM was explored by 47 studies[31,34,36,38,40,41,44,45,51-53,57-59,61-63,65,66,70,75,76,78,79,85-87,92,93,95-99,102-105,110,113,120,121,124,128,129,131,132] (n = 14180) within the meta-analysis. All-cause mortality, cardiovascular mortality, arrhythmic events, heart failure events, and MACE in relation to every 1% higher LVEF were reported by 5 (n = 3220), 7 (n = 3522), 12 (n = 5055), 10 (n = 4576), and 24 (n = 5446) studies, respectively. No significant association with all-cause mortality (HR, 0.99 [95% CI, 0.97-1.02]; $P = .47$), cardiovascular mortality (HR, 0.97 [95% CI, 0.94-1.00]; $P = .05$), and arrhythmic events (HR, 0.99 [95% CI, 0.97-1.01]; $P = .34$) per 1% higher LVEF was observed (**Figure 4A**-C). Statistically significantly lower risks of heart

Figure 2. Association of Late Gadolinium Enhancement (LGE) Presence With All-Cause and Cardiovascular Mortality

A LGE presence and all-cause mortality

Study	Patients, No.	HR (95% CI)	Weight, %
Kono et al,[73] 2010	32	0.78 (0.18-3.28)	0.7
Li et al,[77] 2013	293	2.26 (1.26-4.07)	4.2
Doesch et al,[54] 2014	140	2.30 (1.01-5.24)	2.1
Sadahiro et al,[103] 2015	76	5.69 (0.72-45.05)	0.3
Venero et al,[116] 2015	31	3.68 (0.19-70.87)	0.2
Gaztanaga et al,[59] 2016	105	3.83 (0.50-29.38)	0.3
Puntmann et al,[99] 2016	637	2.90 (1.37-6.15)	2.6
Leyva et al,[75] 2017	252	1.86 (1.19-2.90)	7.3
Marume et al,[84] 2018	531	3.15 (1.27-7.82)	1.8
Romano et al,[102] 2018	507	1.91 (1.09-3.35)	4.6
Gutman et al,[63] 2019	452	1.92 (1.16-3.18)	5.7
Halliday et al,[64] 2019	874	1.81 (1.30-2.52)	13.3
Muthalaly et al,[90] 2019	130	5.20 (0.64-42.39)	0.3
Shanbhag et al,[107] 2019	689	1.15 (0.77-1.72)	8.9
Behera et al,[40] 2020	112	3.09 (0.59-16.17)	0.5
Elming et al,[55] 2020	236	1.82 (1.00-3.30)	4.1
Chen et al,[44] 2021	157	4.55 (0.27-77.79)	0.2
Guaricci et al,[61] 2021	1000	1.56 (0.94-2.59)	5.6
Klem et al,[71] 2021	1020	1.68 (1.29-2.18)	21.1
Shams et al,[106] 2021	75	4.71 (1.09-20.41)	0.7
Mirelis et al,[88] 2022	600	4.09 (1.68-9.97)	1.8
Claver et al,[50] 2023	1165	1.63 (0.99-2.68)	5.9
Li et al,[79] 2023	624	1.68 (1.09-2.59)	7.8
Random-effects model (HK)		1.81 (1.60-2.04)	100.0

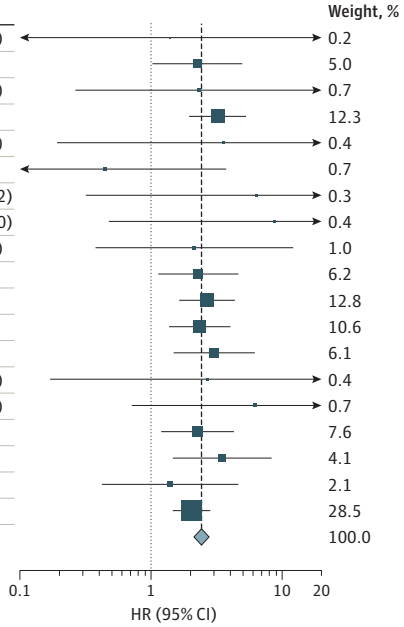
Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $\chi^2_{22} = 19.57$ ($P = .61$)
Test for overall effect: $t_{22} = 10.22$ ($P < .001$)



B LGE presence and cardiovascular mortality

Study	Patients, No.	HR (95% CI)	Weight, %
Wu et al,[117] 2008	65	1.39 (0.03-68.09)	0.2
Hombach et al,[65] 2009	141	2.26 (1.03-4.97)	5.0
Kono et al,[73] 2010	32	2.33 (0.27-20.53)	0.7
Gulati et al,[62] 2013	472	3.22 (1.95-5.31)	12.3
Machii et al,[81] 2014	72	3.57 (0.19-66.47)	0.4
Rodriguez-Capitan et al,[101] 2014	64	0.45 (0.05-3.75)	0.7
Yamada et al,[119] 2014	57	6.35 (0.32-126.52)	0.3
Tateishi et al,[114] 2015	207	8.75 (0.48-160.40)	0.4
Hu et al,[66] 2016	85	2.14 (0.38-12.16)	1.0
Arenja et al,[36] 2017	441	2.30 (1.14-4.65)	6.2
Leyva et al,[75] 2017	252	2.68 (1.64-4.37)	12.8
Zhang et al,[125] 2018	220	2.36 (1.38-4.04)	10.6
Gutman et al,[63] 2019	452	3.04 (1.49-6.20)	6.1
Raman et al,[111] 2019	49	2.69 (0.17-42.56)	0.4
Behera et al,[40] 2020	112	6.18 (0.71-53.51)	0.7
Elming et al,[55] 2020	236	2.27 (1.20-4.30)	7.6
Di Marco et al,[53] 2021	1165	3.50 (1.47- 8.33)	4.1
Infante et al,[68] 2021	86	1.40 (0.42-4.64)	2.1
Klem et al,[71] 2021	1020	2.04 (1.47-2.84)	28.5
Random-effects model (HK)		2.43 (2.13-2.78)	100.0

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $\chi^2_{18} = 8.90$ ($P = .96$)
Test for overall effect: $t_{18} = 14.10$ ($P < .001$)



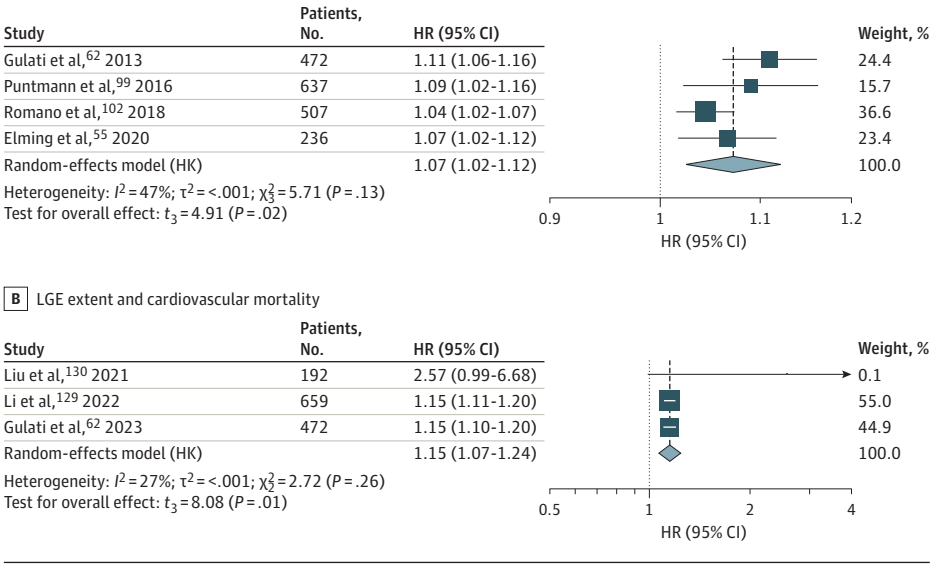
Meta-analysis results for the association of LGE presence with all-cause mortality (A) and cardiovascular mortality (B). The area of each square representing an individual study is proportional to its weight within the random-effects meta-analysis model. Horizontal lines indicate the 95% CI of the hazard ratio (HR) estimate for the individual study. The diamond indicates the pooled HR estimate and its corresponding 95% CI.

failure events (HR, 0.97 [95% CI, 0.95-0.98]; $P = .002$) (Figure 4D) and MACE (HR, 0.98 [95% CI, 0.96-0.99]; $P < .001$) (eFigure 2 in Supplement 1) were seen per 1% higher LVEF.

Native T1 Relaxation Times

Seven studies[49,60,79,91,99,126,133] (n = 2461) exploring the association between native T1 relaxation times and clinical outcomes

Figure 3. Association of Late Gadolinium Enhancement (LGE) Extent With All-Cause and Cardiovascular Mortality



Meta-analysis results for the association of LGE extent with all-cause mortality (A) and cardiovascular mortality (B). The area of each square representing an individual study is proportional to its weight within the random-effects meta-analysis model. Horizontal lines indicate the 95% CI of the hazard ratio (HR) estimate for the individual study. The diamond indicates the pooled HR estimate and its corresponding 95% CI.

in NIDCM were incorporated into the meta-analysis, including studies using both 1.5 and 3.0 Tesla CMR machines (see additional methods in eAppendix 1 in Supplement 1). A paucity of data precluded meta-analysis for all-cause mortality and cardiovascular mortality. Data on arrhythmic events, heart failure events, and MACE per 10-ms higher native T1 relaxation times were reported by 5 (n = 1778), 3 (n = 2198), and 3 (n = 962) studies, respectively. We observed statistically significantly higher risks for arrhythmic events (HR, 1.07 [95% CI, 1.01-1.14]; *P* = .04) (**Figure 5**A) and MACE (HR, 1.06 [95% CI, 1.01-1.11]; *P* = .03) (eFigure 3A in Supplement 1) with every 10-ms higher measurement of native T1 relaxation times. No association with heart failure event risk (HR, 1.03 [95% CI, 0.93-1.13]; *P* = .37) was identified (Figure 5B). Singular studies reported increased risks of all-cause mortality (Puntmann et al; adjusted HR, 1.10 [95% CI, 1.07-1.17]; n = 637)[99] and cardiovascular mortality (Li et al; adjusted HR, 1.19 [95% CI, 1.13-1.24]; n = 659)[129] per 10- and 1-ms higher measure of native T1 relaxation times, respectively.

Extracellular Volume

A paucity of data precluded pooled analysis for all-cause mortality, cardiovascular mortality, arrhythmic events, and MACE in relation to higher ECV. Three studies[99,124,133] comprising 1372 patients reporting data on the association between ECV and heart failure events were incorporated into the meta-analysis. No significant association with heart failure event risk was observed per 1% higher ECV (HR, 1.09 [95% CI, 0.91-1.30]; *P* = .18) (Figure 5C). Singular studies found higher all-cause mortality (Puntmann et al; unadjusted HR, 1.10 [95% CI, 1.05-1.14]; n = 637)[99] and cardiovascular mortality (Li et al; adjusted HR, 1.22 [95% CI, 1.12-1.33]; n = 659)[129] risk per 1% higher ECV. Two studies reported higher risks of arrhythmic events per 1% (Di Marco et al; adjusted HR, 1.20 [95% CI, 1.10-1.40]; n = 618)[133] and 3% (Li et al; adjusted HR, 1.26 [95% CI, 1.11-1.44]; n = 858)[79] higher ECV. Four studies observed higher MACE risk with every 1% higher ECV (Chen et al; adjusted HR, 1.48 [95% CI, 1.13-1.94]; n = 46; Vita et al; adjusted HR, 1.11 [95% CI, 1.05-1.16]; n = 240),[126,134] per 3% (Li et al; adjusted HR, 1.08 [95% CI, 1.04-1.11]; n = 858),[79] or per 1 standard deviation (Seno et al; adjusted HR, 1.37 [95% CI, 1.06-1.78]; n = 474).[105]

Global Longitudinal Strain

The association between reduced GLS (ie, less negative; as defined in the additional methods in eAppendix 1 in Supplement 1) and clinical outcomes in NIDCM was evaluated by 9 studies[35,41,45,51,57,96,110,113,133] (n = 2226) incorporated into the meta-analysis. Data on heart failure events and MACE per 1% reduced GLS were reported by 3 (n = 1001) and 7 (n = 1397) studies, respectively. A paucity of data precluded pooled analysis for all-cause mortality, cardiovascular mortality, and arrhythmic events per 1% reduced GLS. No significant association with heart failure events (HR, 1.06 [95% CI, 0.95-1.18]; *P* = .15) (Figure 5D) and MACE risk (HR, 1.03 [95% CI, 0.94-1.14]; *P* = .43) (eFigure 3B in Supplement 1) was observed per 1% reduced GLS. Singular studies reported higher all-cause mortality (Romano et al; adjusted HR, 2.14 [95% CI, 1.56-2.91]; n = 507),[102] but no association with cardiovascular mortality risk (Liu et al; unadjusted HR, 1.10 [95% CI, 0.91-1.32]; n = 192)[130] per 1% reduced GLS. Two studies (Di Marco et al; adjusted HR, 1.20 [95% CI, 1.10-1.40]; n = 703; Li et al; unadjusted HR, 1.10 [95% CI, 1.00-1.20]; n = 466)[76,133] reported associations between reduced GLS (per 1%) and higher risk of arrhythmia.

Meta-Regression

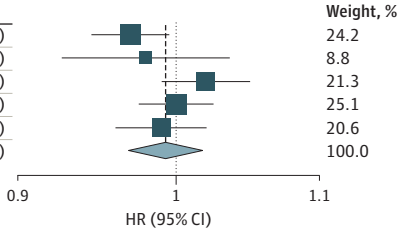
Meta-regression exploring heterogeneity in the associations between CMR imaging–derived measurements and clinical outcomes was feasible for LVEF, LGE presence, and LGE extent (eTable 2 for quantitative values, eAppendix 7 in Supplement 1

Figure 4. Left Ventricular Ejection Fraction and Risk of Cardiovascular Events

A All-cause mortality

Study	Patients, No.	HR (95% CI)	Weight, %
Puntmann et al,[99] 2016	637	0.97 (0.95-1.00)	24.2
Romano et al,[102] 2018	507	0.98 (0.93-1.04)	8.8
Gutman et al,[63] 2019	452	1.02 (0.99-1.05)	21.3
Guaricci et al,[61] 2021	1000	1.00 (0.98-1.03)	25.1
Li et al,[79] 2023	624	0.99 (0.96-1.02)	20.6
Random-effects model (HK)		0.99 (0.97-1.02)	100.0

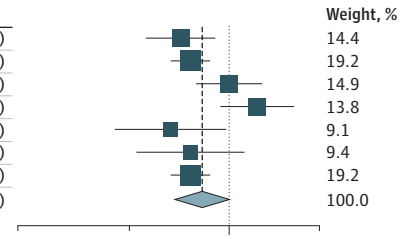
Heterogeneity: $I^2 = 42\%$; $\tau^2 = <.001$; $\chi^2_4 = 6.89$ ($P = .14$)
Test for overall effect: $t_4 = -0.79$ ($P = .47$)



B Cardiovascular mortality

Study	Patients, No.	HR (95% CI)	Weight, %
Hombach et al,[65] 2009	141	0.95 (0.92-0.99)	14.4
Gulati et al,[62] 2013	472	0.96 (0.94-0.98)	19.2
Arenja et al,[36] 2017	441	1.00 (0.97-1.04)	14.9
Gutman et al,[63] 2019	452	1.03 (0.99-1.07)	13.8
Di Marco et al,[53] 2021	1165	0.94 (0.89-1.00)	9.1
Liu et al,[130] 2021	192	0.96 (0.91-1.02)	9.4
Li et al,[129] 2022	659	0.96 (0.94-0.98)	19.2
Random-effects model (HK)		0.97 (0.94-1.00)	100.0

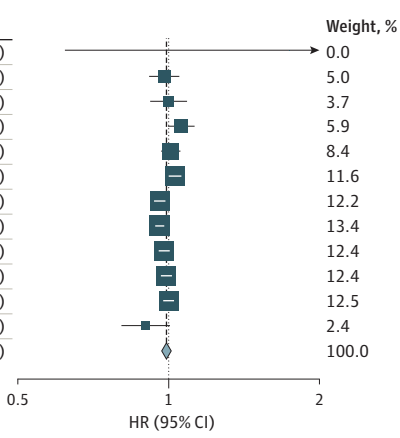
Heterogeneity: $I^2 = 63\%$; $\tau^2 = <.001$; $\chi^2_6 = 16.40$ ($P = .01$)
Test for overall effect: $t_6 = -2.42$ ($P = .05$)



C Arrhythmic events

Study	Patients, No.	HR (95% CI)	Weight, %
Gao et al,[58] 2012	65	1.74 (0.62-4.88)	0.0
Perazzolo Marra et al,[95] 2017	137	0.98 (0.91-1.05)	5.0
Jablonowski et al,[128] 2017	34	1.00 (0.92-1.09)	3.7
Barison et al,[38] 2020	183	1.06 (1.00-1.13)	5.9
Balaban et al,[131] 2021	156	1.01 (0.97-1.06)	8.4
Chen et al,[44] 2021	157	1.03 (1.00-1.06)	11.6
Di Marco et al,[53] 2021	1165	0.96 (0.94-0.99)	12.2
Guaricci et al,[61] 2021	1000	0.96 (0.94-0.98)	13.4
Mikami et al,[87] 2021	719	0.98 (0.96-1.01)	12.4
Li et al,[78] 2022	858	0.99 (0.97-1.02)	12.4
Piers et al,[97] 2022	115	1.00 (0.98-1.03)	12.5
Li et al,[76] 2023	466	0.90 (0.80-1.01)	2.4
Random-effects model (HK)		0.99 (0.97-1.01)	100.0

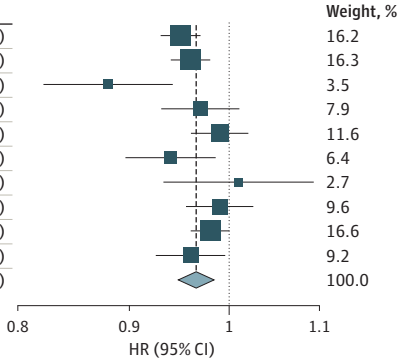
Heterogeneity: $I^2 = 64\%$; $\tau^2 = <.001$; $\chi^2_{11} = 30.88$ ($P = .001$)
Test for overall effect: $t_{11} = -0.99$ ($P = .34$)



D Heart failure events

Study	Patients, No.	HR (95% CI)	Weight, %
Gulati et al,[62] 2013	472	0.95 (0.93-0.97)	16.2
Puntmann et al,[99] 2016	637	0.96 (0.94-0.98)	16.3
Youn et al,[124] 2017	117	0.88 (0.82-0.94)	3.5
Pi et al,[96] 2018	172	0.97 (0.93-1.01)	7.9
Saito et al,[104] 2020	55	0.99 (0.96-1.02)	11.6
Di Marco et al,[53] 2021	1165	0.94 (0.90-0.99)	6.4
Fu et al,[57] 2021	126	1.01 (0.93-1.09)	2.7
Yazaki et al,[120] 2021	255	0.99 (0.96-1.03)	9.6
Mikami et al,[87] 2021	719	0.98 (0.96-1.00)	16.6
Li et al,[78] 2022	858	0.96 (0.93-1.00)	9.2
Random-effects model (HK)		0.97 (0.95-0.98)	100.0

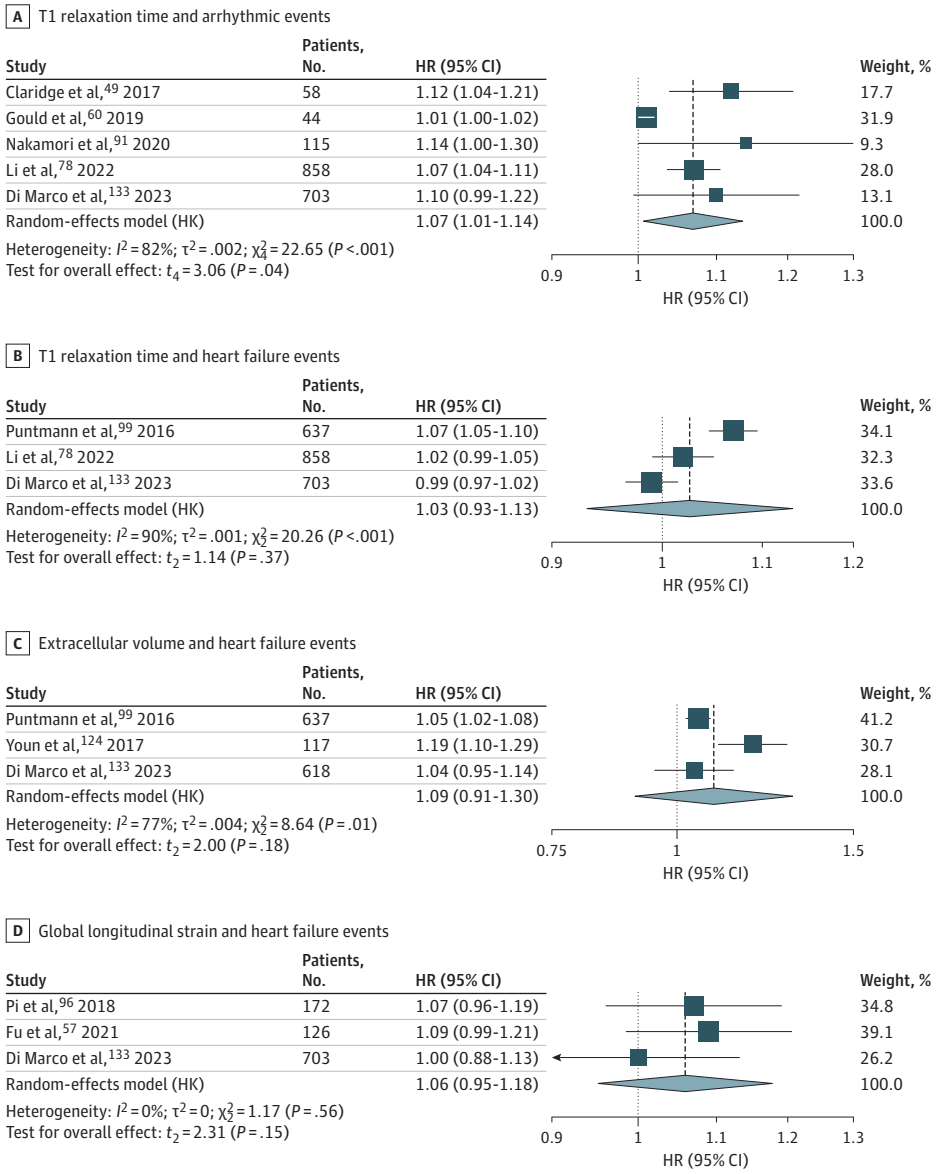
Heterogeneity: $I^2 = 52\%$; $\tau^2 = <.001$; $\chi^2_9 = 18.80$ ($P = .03$)
Test for overall effect: $t_9 = -4.17$ ($P = .002$)



Meta-analysis results for the risk of all-cause mortality (A), cardiovascular mortality (B), arrhythmic events (C), and heart failure events (D) per 1% increase in left ventricular ejection fraction. The area of each square representing an individual study is proportional to its weight within the random-effects meta-analysis model. Horizontal lines indicate the 95% CI of the hazard ratio (HR) estimate for the individual study. The diamond indicates the pooled HR estimate and its corresponding 95% CI.

for meta-regression bubble plots). The association between LGE presence and all-cause mortality was significantly modified by patient age ($P = .001$), gender ($P = .004$), and baseline LVEF ($P = .02$). Stronger associations were seen in populations of

Figure 5. Risk of Cardiovascular Events Due to Various Factors



Meta-analysis results for the risk of arrhythmic events (A) and heart failure events (B) for every 10-ms increase in native T1 relaxation time, heart failure events with every 1% increase in extracellular volume fraction (C), and heart failure events with every 1% reduction in global longitudinal strain (D). The area of each square representing an individual study is proportional to its weight within the random-effects meta-analysis model. Horizontal lines indicate the 95% CI of the hazard ratio (HR) estimate for the individual study. The diamond indicates the pooled HR estimate and its corresponding 95% CI.

younger patients, with more severely impaired systolic function and higher proportions of male participants. Baseline LVEF did not modify the association between LGE presence and cardiovascular mortality, arrhythmic events, heart failure events, and MACE. Similarly, no modifying effect of baseline LVEF on the association between LGE extent and arrhythmic events or MACE was observed. For the remaining CMR imaging-derived measurements and outcomes, results following meta-regression remained largely consistent with primary analyses (eTable 2 in Supplement 1).

Discussion

In this meta-analysis of observational studies exploring CMR imaging-derived measurements as risk factors for adverse clinical end points in NIDCM, the main findings were: (1) Both presence and extent of LGE were associated with all-cause mortality, cardiovascular mortality, arrhythmia, heart failure events, and MACE; (2) higher LVEF was associated with lower risk for heart failure events and MACE, but no significant association with all-cause mortality, cardiovascular mortality, and arrhythmic risk was observed; (3) higher risks for arrhythmic events and MACE were seen with higher native T1 relaxation times; (4) there was no association between GLS and heart failure events or MACE; and (5) a paucity of data precluded pooled analysis for native T1 relaxation times, ECV, and GLS with respect to mortality end points.

Based on historic ICD trials, risk stratification in NIDCM continues to be centered around LVEF threshold values at or below 35% as the main indicator for primary prophylactic

ICD implantation.[1,135] Long-term follow-up from the landmark SCD-HeFT,[9] DEFINITE,[11] and, most recently, DANISH[10] trials demonstrated no overall survival benefit from prophylactic ICD implantation in NIDCM under LVEF-based criteria; all 3 trials reported low rates of appropriate ICD discharge of 5.1% over 1 year, 17.9% over 3 years, and 11.5% over 5.6 years, respectively. Only the DANISH trial demonstrated a benefit in all-cause mortality during long-term follow-up for the subgroup of patients aged 70 years or younger,[10] presenting a potential target for future trials. In the present analysis, LVEF was not significantly associated with all-cause mortality and arrhythmic events in NIDCM; merely a trend toward lower risk of cardiovascular mortality (HR, 0.97 [95% CI, 0.94-1.00]; $P = .05$) was observed with higher LVEF values. Overall, these findings cast further doubt on the status of LVEF as the pivotal imaging criterion in risk stratification and selection of patients for prophylactic ICD implantation in NIDCM.

Replacement fibrosis resulting from collagen deposition following apoptosis or necrosis of cardiac myocytes due to irreversible injury can be detected in approximately 30% of patients with NIDCM depicted by LGE. Analysis findings illustrate that not only the presence, but also the extent of LGE is consistently and strongly associated with mortality, arrhythmia, and heart failure events in NIDCM (Figure 1). The wide-ranging association of LGE across arrhythmic and nonarrhythmic outcomes may be explained by replacement fibrosis not only forming the major histological substrate for myocardial reentry and malignant arrhythmias, but also promoting secondary ventricular remodeling and contractile impairment.[32] The association between LGE and clinical outcomes remained consistent on meta-regression, including exploration of results across the spectrum of LVEF, with the exception of all-cause mortality, likely due to competing noncardiac causes of death in older patients with more preserved systolic function (eTable 2 in Supplement 1). Analysis results support findings from previous meta-analyses, although the present analysis incorporates substantially larger numbers of patients and reports data across all relevant clinical outcome categories. The observations further strengthen the notion of incorporating LGE detection and quantification into the definition of high-risk NIDCM phenotypes.[136] Ultimately, randomized trials examining the value of prophylactic ICD implantation in LGE-positive patients with NIDCM are warranted and underway. The CMR-ICD (NCT04558723) and BRITISH (NCT05568069) studies are open-label, government-funded trials randomizing adult patients with NIDCM who have severely impaired systolic function (LVEF ≤35%) and evidence of LGE on CMR imaging in a 1:1 fashion to receive either primary prophylactic ICD implantation or optimal medical therapy only, with all-cause mortality as the primary end point. These trials will provide definitive answers to whether LGE assessment can tangibly improve therapeutic decision-making in patients with NIDCM and advanced contractile impairment. However, there continues to be a lack of randomized evidence exploring LGE assessment as a selection criterion for prophylactic ICD implantation in patients with NIDCM and nonseverely reduced systolic function (LVEF >35%), as these patients remain at risk of SCD.[14] Analysis findings indicate that such trials are warranted. Furthermore, standardized protocols for detecting and quantifying LGE are needed to ensure consistent application of its evident prognostic value in clinical practice.

Interstitial fibrosis, as depicted by native T1 mapping and ECV, is near ubiquitous in NIDCM and may contribute to arrhythmogenesis through maintenance of reentry circuits and heterogeneous conduction slowing.[133,137] Accordingly, higher arrhythmic risk with higher native T1 relaxation times were observed. Although meta-analysis for ECV regarding arrhythmic events was not feasible, results from singular studies appear to complement observations generated from native T1 mapping (Di Marco et al,[133] Li et al).[79] Neither native T1 relaxation times nor ECV demonstrated an association with heart failure events, potentially suggesting that interstitial fibrosis may not primarily contribute to contractile dysfunction and progressive pump failure in NIDCM. However, this interpretation may not accurately mirror the true pathophysiology and should be approached with caution due to the limited availability of data. Moreover, insufficient data precluded pooled analysis of mortality outcomes for both measurements, yet singular studies observed higher all-cause (Puntmann et al)[99] and cardiovascular mortality (Li et al)[129] with higher native T1 relaxation times and ECV. Although analysis observations suggest promise for a role of native T1 relaxation times in NIDCM risk assessment, additional data from prospective, large-scale studies with mortality- and arrhythmia-related end points are required to establish whether measures of interstitial fibrosis provide incremental value over LGE measurement.

Myocardial strain quantitatively assesses tissue mechanics during the cardiac cycle, enabling refined evaluation of systolic function beyond CMR imaging–derived volumes and ejection fraction.[138] GLS represents the most widely used type of myocardial strain in clinical practice. Although no clear associations between GLS and adverse outcomes were identified in the analysis (Figure 1), current data are insufficient to draw strong conclusions. Considering the advanced severity of systolic impairment of enrolled patients, GLS may provide higher utility in NIDCM risk assessment at earlier disease stages given its sensitivity for discerning subclinical contractile dysfunction.

Although the present analysis summarizes the association of individual measurements with adverse outcomes, risk assessment, and selection of patients for ICD implantation, analysis may be further enhanced by integrating various CMR imaging measurements and combining them with clinical risk factors, biomarkers,[139] electrophysiological data,[140] and genetic variants[141-143] to derive multiparametric risk stratification algorithms. CMR imaging represents one of the more resource-intensive imaging modalities in cardiovascular medicine and is primarily restricted to more developed health care systems, generating questions regarding the cost-effectiveness of CMR imaging–based risk assessment. Conversely, enhanced risk stratification and refined selection of ICD candidates through CMR imaging

may avert considerable costs related to unnecessary ICD implantations and subsequent lifetime management (generator changes, lead revisions, procedural and infectious complications) while allowing the provision of life-saving treatment for SCD-prone patients with NIDCM not captured by current selection criteria.

Limitations

This analysis is limited by underlying study quality with considerable proportions of studies featuring single-center retrospective designs, limited patient numbers, and moderate to high risks for bias. Substantial interstudy heterogeneity exists regarding definitions of NIDCM, inclusion criteria, end point compositions, adjustment for covariates, as well as thresholds, units, and increments used for measuring CMR imaging-derived variables. Accordingly, the analysis employed random-effects meta-analyses applying the method of Hartung, Knapp, Sidik, and Jonkman to better account for interstudy variance and conducted meta-regression to explore the heterogeneity in the magnitude of associations between CMR imaging parameters and clinical outcomes. Specifically, the definition and composition of MACE end points varied considerably, hence caution is advised when interpreting results in relation to this outcome. Further, a number of studies may have had the technical and statistical capabilities to report data on relevant CMR imaging-derived variables and end points other than the ones selected for publication, thereby generating the potential for outcome or analysis reporting bias. Small-study effects, including publication bias, may have resulted in the overestimation of the associations, particularly for LGE-based variables (eTable 1 for quantitative values, eAppendix 6 for funnel plots in Supplement 1). Where continuous variables have been studied, infrequent reporting of dichotomized thresholds or outcomes pertaining to different age groups precluded any such analysis. Native T1 relaxation times and, to a lesser degree, ECV were dependent on scanner type and magnetic field strength, and post-processing software applied to GLS measurements varied along with the normal values used. A paucity of data regarding native T1 relaxation times, ECV, and GLS precluded meta-analysis for bias-resistant mortality end points; and sample size restrictions for nonmortality end points generated the potential for type II errors, clearly outlining the need for future large-scale studies in this area. Lastly, available studies predominantly included NIDCM populations with advanced contractile impairment, thereby impeding the extrapolation of results to patients at earlier disease stages.

Conclusions

This meta-analysis examined the value of CMR imaging-derived measurements for risk stratification in patients with NIDCM. The presence and extent of LGE were associated with mortality and both arrhythmic and nonarrhythmic clinical end points. However, small-study effects may have led to an overestimation of the summary estimates. LVEF was not associated with arrhythmic and mortality end points, questioning its central role in risk stratification for prophylactic ICD implantation in NIDCM. The lack of data on bias-resistant mortality end points, along with the nonstandardized measurement and reporting for native T1 relaxation times, ECV, and GLS, represent significant evidence gaps, which are clear targets for future research in CMR imaging-based risk stratification of NIDCM. Ongoing randomized clinical trials will provide insights into whether LGE-based risk stratification can improve therapeutic decision-making regarding prophylactic ICD implantation in advanced NIDCM. Finally, further evaluation is needed to determine if the findings of this analysis apply across the entire clinical spectrum of NIDCM, including patients with less severe contractile impairment.

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