Association of late gadolinium enhancement in cardiac magnetic resonance with mortality, ventricular arrhythmias, and heart failure in patients with nonischemic cardiomyopathy: A systematic review and meta-analysis

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BACKGROUND Late gadolinium enhancement (LGE) on cardiac magnetic resonance is a predictor of adverse events in patients with nonischemic cardiomyopathy (NICM).

OBJECTIVE This meta-analysis evaluated the correlation between LGE and mortality, ventricular arrhythmias (VAs) and sudden cardiac death (SCD), and heart failure (HF) outcomes.

METHODS A literature search was conducted for studies reporting the association between LGE in NICM and the study endpoints. The primary endpoint was mortality. Secondary endpoints included VA and SCD, HF hospitalization, improvement in left ventricular ejection fraction (LVEF) to >35%, and heart transplantation referral. The search was not restricted to time or publication status. The minimum follow-up duration was 1 year.

RESULTS A total of 46 studies and 10,548 NICM patients (4610 with LGE, 5938 without LGE) were included; mean follow-up was 3 years (range 13–71 months). LGE was associated with increased mortality (odds ratio [OR] 2.9; 95% confidence interval [CI] 2.3–3.8; $P < .01$) and VA and SCD (OR 4.6; 95% CI 3.5–6.0; $P < .01$). LGE was associated with an increased risk of HF hospitalization (OR 3.4; 95% CI 2.3–5.0; $P < .01$), referral for transplantation (OR 5.1; 95% CI 2.5–10.4; $P < .01$), and decreased incidence of LVEF improvement to >35% (OR 0.2; 95% CI 0.03–0.85; $P = .03$).

CONCLUSION LGE in NICM patients is associated with increased mortality, VA and SCD, and HF hospitalization and heart transplantation referral during long-term follow up. Given these competing risks of mortality and HF progression, prospective randomized controlled trials are required to determine if LGE is useful for guiding prophylactic implantable cardioverter-defibrillator placement in NICM patients.

KEYWORDS LGE; CMR; Mortality; Ventricular arrhythmia

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Introduction

Nonischemic cardiomyopathy (NICM) is a highly prevalent chronic disease that has been associated with increased morbidity and mortality through progressive pump failure and life-threatening arrhythmias.[1] With an estimated disease prevalence ranging between 0.05% to 5% of all patients seen in the inpatient and outpatient settings and accounting for 1% to 2% of all annual healthcare costs, NICM places a large burden on the healthcare system in the United States and worldwide.[1,2] It is imperative to identify patients who are at elevated risk for disease progression and mortality.

Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) is a promising technique for risk stratification of patients with NICM. LGE is useful for the detection of myocardial scar and fibrosis in patients with ischemic cardiomyopathy (ICM).[3,4] While LGE is present in approximately 30% to 35% of patients with NICM, studies evaluating its association with clinical outcomes have mostly been limited to single-center observational studies.[5]

The goal of this systematic review and meta-analysis was to conduct a comprehensive evaluation of the association between LGE and clinical outcomes in patients with NICM. We examined the association of LGE with all-cause mortality, ventricular arrhythmias (VAs) and sudden cardiac death (SCD), heart failure (HF) hospitalization, improvement of left ventricular ejection fraction (LVEF) to >35%, and referral for heart transplantation in NICM patients.

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KEY FINDINGS

- Late gadolinium enhancement in nonischemic cardiomyopathy (NICM) patients is associated with increased mortality, ventricular arrythmia and sudden cardiac death, heart failure hospitalization, and heart transplantation referral during long-term follow up.
- Prospective randomized controlled trials are required to determine if late gadolinium enhancement is useful for guiding prophylactic implantable cardioverter-defibrillator placement in NICM patients who meet current guideline indications and NICM patients with less severe left ventricular dysfunction.

Methods

Data search

This systematic review was performed in adherence to the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement. The review was performed using a preplanned protocol in January 2022. The primary endpoint was mortality. Secondary endpoints included the composite of VA and SCD, HF hospitalization, interval improvement in LVEF to >35%, and heart transplantation referral. VAs were defined as the combined incidence of premature ventricular contractions (PVCs), nonsustained and sustained ventricular tachycardia, and appropriate implantable cardioverter-defibrillator (ICD) shocks. The studies were inconsistent regarding the amount of PVCs that qualified as VAs.

Search strategy

A systematic search was conducted using Ovid MEDLINE, EMBASE, Scopus, Web of Science, and Google Scholar for relevant literature that reported an association between LGE in CMR and VA, SCD, mortality, and HF outcomes. The search was not restricted to time or publication status. Two independent reviewers (M.A.-S. and M.T.) performed an electronic search using the following keywords: "late," "gadolinium," "enhancement," "enhanced," "enhance," "enhancer," "enhancers," "enhances," "enhancing," "nonischaemic," "nonischemic," "nonischemics," "cardiomyopathy," "dilated," "sensitivity," "specificity," "Predictive Value of Tests," "Diagnostic Value," and "Prediction." The references of the included studies, other systematic reviews, and meta-analyses were also manually reviewed to obtain a comprehensive list of studies. After identifying relevant studies, the full texts of the selected articles were examined by both reviewers based on inclusion criteria. Disagreements were resolved by consensus.

Study selection

Studies were selected using the PICO (patient/population, intervention, comparison and outcomes) format to include those that studied patients with NICM (population), comparing LGE present (intervention) with LGE absent (comparison), and assessing for all-cause mortality, SCD, VA, appropriate ICD shock, SCD, HF hospitalization, referral for heart transplantation, and improvement in LVEF to >35% in subjects with baseline LVEF ≤35% (outcomes). Studies that did not separate mixed ICM and NICM patient populations were excluded. LGE presence was assessed either by visual estimation (present/absent) or quantitatively. When quantitative analysis was performed, the mean signal intensity and standard deviation of the region of interest were measured, and enhanced myocardium was defined as myocardium with signal intensity >5 SD above the remote normal myocardial signal. Patients with hypertrophic cardiomyopathy were excluded.

Data extraction

Two reviewers (M.A.-S. and M.T.) independently extracted the study data using a predefined data extraction sheet. Variables that were extracted from the studies included lead author, year of publication, study design, all-cause mortality, SCD, total patients with LGE, total patients without LGE, VAs, HF hospitalization, referral for transplantation, mean follow-up, mean age, mean LVEF, sex, left ventricular end-diastolic volume, and qualitative vs quantitative interpretation of LGE.

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis software, version 3.[6] We used a random-effects model to examine the association between LGE and outcomes, which were presented with an odds ratio (OR) with 95% confidence interval (CI) and Z value. The extent of heterogeneity was determined by I^2 (ranging from 0% to 100%). Statistical significance was considered with a P value <.05, and all tests were 2-sided.

Results

Literature search and study selection

We identified 216 eligible studies from our literature search. After reviewing all studies in full text for relevance, 46 studies were identified to be eligible for meta-analysis for the outcomes of all-cause mortality (primary endpoint) and the composite of VAs, SCD, and appropriate ICD therapy (secondary endpoint). For the secondary endpoints of HF hospitalization, referral for heart transplantation, and LVEF improvement to >35%, 25 studies met inclusion criteria (Figure 1).

Study and patient characteristics

This meta-analysis included prospective and retrospective (Table 1). A total of 10,548 patients (4610 with LGE and 5938 without LGE) were reported in the studies evaluating the association between LGE and all-cause mortality, and the combined incidence of VAs, SCD, and appropriate ICD shocks. A total of 3039 patients (1265 with LGE and 1774 without LGE) were reported in the studies evaluating the association between LGE and HF hospitalization, referral for heart

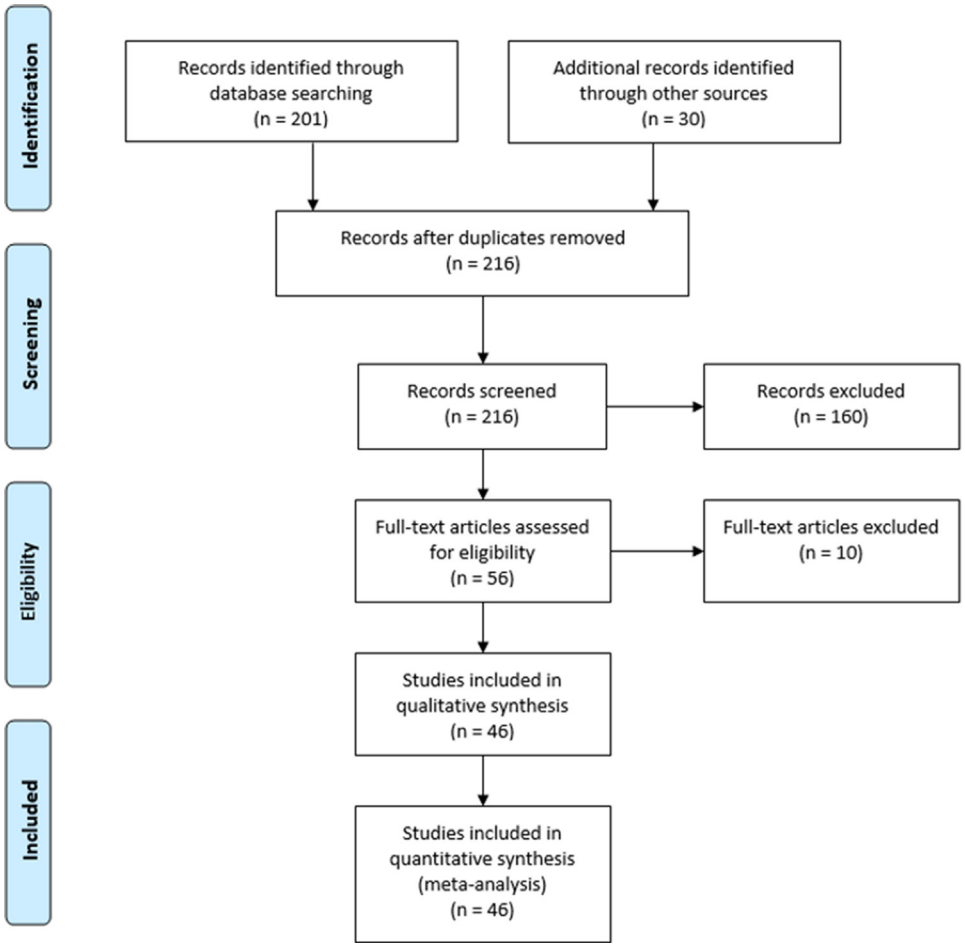

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow chart. The flow diagram depicts study selection for inclusion in the meta-analysis according to the PRISMA statement for reporting systematic reviews and meta-analyses.

transplantation, and LVEF improvement. The mean duration of follow-up was 36 (range 13–71) months (Figure 1).

Association of LGE with all-cause mortality and VAs, SCD, and appropriate ICD shocks

LGE was associated with an increased risk of all-cause mortality (OR 2.9; 95% CI 2.3–3.8; $P < .01$) (Figure 2). There was low heterogeneity ($\chi^2_{32} = 51.26$; $P = .017$; $I^2 = 37\%$). LGE was also associated with an increased risk for the combined incidence of VAs, SCD, and appropriate ICD shocks (OR 4.6; 95% CI 3.5–6.0; $P < .01$) (Figure 3). There was low to moderate heterogeneity ($\chi^2_{45} = 82.2$; $P = .001$; $I^2 = 45\%$).

Association of LGE with HF hospitalization, referral for transplantation, and recovery of LVEF

LGE was associated with an increased risk of HF hospitalization (OR 3.4; 95% CI 2.3–5.0; $P < .01$) (Figure 4). The heterogeneity was moderate ($\chi^2_{21} = 49.5$; $P = .001$; $I^2 = 57\%$). LGE was associated with increased referral for heart transplantation (OR 5.1; 95% CI 2.5–10.4; $P < .01$) (Figure 5). The heterogeneity was low ($\chi^2_9 = 4$; $P = .87$; $I^2 = 0\%$). LGE was associated with an increased risk for lack of improvement in LVEF to >35% (OR 0.2; 95% CI 0.03–0.85; $P = .03$) (Figure 6). The heterogeneity was moderate to high ($\chi^2_4 = 30$; $P = .001$; $I^2 = 86\%$).

Discussion

The major findings of this study are that LGE identifies NICM patients who are at increased risk for all-cause mortality and the combined incidence of VAs, SCD, and appropriate ICD shocks. LGE also identified NICM patients who are at increased risk for HF hospitalization, referral for heart transplantation, and lack of improvement in LVEF. To our knowledge, this meta-analysis is the most comprehensive evaluation to date of the association of LGE and clinical outcomes in NICM.

The initial American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommending defibrillator implantation in NICM were primarily based on the results of The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) published over a decade ago.[7,8] However, the SCD-HeFT trial was conducted on a mixed population (52% ICM and 48% NICM). At 10-year follow-up of the SCD-HeFT population, there was no mortality benefit for ICD placement in the patients with NICM.[9] Similarly, the Defibrillator Implantation in Patients with Nonischemic

Table 1 Demographic data of the included studies

First author	Year	Type	LGE	No LGE	Mean follow-up (mo)	Mean Age (y)	Mean LVEF (%)	Male (%)	LGE reading
Park[37]	2006	pro	24	22	8.1	55.9	26.3	58.7	V
Assomull[33]	2006	pro	35	66	32	51	35.6	69.3	V
Wu[3]	2008	pro	27	38	17	55	24	64.6	SD
Cheong[38]	2009	retro	37	178	52.8	51	52	57	V
Yokokawa[39]	2009	retro	18	11	20	65	24	58.6	SD
Cho[40]	2010	retro	42	37	33.4	56	26.6	60.8	V
Kono[41]	2010	pro	18	14	30.8	61	21.3	59.4	SD
Looi[42]	2010	pro	31	72	32	58	32	75.7	V
Shimizu[31]	2010	pro	11	40	14.1	59	30	76.7	V
Iles[43]	2011	retro	31	30	19	53	25	68.9	SD
Lehrke[20]	2011	retro	72	112	22	52	39	75	SD
Fernández-Armenta[44]	2012	pro	15	22	25	64	22	83	SD
Gao[45]	2012	pro	46	19	21	61	26.2	81	V
Klem[46]	2012	pro	37	27	24	52	41	50	V
Leyva[47]	2012	pro	20	77	35	66	22.3	61.9	V
Masci[48]	2012	pro	50	75	14.2	58.2	34	65.6	SD
Gulati[19]	2013	pro	142	330	64	51	37.2	68.6	V
Kubanek[49]	2013	pro	30	14	12	43	23	71	V
Masci[50]	2013	pro	26	32	24	55	37	33	SD
Müller[51]	2013	pro	94	91	21	51	43.3	71.4	V
Neilan[21]	2013	pro	81	81	29	55	26	65	V
Šramko[52]	2013	retro	28	14	25	44	26	68.2	V
Almehmadi[53]	2014	retro	107	62	15.6	62	33	73	SD
Hasselberg[54]	2014	retro	4	9	29	52	32	—	V
Machii[55]	2014	retro	48	24	36.2	64	24.8	72	V
Perazzolo Marra[56]	2014	pro	76	61	36	49	32.5	78.8	V
Masci[57]	2014	pro	61	167	23	50	43	79	V
Mordi[58]	2014	pro	76	20	30.5	46	27	78.1	SD
Nabeta[59]	2014	pro	36	39	11	56	30.2	65	SD
Rodríguez-Capitán[60]	2014	retro	23	41	31.5	56.2	29.1	75	V
Yamada[61]	2014	pro	25	32	71	55	33.5	70	V
Amzulescu[62]	2015	pre	63	99	41	55	25	63	V
Barison[63]	2015	pro	39	50	24	59	41	X	V
Chimura[64]	2015	retro	122	53	61	60	29	63	V
Piers[65]	2015	pro	55	32	45	56	29	62	V
Tateishi[66]	2015	pro	105	102	44	50	27	80	V
Venero[67]	2015	pro	21	10	12	45	17.6	67.7	V
Gaztanaga[68]	2016	retro	71	34	27	50	25.3	56.2	SD
Hu[69]	2016	pro	35	50	42.7	55	84	75.3	V
Ishii[70]	2016	retro	37	41	47.7	56	31	68	SD
Mikami[71]	2016	pro	66	52	25.2	57	32	57.6	SD
Shin[72]	2016	retro	261	104	44.3	54.1	26.5	61.9	SD
Tachi[73]	2016	pro	22	19	—	60	19.5	83	SD
Voskoboinik[74]	2016	retro	17	11	32	44.2	20.3	64	V
Riffel[75]	2016	retro	64	82	51.6	53	29.3	80	V
Halliday[28]	2017	pro	101	298	55.2	49.9	49.6	63.7	V
Chimura[77]	2017	retro	100	79	45.6	61	33	68	V
Acosta[76]	2018	pros	22	109	35.5	65.1	24	72	SD
Marume[78]	2018	pro	118	162	45.6	52.2	27.6	73.6	V
Muthalaly[79]	2018	retro	62	68	38.4	54.8	29.4	83	V
Voskoboinik[80]	2018	retro	147	189	39	50.7	36.8	67.3	SD
Zhang[81]	2018	pro	101	119	61	49.6	25.6	73.2	SD
Gutman[12]	2019	retro	174	72	37.9	52.4	24.3	74.8	V
Halliday[34]	2019	pro	300	574	58.8	52.1	39	67.3	V
Alba[82]	2020	retro	650	1022	60	57	33	71	V
Barison[83]	2020	pro	116	77	30	66	27	73.2	V
Behera[22]	2020	pro	44	68	24.8	43.3	24.6	64.2	V
Yi[84]	2020	pro	258	120	40.8	55	24.1	62.7	SD
Chen[85]	2021	retro	121	36	13	52.3	27	70.7	SD
Di Marco[14]	2021	retro	486	679	36	58	39	66	V
Guarici[86]	2021	pro	457	543	32	56.7	33	68.6	V

LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; pro = prospective; retro = retrospective; V = visual estimation.

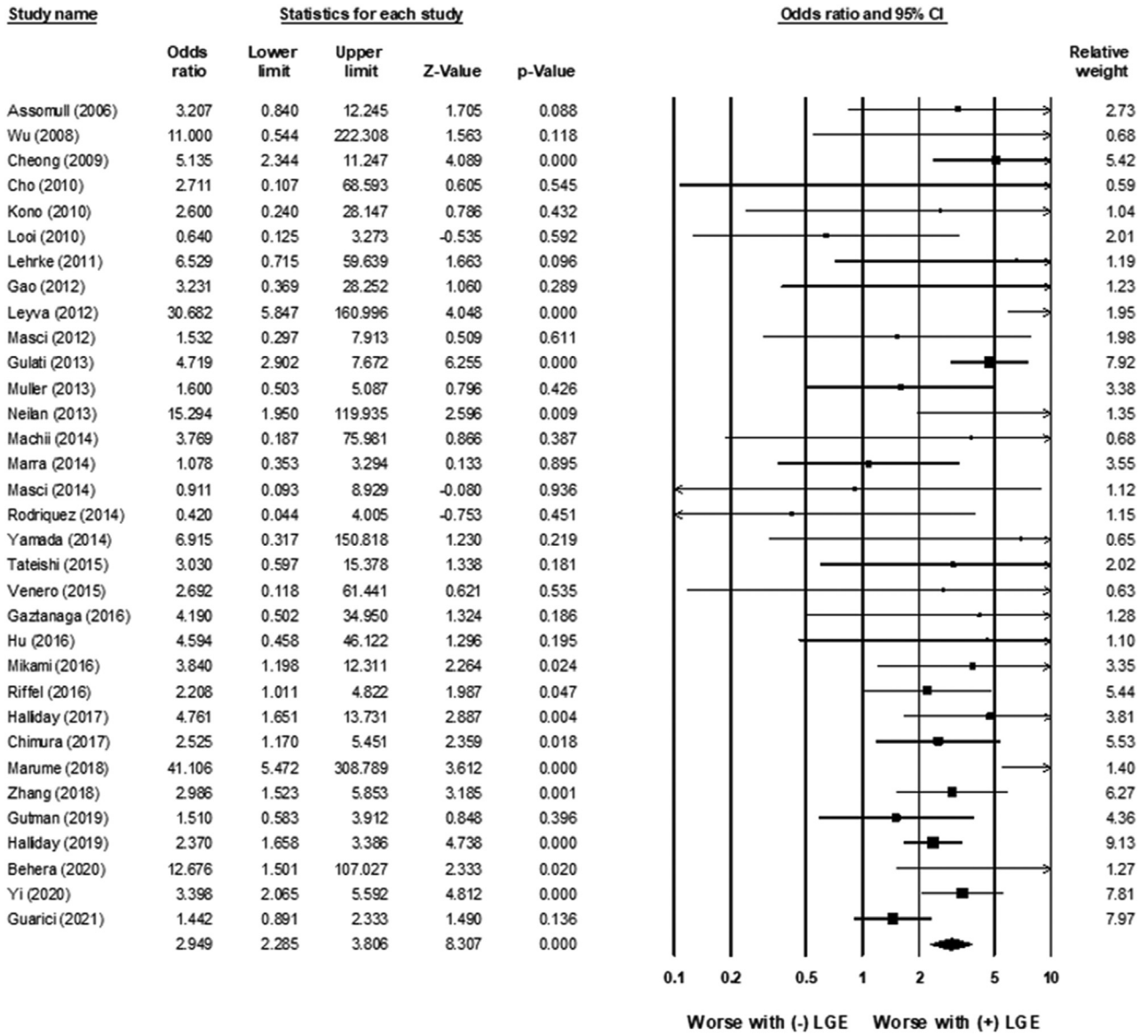

Figure 2 Association between late gadolinium enhancement (LGE) and mortality. LGE was associated with an increased risk of all-cause mortality (odds ratio 2.9; 95% confidence interval [CI] 2.3–3.8; $P < .01$). There was low heterogeneity ($\chi^2_{32} = 51.26$; $P = .017$; $I^2 = 37\%$).

Systolic Heart Failure (DANISH) trial demonstrated no significant difference in all-cause mortality with ICD implantation in patients with NICM.[10] However, in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, ICD placement did not reduce mortality but was associated with a reduction in sudden death from arrhythmia.[11] One possible explanation for these findings may be that NICM represents a heterogeneous group of diseases in which certain disease etiologies place patients at higher cardiovascular risk than others.[10] The lack of benefit of prophylactic ICD implantation in these studies highlights the need for additional risk stratification beyond LVEF, such as LGE. In one study, ICD placement was associated with a reduction in mortality only in patients with LGE (hazard ratio 0.45 vs 1.22 for LGE and no LGE, respectively; $P < .05$).[12]

LGE may also be utilized to identify high-risk patients that are excluded from current guidelines for ICD implantation. Although LVEF <35% is the current standard for recommending ICD implantation in NICM patients, it has low sensitivity (71.7%) and specificity (50.5%) for identifying patients at risk for SCD.[13] As a result, some high-risk patients are not receiving ICD implantation due to not meeting LVEF criteria, while other low-risk patients with LVEF <35% and no LGE are having ICDs implanted and are exposed to device complications such as inappropriate shocks, lead or pulse generator malfunction, and infection. One study demonstrated that LGE is associated with VAs and SCD even in patients with LVEF >35%.[14]

The stark contrast in the utility of LVEF for predicting risk in NICM and ICM may be due to the fact that in ICM, a

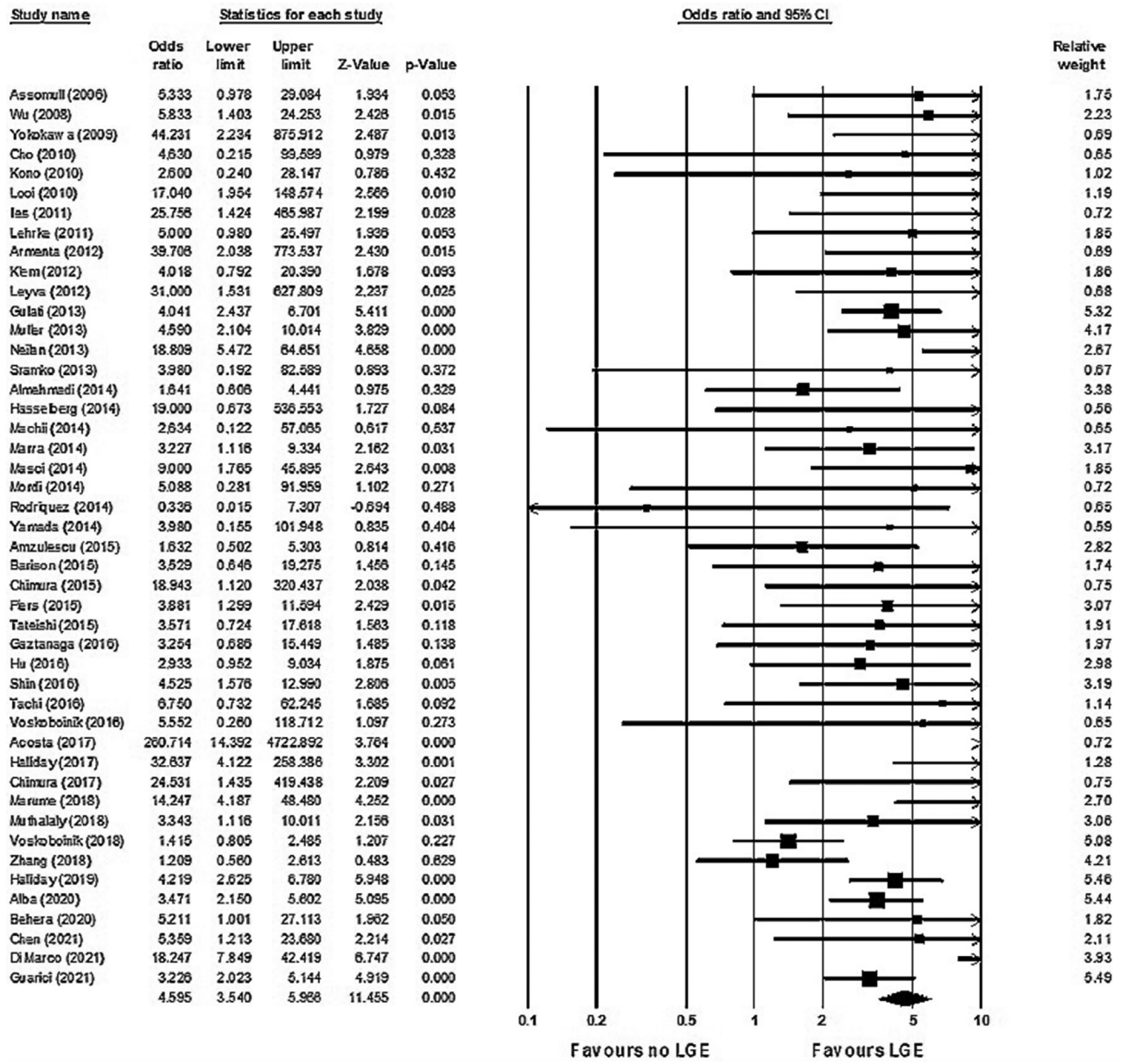

Figure 3 Association between late gadolinium enhancement (LGE) and ventricular arrhythmias/sudden cardiac death. LGE was associated with an increased risk for the combined incidence of ventricular arrhythmias, sudden cardiac death, and appropriate implantable cardioverter-defibrillator shocks (odds ratio 4.6; 95% confidence interval [CI] 3.5–6.0; $P < .01$). Heterogeneity was low to moderate ($\chi^2_{45} = 82.2$; $P = .001$; $I^2 = 45\%$).

significant reduction in LVEF represents more extensive myocardial injury and scar formation. Several previous studies have suggested a strong correlation between reduction in LVEF and the extent of myocardial scarring in patients with ICM.[15,16] In comparison, the pathogenesis of myocardial fibrosis in NICM remains unclear and may occur in varying distributions of myocardial tissue.[17] While this development of fibrosis may not significantly impact LVEF, it may still place patients at risk for adverse events. In one study, the presence of LGE was not associated with initial low LVEF, but it predicted subsequent worsening of LVEF over time.[18]

The existing literature has been mixed regarding whether LGE is associated with adverse left ventricular remodeling and differences in left ventricular dimensions.[5,19–22] In the present study, LGE identified NICM patients who are at increased risk for HF hospitalization, referral for heart transplantation, and lack of improvement in LVEF. The clinical implications of these results are 2-fold. First, patients at high risk for HF progression may require close monitoring by an HF specialist and earlier referral to specialty centers for evaluation of advanced therapeutic options. Second, patients with LVEF <35% who do not have LGE may not need a prophylactic ICD or could be considered for a cardiac resynchronization therapy (CRT) pacemaker if they meet CRT criteria, given the higher likelihood for left ventricular reverse remodeling. These findings await confirmation in

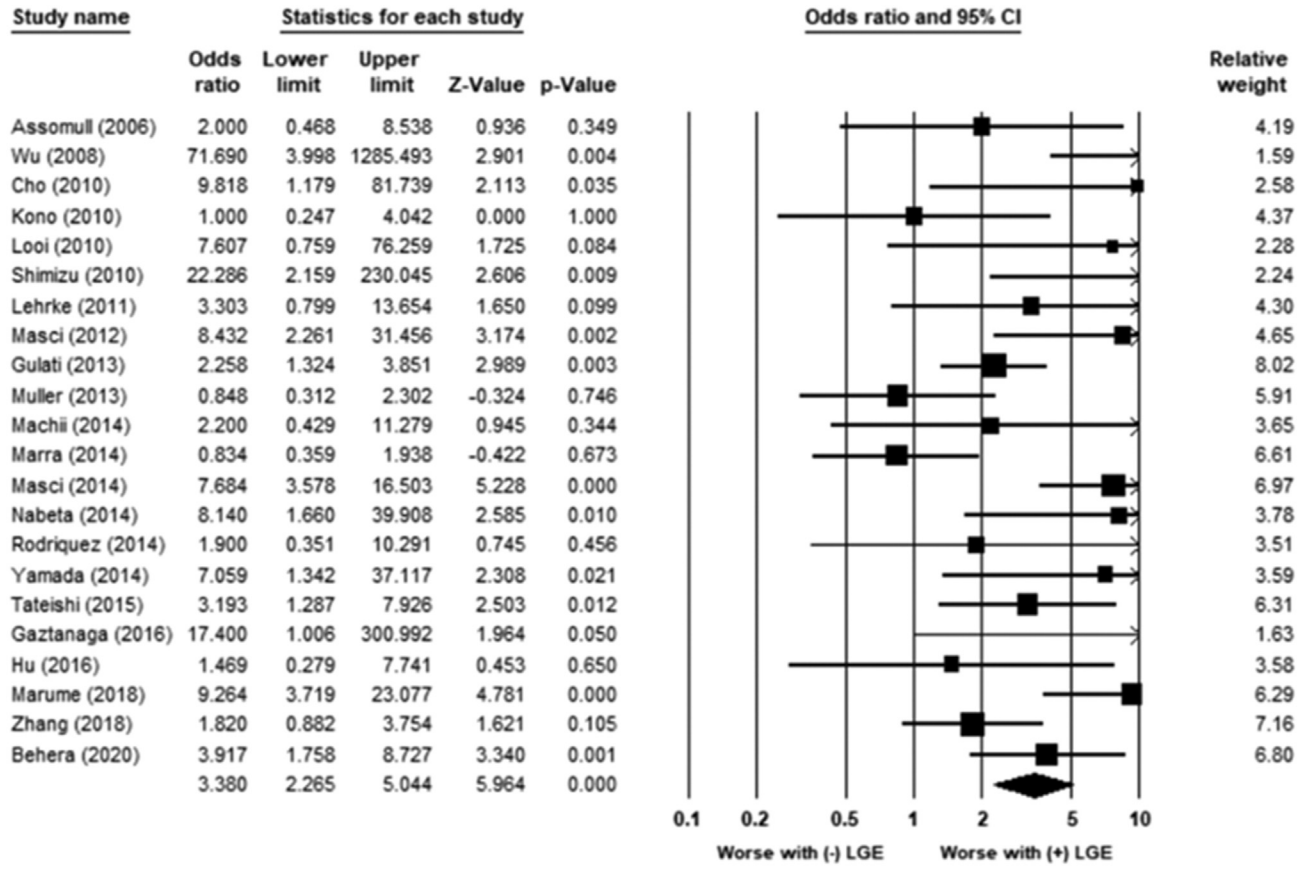

Figure 4 Association between late gadolinium enhancement (LGE) and heart failure hospitalization. LGE was associated with an increased risk of heart failure hospitalization (odds ratio 3.4; 95% confidence interval [CI] 2.3–5.0; $P < .01$). The heterogeneity was moderate ($\chi^2_{21} = 49.5$; $P = .001$; $I^2 = 57\%$).

adequately powered, prospective studies before withholding ICD therapy from patients that meet current guidelines. The available data on the utility of adding ICD therapy to CRT in NICM patients is conflicting, as several studies have demonstrated no added mortality benefit,[23–25] while the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial reported the opposite result.[26]

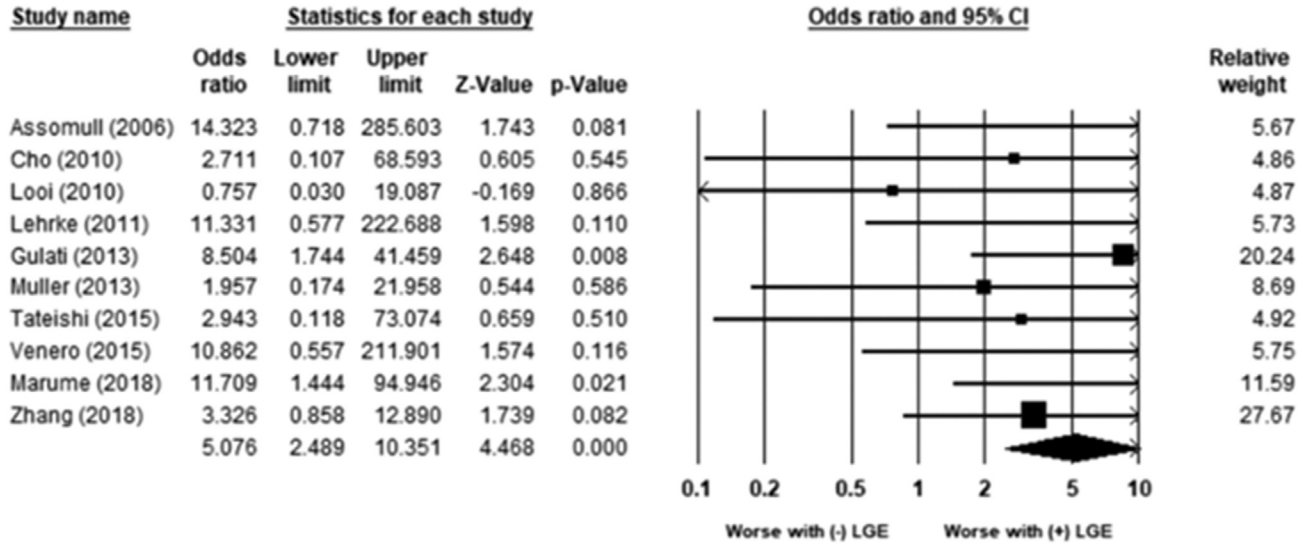

Figure 5 Association between late gadolinium enhancement (LGE) and referral for heart transplantation. LGE was associated with increased referral for heart transplantation (odds ratio 5.1; 95% confidence interval [CI] 2.5–10.4; $P < .01$). The heterogeneity was low ($\chi^2_9 = 4$; $P = .87$; $I^2 = 0\%$).

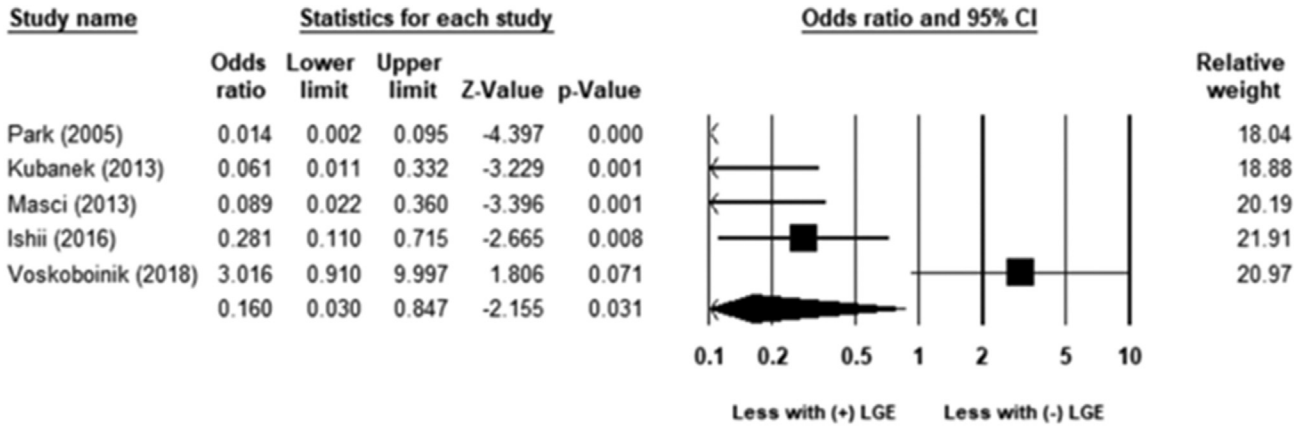

Figure 6 Association between late gadolinium enhancement (LGE) and ejection fraction improvement to >35%. LGE was associated with an increased risk for lack of improvement in left ventricular ejection fraction to >35% (odds ratio 0.2; 95% confidence interval [CI] 0.03–0.85; $P = .03$). The heterogeneity was moderate to high ($\chi^2_4 = 30$; $P = .001$; $I^2 = 86\%$).

Study limitations

There are several limitations that need to be taken into consideration when assessing the results of this present study. Given that currently there are no standardized methods for defining the presence or extent of LGE, the interpretation of LGE varied across the studies included in this meta-analysis. The presence of LGE was defined in several ways, ranging from visual estimation to different threshold-based methods of analysis where the signal intensity of contrast-enhanced areas was compared with nonenhanced areas of myocardium.

While our results suggest that the presence of LGE has significant associations with clinical outcomes, we did not evaluate whether patterns of LGE result in differences in associated risk. There have been several studies demonstrating septal, subepicardial, and multiple LGE lesions to be independent predictors of cardiovascular outcomes.[22,27,28] However, we could not identify enough current literature on this topic to further investigate in this meta-analysis.

Because there is a lack of standardization for defining the extent of LGE, we could not evaluate whether the extent of LGE correlates with differences in clinical outcomes. LGE extent can be interpreted in various ways, including summation of segments with hyperenhancement, percentage of involved myocardium, or absolute weight of enhanced myocardium.[29] Interpretation is further complicated, as different LGE quantification techniques have been shown to cause wide variations in results in a single patient.[30] Perhaps it is because of these reasons that there is no current consensus on what extent of LGE is predictive of clinical events. Cutoff values of significance for LGE extent range as broadly as >5% to >17%, and even results on the clinical significance of small areas of LGE have been mixed.[22,31–34]

LGE on CMR is only able to detect regional myocardial fibrosis. While this pattern is typical in ICM, in which regional fibrosis is present, fibrosis patterns in NICM can occur either regionally or diffusely.[22,35] Studies that utilized T1 mapping and extracellular volume fraction to detect diffuse myocardial fibrosis have shown this pattern to be significantly associated with adverse cardiovascular outcomes as well.[36] Future studies should examine whether combined assessment of regional and diffuse fibrosis is useful for risk stratifying NICM patients.

The definition of VAs varied between studies, and some studies included VAs that are not life threatening in the composite endpoint, such as PVCs and nonsustained ventricular tachycardia.

Conclusion

LGE in NICM patients is associated with increased mortality, VA and SCD, HF hospitalization, and heart transplantation referral during long-term follow up. Given these competing risks of mortality and HF progression, prospective randomized controlled trials are required to determine if LGE is useful for guiding prophylactic implantable cardioverter-defibrillator placement in NICM patients who meet current guideline indications and NICM patients with less severe left ventricular dysfunction.

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Ethics Statement: This systematic review was performed in adherence to the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

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