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ABOUT COVER

Peer Reviewer of *World Journal of Radiology*, Melissa Bersanelli, MD, Adjunct Professor, Chief Doctor, Medical Oncology Unit, University Hospital of Parma, Parma 43126, Italy. bersamel@libero.it

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Association between late gadolinium enhancement and outcome in dilated cardiomyopathy: A meta-analysis

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Abstract

BACKGROUND

The prognostic value of late gadolinium enhancement (LGE) derived from cardiovascular magnetic resonance (CMR) is well studied, and several new metrics of LGE have emerged. However, some controversies remain; therefore, further discussion is needed, and more precise risk stratification should be explored.

AIM

To investigate the associations between the positivity, extent, location, and pattern of LGE and multiple outcomes in dilated cardiomyopathy (DCM).

METHODS

PubMed, Ovid MEDLINE, and Cochrane Library were searched for studies that investigated the prognostic value of LGE in patients with DCM. Pooled hazard ratios (HRs) and 95% confidence intervals were calculated to assess the role of LGE in the risk stratification of DCM.

RESULTS

Nineteen studies involving 7330 patients with DCM were included in this meta-analysis and covered a wide spectrum of DCM, with a mean left ventricular ejection fraction between 21% and 50%. The meta-analysis revealed that the presence of LGE was associated with an increased risk of multiple adverse outcomes (all-cause mortality, HR: 2.14; arrhythmic events, HR: 5.12; and composite endpoints, HR: 2.38; all $P < 0.001$). Furthermore, every 1% increment in the extent of LGE was associated with an increased risk of all-cause mortality. Analysis of a subgroup revealed that the prognostic value varied based on different location and pattern of LGE. Additionally, we found that LGE was a

stronger predictor of arrhythmic events in patients with greater left ventricular ejection fraction.

CONCLUSION

LGE by CMR in patients with DCM exhibited a substantial value in predicting adverse outcomes, and the extent, location, and pattern of LGE could provide additional information for risk stratification.

Key Words: Cardiac magnetic resonance; Dilated cardiomyopathy; Late gadolinium enhancement; Meta-analysis; Myocardial fibrosis; Prognosis

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Core Tip: The prognostic value of late gadolinium enhancement (LGE) is well studied, and several new metrics of LGE have emerged. However, some controversies remain; therefore, further discussion is needed, and a more precise risk stratification should be explored.

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INTRODUCTION

Dilated cardiomyopathy (DCM) is a heterogeneous heart muscle disease with a prevalence of 1 in 2500 adults. Even with advances in therapy, the prognosis of patients with DCM remains poor (the 5-year mortality rate was as high as 20%) and varies considerably among individuals[1]. Therefore, prognostic stratification in DCM has become a demanding issue in clinical practice.

Currently, the left ventricular ejection fraction (LVEF) is a common applicable indicator for risk stratification in patients with DCM. However, the strategy of using the LVEF alone as a prognostic factor is inadequate in predicting adverse outcomes[2]. Occurring in approximately 30% of patients with DCM, myocardial scar is the most important underlying pathology of sudden cardiac death (SCD) events and the major substrate for ventricular arrhythmia. Late gadolinium enhancement (LGE) based on cardiovascular magnetic resonance (CMR) is currently the gold standard for evaluating localized myocardial fibrosis. Studies have confirmed that LGE is an independent and powerful predictor of adverse outcomes in DCM and could increase the prognostic value of LVEF[2-4].

However, most studies have focused on the presence of LGE and adverse outcomes. With the continuously developing research on LGE in patients with DCM, more studies have incorporated new indicators (the extent, location, and pattern of LGE) to assess the outcomes in patients with DCM, other than just the presence of LGE. Therefore, this meta-analysis was designed to evaluate the role of those novel indicators of LGE in the risk stratification of DCM.

MATERIALS AND METHODS

The network meta-analysis extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-NMA) guidelines provided support in guiding this review[5].

Data sources and search strategy

The following databases were searched according to the methods recommended by the Cochrane Handbook: PubMed, Ovid MEDLINE, and Cochrane Library. Studies were searched using relevant controlled vocabulary thesauruses (Medical Subject Headings terms for PubMed) and synonyms for these terms: “dilated cardiomyopathy,” “cardiac magnetic resonance,” “late gadolinium enhancement,” and “prognosis.” The details of the search strategy adopted for PubMed, Ovid MEDLINE, and the Cochrane Library are shown in the Appendix. These searches were limited to cohort studies and were finalized in December 2021.

Eligibility criteria and outcomes

Observational cohort studies, both prospective and retrospective, were included in the meta-analysis if they reported the prognostic value of LGE in DCM and specified the exclusion of ischemic heart disease (*i.e.*, any medical documentation (coronary angiography, myocardial perfusion imaging, or medical records) that indicated the presence of ischemic heart disease and significant coronary artery disease); moreover, studies with transmural LGE without any history of coronary artery disease or myocardial infarction were included if the imaging phenotype including LGE distribution was not coherent with an ischemic insult in a specific coronary artery territory. When the population of a study also included

patients with cardiomyopathies other than DCM, only those with DCM were considered for the meta-analysis. Furthermore, only studies that quantified the extent of LGE as a percentage of left ventricular mass were included in the meta-analysis. The endpoints were classified into three subgroups: (1) All-cause mortality; (2) arrhythmic events, including SCD, cardiac arrest due to ventricular fibrillation (VF), sustained ventricular tachycardia (VT), or appropriate implantable cardioverter-defibrillator (ICD) intervention; and (3) composite endpoints, including all-cause mortality and cardiac events. Cardiac events, included cardiac death[2] (death after a period of clinical deterioration in the signs and symptoms of heart failure despite medical treatment), arrhythmic events, and heart failure. SCD was defined as an unexpected death either within 1 h of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 h of last being seen alive[6]. VF was defined as irregular or regular tachycardia with regards to polarity, amplitude, morphology, and sequence of intracardiac electrograms, with a mean cycle length of ≤ 240 ms (*i.e.*, ≤ 250 beats/min). Sustained VT was defined as tachycardia originating in the ventricle with a rate >100 beats/min and lasting > 30 s or requiring an intervention for termination. Appropriate ICD intervention was defined as a device shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia and documented by stored intracardiac electrocardiogram data[7].

Data extraction and quality assessment

Data were extracted and analyzed by two independent investigators and were reported on standardized forms; consensus was reached through a discussion in case of disagreements. Moreover, data on hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted and unadjusted variables in the regression model, author names, year of publication, sample size, age, percentage of male patients, LGE status (its presence, extent, location, and pattern), follow-up duration, LVEF, and left ventricular end-diastolic volume index (LVEDVi) were recorded if available.

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment, as shown in **Table 1**, and the quality of the selected studies was evaluated and determined based on the selection of the study groups and the outcomes of interest. The NOS scoring system is as follows. A study scored 1 star for each item within the selection and outcome categories, and a maximum of 2 stars was given for comparability. Nine NOS stars were used to assess the risk of bias. A study with nine stars (four for selection, two for comparability, and three for outcome) was considered to have a low risk of bias, and a study with ≥ 5 stars (two for selection, one for comparability, and two for outcome) was considered to have a medium risk of bias. A study with < 5 stars (0 stars for either of the three fields or 1 star for comparability or outcome) was considered to have a high risk of bias.

Data analysis

Pooled HR and 95% CIs were calculated using a fixed-effects model. The heterogeneity between studies was assessed using Q and I^2 tests; heterogeneity was considered significant if $I^2 \geq 50\%$, and the studies will be recalculated using a random-effects model. Furthermore, the meta-analysis was performed using the D–L method if heterogeneity existed, and sensitivity analysis was used to assess the stability of the results.

Publication bias was evaluated using Egger's and Begg's tests; trim and fill analysis was used if there was publication bias. Sensitivity analysis using the leave-one-out method was performed, which allowed the calculation of estimates by omitting one study at a time. All analyses were performed using STATA, version 16. P values of < 0.05 were used to denote statistical significance.

The study has been registered with PROSPERO (number: CRD42023382021).

RESULTS

Search results

Figure 1 shows a flow chart for the search process and study selection. Overall, 147 citations were identified using PubMed (117 citations), Ovid MEDLINE (12 citations), and the Cochrane Library (18 citations). After screening the article titles and abstracts, 26 full-text articles of possible relevance were recruited, and 121 duplicate or irrelevant articles were excluded. Finally, 19 of the 26 relevant articles were included based on the inclusion criteria.

Quality assessment of the included studies

The quality of the included studies was assessed using the NOS, as shown in **Table 1**. None of the included studies had a high risk of bias; however, two studies had a low risk of bias[7,8]. For the study selection, 14 studies had a low risk of bias [6-19], and 5 had a medium risk of bias[3,5,20-22]. In terms of comparability, 8 studies had a low risk of bias[7-9,12,13,15,16,19], 7 studies had a medium risk of bias [3,11,14,17,18,21], and 5 studies had a high risk of bias[5,6,10,20,22]. Regarding outcomes, 8 studies had a low risk of bias [3,5,6,7,8,10,14,18] and 11 studies had a medium risk of bias[9,11-13,15-17,19-21,22].

Study characteristics

This study analyzed data from 7330 individuals (age ranging from 33 to 76 years; 68% were men) from 19 full-text studies from Asia, Europe, and North America. Of the 7330 patients, 2856 (39.0%) had myocardial LGE, and the follow-up duration ranged from 1 to 132 mo.

Among the 19 selected studies, 4 studies were multicenter[12,16,21,22] and 3 studies were retrospective studies[9,21,22]. 14 studies reported the relationship between the presence of LGE and adverse outcomes[3,5,7,6-14,17,18,21,22], 4

Table 1 Risk of bias assessment in the meta-analysis

Ref.	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Halliday <i>et al</i> [6], 2019	1	1	1	1	0	1	1	1	7
Gulati <i>et al</i> [2], 2013	0	1	1	1	1	1	1	1	7
Behera <i>et al</i> [9], 2020	1	1	1	1	2	0	1	1	8
Tateishi <i>et al</i> [10], 2015	1	1	1	1	0	1	1	1	7
Lehrke <i>et al</i> [11], 2011	1	1	1	1	1	1	0	1	7
Perazzolo <i>et al</i> [7], 2014	1	1	1	1	2	1	1	1	9
Neilan <i>et al</i> [12], 2013	1	1	1	1	2	1	0	1	8
Yamada <i>et al</i> [13], 2014	1	1	1	1	2	0	1	1	8
Buss <i>et al</i> [14], 2015	1	1	1	1	1	1	1	1	8
Mikami <i>et al</i> [15], 2016	1	1	1	1	2	1	0	1	8
Puntmann <i>et al</i> [16], 2016	1	1	1	1	2	1	0	1	8
Masci <i>et al</i> [17], 2012	1	1	1	1	1	1	0	1	7
Šramko <i>et al</i> [8], 2013	1	1	1	1	2	1	1	1	9
Amzulescu <i>et al</i> [20], 2015	0	1	1	1	0	0	1	1	5
Alba <i>et al</i> [21], 2020	1	1	1	0	1	0	1	1	6
Xu <i>et al</i> [18], 2021	1	1	1	1	1	1	1	1	8
Barison <i>et al</i> [19], 2020	1	1	1	1	2	0	1	1	8
Halliday <i>et al</i> [4], 2017	0	1	1	1	0	1	1	1	6
Di Marco <i>et al</i> [22], 2021	1	1	1	0	0	0	1	1	5

The total score was 9, and the higher the score, the lower the bias, besides, scores ≤ 5 means a relative high risk of bias.

studies that reported on the extent of LGE[3,12,16,20], 2 studies[6,15] that reported on the location of LGE and 1 study[6] that reported on the pattern of LGE were adjusted for age, sex, and LVEF, and a portion of those studies were modified for the New York Heart Association Functional Classification[5,6,10,11,21].

The detailed data on the author, year of publication, sample size, age, percentage of male patients, LGE status, follow-up duration, LVEF, and LVEDVi are shown in Table 2.

Data synthesis

Positivity for LGE and adverse outcomes: Overall, 18 studies, involving 7168 patients (2793 had LGE), reported the association between the positivity of LGE and adverse outcomes. The included outcomes of the subgroup analysis were all-cause mortality (4 articles), arrhythmic events (9 articles), and composite endpoints (12 articles). All-cause mortality

Table 2 Description of the studies included in the meta-analysis

Ref.	Type of study	Patients enrolled	Mean/median age (yr)	Male (%)	LGE present, n (%)	Mean/Median Follow-Up Time	Endpoint included in analysis	Mean/median LVEF (%)	Mean/median LVEDVi (mL/m ²)
Halliday <i>et al</i> [6], 2019	Prospective	874	LGE negative: 51.0 ± 15.1; LGE extent (0.00%-2.55%): 52.8 ± 14.4; LGE extent (2.55%-5.10%): 53.7 ± 14.6; LGE extent (> 5.10%): 56.2 ± 14.6	588 (67.3)	300 (34.3)	4.9 yr (range, 3.5-7.0 yr)	All cause mortality; arrhythmic events: SCD and aborted SCD.	39 (range, 29-50)	LGE negative: 126.3 ± 36.6; the extent of LGE (0.00-2.55%): 147.9 ± 46.1; the extent of LGE (2.55%-5.10%): 142.8 ± 49.8; the extent of LGE (> 5.10%): 135.5 ± 37.3
Gulati <i>et al</i> [2], 2013	Prospective	472	51.1 ± 14.7	324 (68.6)	142 (30.1)	5.3 yr (range, 31 d-11.0 yr)	Arrhythmic events: SCD and aborted SCD; all cause mortality	37±13	135.1 ± 44.3
Behera <i>et al</i> [9], 2020	Retrospective	112	LGE negative: 45.5 (range, 33.0-58.7); LGE positive: 40.0 (range, 24.5-54.5)	LGE negative: 42 (61.8); LGE positive: 30 (68.2)	44 (39.3)	745 ± 320 d	Composite endpoint: All-cause mortality, resuscitated cardiac arrest, sustained VT/appropriate ICD shock, HF hospitalization	LGE negative: 31.5 (range, 28.0-36.2); LGE positive: 32.5 (range, 27.0-41.0)	LGE negative: 104.0 (range, 77.0-125.0); LGE positive: 137.0 (range, 87.5-225.2)
Tateishi <i>et al</i> [10], 2015	Prospective	207	50 ± 16	165 (80)	105 (50.7)	44 mo (range, 23-62 mo)	Composite endpoint: Cardiac death, cardiac transplantation, LV assist device implantation, appropriate ICD discharge for VT or VF, and rehospitalisation for HF	27 ± 11	143 ± 57
Lehrke <i>et al</i> [11], 2011	Prospective	184	51.55 ± 1.1	138 (75)	72 (39.1)	685 ± 30 d	Composite endpoint: Cardiac death, hospitalisation for decompensated HF, or appropriate ICD discharge	LGE negative: 44 (range, 33.1-50.9); LGE positive: 31 (range, 20.9-42.2)	LGE negative: 109 (range, 92.7-137.6); LGE positive: 133 (range, 116-161)
Perazzolo <i>et al</i> [7], 2014	Prospective	137	No arrhythmic events: 47 (range, 37-60); arrhythmic events: 59 (range, 43-70)	108 (78.8)	76 (55.5)	3 yr (range, 31 d-9.6 yr)	Arrhythmic events: SCD, cardiac arrest due to VF, sustained VT, or appropriate ICD intervention.	No arrhythmic events:33 (range, 28-40); arrhythmic events: 30 (range, 29-40)	No arrhythmic events: 109 (range, 87-140); arrhythmic events: 123 (range, 105-143)
Neilan <i>et al</i> [12], 2013	Prospective	162	55 ± 14	106 (65)	81 (50)	29 ± 18 mo	Composite endpoint: Cardiovascular death and appropriate ICD therapy; arrhythmic events: ATP, ICD discharge, and non-heart failure cardiovascular death	28 ± 9	140 ± 50
Yamada <i>et al</i> [13], 2014	Prospective	57	55 ± 13	40 (70.2)	25 (44)	71 ± 32 mo	Composite endpoint: Cardiac death, hospitalization for decompensated HF, or documented	LGE negative: 36 ± 13; LGE positive: 30 ± 11	LGE negative: 120 ± 39; LGE positive: 141 ± 47

								lethal arrhythmia, including VT and VF		
Buss <i>et al</i> [14], 2015	Prospective	210	52 ± 15	159 (76)	79 (38)	5.3 yr	Composite endpoint: Cardiac events together with the occurrence of hospitalization due to congestive HF	36.1 ± 13.8	132 ± 48	
Mikami <i>et al</i> [15], 2016	Prospective	118	57 ± 14	68 (58)	66 (56)	2.1 ± 1.3 yr	Composite endpoint: Cardiac mortality or appropriate ICD therapy; arrhythmic events: Appropriate ICD therapy or SCD	32 ± 12	119 ± 42	
Puntmann <i>et al</i> [16], 2016	Prospective	637	50 (range, 37-76 yr)	395 (62)	171 (27)	22 mo (range, 19-25 mo)	All cause mortality	47 (range, 29-50)	109 (range, 89-132)	
Masci <i>et al</i> [17], 2012	Prospective	125	59 ± 14	82 (65.6)	50 (40)	14.2 mo (range, 6.5–28.8 mo)	Composite endpoint: Cardiac death and HF hospitalization	33 ± 10	LGE negative: 124 ± 35; LGE positive: 140 ± 39	
Šramko <i>et al</i> [8], 2013	Prospective	42	Idiopathic: 45 ± 12; inflammatory: 42 ± 8	30 (71.4)	28 (66.7)	25 ± 9 mo	Composite endpoint: Cardiac death, urgent heart transplantation, and hospitalization for worsening HF	Idiopathic DC: 22 ± 11; Inflammatory DC: 21 ± 9	Idiopathic: 137 ± 39; Inflammatory: 148 ± 46	
Amzulescu <i>et al</i> [20], 2015	Prospective	162	55 ± 15	102 (63.0)	63 (39)	3.4 yr (range, 1.5-6.3 yr)	Composite endpoint: Cardiovascular death, heart transplantation, LV assist device implantation, resuscitated cardiac arrest, and appropriate device shocks	24.6 ± 8.4	161.6 ± 52	
Alba <i>et al</i> [21], 2020	Retrospective	1672	56 ± 14	1185 (70.9)	650 (39)	2.3 yr (range, 1.0-4.3 yr)	Composite endpoint: All-cause mortality, heart transplantation, or left ventricular assist device implant; arrhythmic events: SCD or appropriate ICD shock	33 ± 11	118 ± 27	
Xu <i>et al</i> [18], 2021	Prospective	412	48.0 ± 14.4	300 (72.8)	201 (48.8)	28.1 mo (range, 19.3-43.0 mo)	Composite endpoint: All-cause mortality and HF readmission; all-cause mortality	23.7 ± 9.8	185.6 ± 58.9	
Barison <i>et al</i> [19], 2020	Prospective	183	66 (range, 56-73 yr)	134 (73)	116 (63)	30 mo (range, 10-65 mo)	Composite endpoint: Appropriate ICD shock and cardiac death; arrhythmic events: appropriate ICD shock	24 (range, 21-31)	143 (range, 120-168)	

Halliday <i>et al</i> [4], 2017	Prospective	399	49.9 ± 15.3	254 (63.7)	101 (25.3)	4.6 yr (range, 3.5-7.0 yr)	Arrhythmic events: SCD or Aborted SCD	49.6 ± 4.9	111.1 ± 19.4
Di Marco <i>et al</i> [22], 2021	Retrospective	1165	58 (range, 48-68)	768 (65.9)	486 (41.7)	36 mo (range, 20-58 mo)	Arrhythmic events: Appropriate ICD therapies, sustained VT, resuscitated cardiac arrest, and sudden death	39 (range, 30-46)	118 (range, 99-142)

Values are *n*, mean ± SD, or *n* (%) unless otherwise indicated; LGE: Late gadolinium enhancement; VT: Ventricular tachycardia; VF: Ventricular fibrillation; HF: Heart failure; ICD: Implantable cardioverter-defibrillator; SCD: Sudden cardiac death; LV: Left ventricular; ATP: Anti-tachycardia pacing.

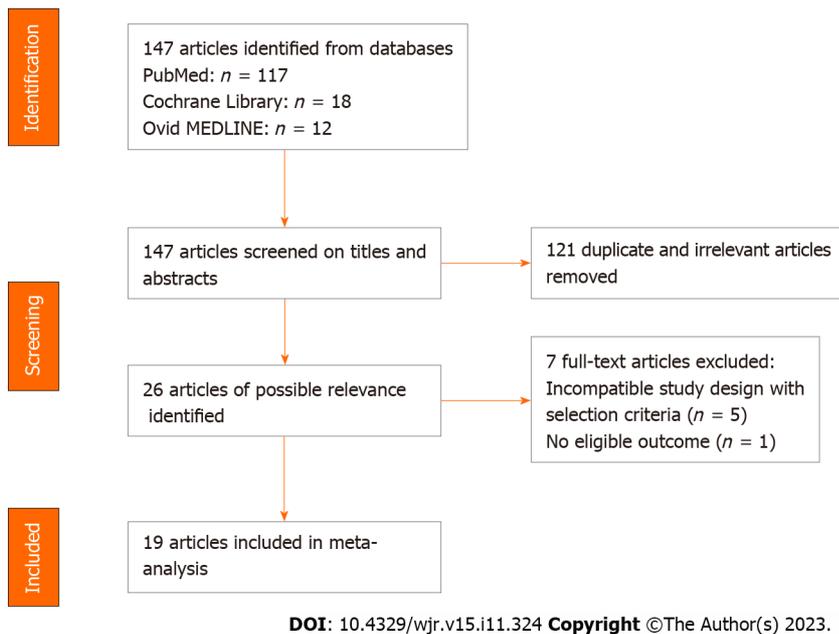


Figure 1 Flow diagram of the selection of articles.

occurred in 313 patients (4.4% of patients of the 18 included studies), of who 172 had LGE (6.2% of LGE-positive patients) and 141 had no LGE (3.2% of LGE-negative patients), with a risk difference between LGE-positive and LGE-negative patients of 12.2% (95%CI: 9.1%–15.3%; $P < 0.001$). Besides, arrhythmic events and composite endpoints occurred in 256 (3.6%) and 603 (8.4%) patients, respectively.

In the pooled analysis, positivity for LGE was associated with an increased risk of all-cause mortality (HR: 2.14; 95%CI: 1.68–2.72; $P < 0.001$), arrhythmic events (HR: 5.12, 95%CI: 3.24–8.07, $P < 0.001$), and composite endpoints (HR: 2.38, 95%CI: 1.83–3.11, $P < 0.001$), as shown in Figure 2. A random-effects model was used for studies on arrhythmic events with significant heterogeneity ($I^2 = 67.9%$; $P = 0.002$), and sensitivity analysis using the leave-one-out method showed that the study by Alba *et al*[21] may be the source of heterogeneity. However, Egger’s and Begg’s tests showed that there was publication bias in the presence of LGE and composite endpoints; after conducting a trim and fill analysis and adjusting for the effect size for funnel plot asymmetry, the P values before and after the trim and fill analysis were less than 0.001, indicating that no significant changes occurred and the results were reliable.

The extent of LGE and adverse outcomes: Two studies were included in the subgroup analysis of all-cause mortality, including 313 participants with LGE and 796 without LGE, with 101 all-cause mortality occurred during the follow-up period, and the pooled HR of all-cause mortality for every 1% increment in the extent of LGE was 1.10 (95%CI: 1.06–1.14; $P < 0.001$) (Figure 3A). In the analysis of the outcome of composite endpoints, two studies recruited 179 patients with LGE and 166 without LGE, with 79 composite endpoints occurred during the follow-up period, however, even random-effects model was used for studies on composite endpoints with significant heterogeneity ($I^2 = 64.0%$; $P = 0.096$); the result showed that every 1% increment in the extent of LGE only has numerically increased the risk of composite endpoints without reaching statistical significance 1.22 (95%CI: 0.91–1.63; $P < 0.001$).

The LGE locations and adverse outcomes: Recently, several LGE metrics, including location and pattern, have emerged as new indicators for risk prediction. Subgroup analysis, which included two studies (LGE was present in 501 patients and absent in 785 patients; all-cause mortality occurred in 212 patients), showed that LGE located in the septum (pooled

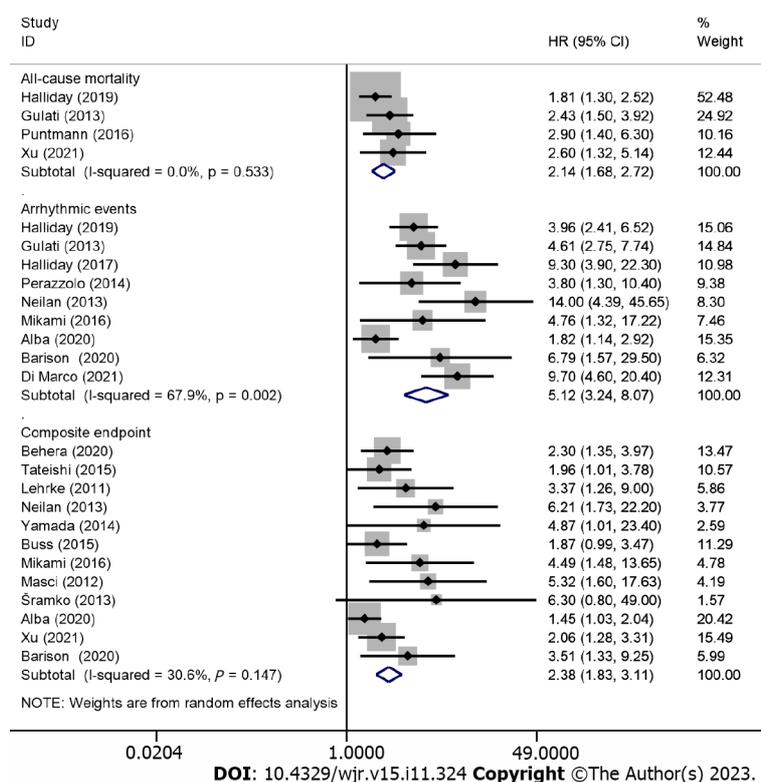


Figure 2 The forest plot of risk of adverse outcomes in dilated cardiomyopathy patients with the presence of late gadolinium enhancement.

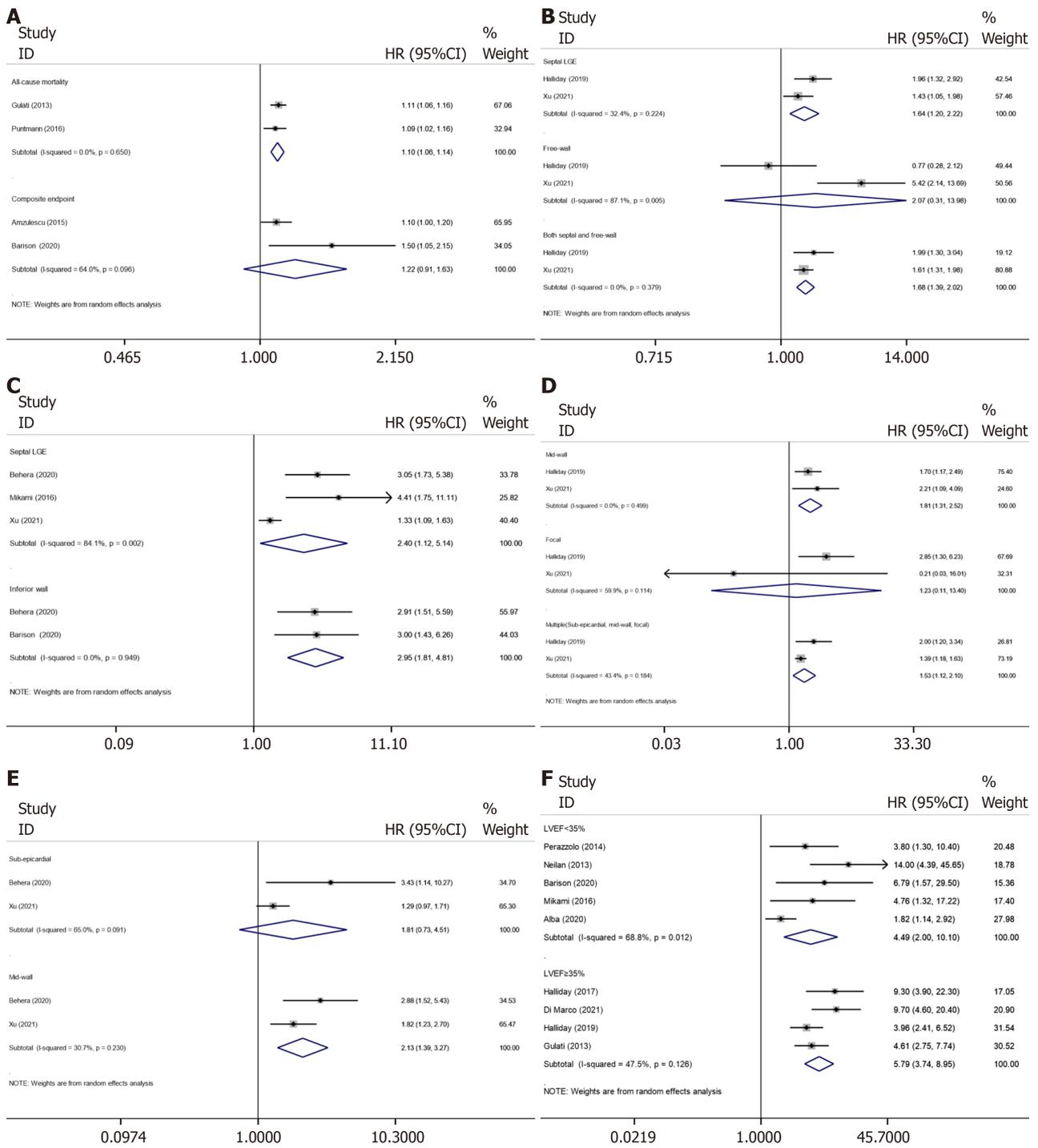
HR: 1.64; 95% CI: 1.20–2.22; $P < 0.001$) and in both the septum and free wall (pooled HR: 1.68; 95% CI: 1.39–2.02; $P < 0.001$) can predict all-cause mortality. However, LGE located in the free wall only has numerically increased the risk of all-cause mortality without reaching statistical significance (pooled HR: 2.07; 95% CI: 0.31–13.98; $P = 0.457$) (Figure 3B). A random-effects model was used for studies on free-wall LGE with significant heterogeneity ($I^2 = 87.1\%$; $P = 0.005$).

The subgroup analysis for predicting composite endpoints included five studies (Figure 3C), including 471 LGE-positive participants and 466 LGE-negative participants, and the number of composite endpoints was 297. The pooled HRs for septal and inferior LGE of composite endpoints were 2.40 (95% CI: 1.12–5.14, $P = 0.025$) and 2.95 (95% CI: 1.81–4.81, $P < 0.001$), respectively; a random-effects model was used to analyze the heterogeneity in the septal LGE group ($I^2 = 84.1\%$; $P = 0.002$), sensitivity analysis using the leave-one-out method showed that the study by Xu *et al*[18]. may be the source of heterogeneity, and the heterogeneity may result from the unadjusted HR.

The LGE patterns and adverse outcomes: In addition to the mid-wall pattern of LGE, recent studies have found that LGE has many other patterns, such as focal and sub-epicardial patterns, which can also provide stratification information for adverse outcomes. Subgroup analysis for all-cause mortality, which included 501 patients with myocardial LGE and 785 without LGE from two studies, was performed for the mid-wall, focal, and multiple (mid-wall, sub-epicardial, and focal) patterns of LGE; death occurred in 212 patients, and the pooled HRs were 1.81 (95% CI: 1.31–2.52; $P < 0.001$), 1.23 (95% CI: 0.11–13.40; $P = 0.867$; not statistical significance), and 1.53 (95% CI: 1.12–2.10; $P < 0.001$), respectively (Figure 3D).

The relationship between the patterns of LGE and composite endpoints was also analyzed; subgroup analysis was performed and included two studies involving 245 LGE-positive patients and 279 LGE-negative patients, with 195 composite endpoints during the follow-up period. Our analysis showed that mid-wall (pooled HR: 2.13; 95% CI: 1.39–3.27; $P = 0.001$) patterns of LGE can predict composite endpoints (Figure 3E), even random-effects model was used for studies on sub-epicardial LGE with significant heterogeneity ($I^2 = 65.0\%$; $P = 0.091$), these results showed that sub-epicardial LGE has numerically increased the risk of composite endpoints without reaching statistical significance (pooled HR: 1.81; 95% CI: 0.73–4.51; $P = 0.202$).

Positive effect of LGE and arrhythmic events on different ranges of LVEF: As the studies included in our meta-analysis all demonstrated indications of LVEF, we also performed a subgroup analysis to assess the impact of LGE on DCM for different ranges of LVEF by dividing those studies into two groups (LVEF $< 35\%$ and LVEF $\geq 35\%$). The analysis, which included nine studies (LGE was present in 2018 patients and absent in 3164 patients; arrhythmic events occurred in 256 patients), showed that LGE is a stronger predictor of arrhythmic events in patients with a greater LVEF, and the pooled HRs for positive LGE with LVEF $< 35\%$ and LVEF $\geq 35\%$ were 4.49 (95% CI: 2.00–10.10; $P < 0.001$) and 5.79 (95% CI: 3.74–8.95; $P < 0.001$), respectively (Figure 3F). A random-effects model was used for studies on LVEF $< 35\%$ with significant heterogeneity ($I^2 = 68.8\%$; $P = 0.012$).



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Figure 3 The forest plot of association between extent, location, and pattern of late gadolinium enhancement and adverse outcomes. A: Association between extent of late gadolinium enhancement (LGE) and adverse outcomes; B: Association between locations of LGE and all-cause mortality; C: Association between locations of LGE and composite endpoint; D: Association between patterns of LGE and all-cause mortality; E: Association between patterns of LGE and composite endpoint; F: Association between the positive of LGE and arrhythmic events in different ranges of left ventricular ejection fraction.

DISCUSSION

LGE detected by CMR represents a myocardial scar, which could provide a foundation for ventricular re-entrant arrhythmia and is the main cause of SCD in multiple cardiomyopathies[23]. Although LGE is observed in approximately 30% of patients with DCM, several studies support the prognostic power of LGE[3,4]. This meta-analysis included 7330 patients with DCM, confirmed the prognostic value of LGE for multiple adverse endpoints, and investigated the association between the extent, location, and pattern of LGE and outcomes.

Prior meta-analyses have evaluated the prognostic value of LGE in DCM[24-26]. However, the sample size of our meta-analysis was larger, and given the increasing numbers of studies published in the past few years about the characteristics

of LGE (extent, location, and pattern), we considered that focusing on novel indicators was appropriate. The relevant number of studies included allowed subgroup analyses between the extent, location, and pattern of LGE and outcomes.

The presence of LGE and adverse outcomes

Myocardial fibrosis is strongly associated with ventricular remodeling[11,27]. The prognostic value of LGE is independent of left ventricular parameters and can provide additional information on LVEF[28]. Additionally, the predictive ability of LGE was found to be better in patients with higher LVEF[22].

In our meta-analysis, LGE was present in approximately 40% of the patients with DCM under study and was strongly and significantly associated with multiple adverse outcomes. The relationship between LGE and the endpoints was particularly obvious for arrhythmic events (pooled HR: 5.12, 95%CI: 3.24–8.07, $P < 0.001$). This will be extremely meaningful for risk stratification mainly based on LVEF, as most SCD cases did not have severely reduced LVEF[23]. Moreover, the finding that the predictive power of LGE was better in patients with greater LVEF regarding the endpoint of arrhythmic events in our subgroup analysis confirmed the results of a previous study[22]. The severely reduced LVEF detected in patients with DCM represents an adversely remodeled left ventricle, which can lead to self-organized criticality and cascading mechanical collapse, and ultimately result in SCD[29]. However, in the absence of a severely remodeled left ventricle, LGE provides the foundation for ventricular re-entrant arrhythmia, which can be the major cause of adverse outcomes.

The extent of LGE and adverse outcomes

A study suggests that the susceptibility to re-entrant arrhythmias may be increased with the extent of LGE[19], indicating that the evaluation of the extent of LGE plays an important role in determining the prognosis of patients with DCM.

As a continuous variable, every 1% increment in LGE extent can predict all-cause mortality in our meta-analysis. However, even though only studies that quantified the extent of LGE as a percentage of the left ventricular mass were included in our meta-analysis, heterogeneity among studies was inevitable because of the differences in the measurement methods and parameters of LGE quantification used among the included studies. However, Halliday *et al*[6] and Behera *et al*[9] demonstrated that the correlation between the extent of LGE and outcomes seems to be nonlinear, as a small increase in the extent of LGE could significantly increase the risk of adverse outcomes.

One potential mechanism is that the induction of arrhythmia can be influenced by the texture and spatial distribution of fibrosis, the formation and dynamics of which are mostly determined by the maximal local fibrosis level; thus, the composition of myocardial fibrosis, rather than volume, may be the main determinant of arrhythmia[30]. Another mechanism that may explain these results is that ventricular arrhythmia most likely originates from the regions between myocardial fibrosis and healthy tissue with slow conduction[31,32]. Therefore, more precise identification of heterogeneous zones between healthy myocardium and myocardial fibrosis and the accurate discrimination of the texture and type of myocardial fibrosis may help better predict the prognosis of patients with DCM.

The LGE locations and adverse outcomes

Studies mainly focused on septal LGE, which is the most common location of LGE. However, recent studies have shown that LGE can also occur in the free wall with a high incidence[6,18], suggesting that LGE located in this location is worth further exploration.

Our meta-analysis found that septal LGE is associated with all-cause mortality and composite endpoints, which is consistent with the findings of previous studies. Furthermore, combined septal and free-wall LGE was more closely associated with all-cause mortality, as multi-location LGE may result in a larger extent of myocardial fibrosis.

The location of LGE may be related to its underlying etiology. LGE of idiopathic DCM is frequently located in the septum for unclear reasons, whereas LGE of DCM caused by viral myocarditis is usually located in the free wall. This is because cardiotropic viruses that originate from the bloodstream can cause pericarditis; the free wall in direct contact with the pericardium is the prime location for migration of inflammatory cells. The scar microstructure may be varied for the underlying etiology and cause a different risk[33].

However, because the number of studies included in this study was small and whether free-wall LGE is a protective or adverse factor remains controversial[6,18], further investigation regarding the prognosis of the distribution of LGE is still required.

The LGE patterns and adverse outcomes

As the most typical LGE pattern, mid-wall LGE was associated with an increased risk of all-cause mortality and composite endpoints in this study. However, our subgroup analyses showed that sub-epicardial and focal pattern of LGE were not statistically significant in predicting adverse outcome; in this case, more studies are required to confirm their prognostic value.

The sub-endocardial and transmural patterns of LGE have been considered to be indicators of previous myocardial infarction[34,35]. However, several studies have investigated the role of transmural LGE, which is not coherent with coronary artery territory (indicating that this pattern is not of an ischemic origin), and sub-endocardial LGE in determining the prognosis of patients with DCM[21,22]. Di Marco *et al*[22] have found that transmural LGE was associated with a heightened risk of adverse outcomes. Through the aforementioned studies, it is suggested that more attention should be paid to those “ischemia LGE patterns” rather than simply seeing it as myocardial infarct in patients with DCM.

In addition to focusing on the pattern of LGE itself, the number of coexisting LGE patterns must also be considered. In our meta-analysis, patients with multiple patterns of LGE (sub-epicardial, mid-wall, and focal) were at a greater risk of

all-cause mortality than those without LGE. One possibility is that more LGE patterns may represent a higher heterogeneity of fibrosis. However, the prognostic ability of multiple LGE patterns is not as good as that of one single pattern in some other studies[6,18]. The limited number of patients with multiple LGE patterns may be responsible for the controversial results. Therefore, more trials are needed to draw a more certain conclusion.

Furthermore, Di Marco *et al*[22] have found that the combination of LVEF strata and LGE status may help improve risk stratification in patients with DCM. Based on the results of this study, the next subdivision of various indicators (extent, location, and pattern) of LGE, particularly the free-wall LGE, and the integration of those indicators with varying clinical parameters may be more helpful in predicting the prognosis of patients with DCM.

Study limitations

The limitations of this study are that most included studies were observational; selection bias should be anticipated; and this meta-analysis can only detect associations but not causality. Additionally, the exclusion and inclusion criteria were different among the included studies, and there was a wide variety on the definitions of the endpoints. Finally, the data on the location and pattern of LGE were limited, which can explain the significant heterogeneity in some subgroup analyses; further studies enrolling more eligible patients are required.

CONCLUSION

CMR-LGE exhibited a substantial prognostic value in predicting all-cause mortality, arrhythmic events and composite endpoints in patients with DCM. The extent, location, and pattern of LGE could provide additional information for risk stratification.

ARTICLE HIGHLIGHTS

Research background

LGE as a prognostic indicator of dilated cardiomyopathy (DCM) has been extensively studied, and several new metrics of late gadolinium enhancement (LGE), such as its extent, location, and pattern, have emerged. However, whether some indicators are protective or risk factors and whether the combination of left ventricular ejection fraction (LVEF) strata and LGE has a better predictive value remains controversial; therefore, further discussion is required, and more precise risk stratification should be explored.

Research motivation

This meta-analysis aimed to detect the predictive performance of the extent, location, and pattern of LGE, to compare and screen these new indicators of LGE, and provide novel concepts for improving the risk stratification algorithm for adverse outcomes of DCM.

Research objectives

The research objectives of this meta-analysis were to investigate the associations between the positivity and extent, location, and pattern of LGE derived from CMR and multiple outcomes. We found that the presence of LGE was associated with an increased risk of multiple adverse outcomes (all-cause mortality, arrhythmic events, and composite endpoints). Furthermore, an increase in the extent of LGE and a different location and pattern of LGE may impact the prognosis. Although the current studies and meta-analyses mainly focus on the relationship between the presence of LGE and prognosis, our study found that LGE is a stronger predictor of arrhythmic events in patients with greater LVEF, and that the different types of LGE were equally predictive, which suggested that these new indicators and their combinations may help improve the risk stratification.

Research methods

We followed the guidelines of PRISMA-NMA, registered with PROSPERO, and extracted data from databases recommended by the Cochrane Handbook. After discussion, we reached a consensus and classified the endpoints into three; the pooled HRs and 95% CIs obtained by using STATA were applied to evaluate the effectiveness of the new metrics of LGE. The Newcastle-Ottawa Quality Assessment Scale was used for quality assessment. Publication bias was assessed using Egger's and Begg's tests, and a sensitivity analysis was performed using the leave-one-out method, to assess the stability of the results.

Research results

CMR-LGE is a strong prognostic marker for patients with DCM. The extent, location, and pattern of LGE provided additional information for risk stratification. Further studies are needed to determine whether free-wall LGE is a protective or risk factor, and whether the focal or sub-epicardial pattern of LGE has predictive value.

Research conclusions

CMR-LGE is a strong prognostic marker for patients with DCM. The extent, location, and pattern of LGE provided

additional information for risk stratification. Further studies are needed to determine whether free-wall LGE is a protective or risk factor, and whether the focal or sub-epicardial pattern of LGE has predictive value.

Research perspectives

The prognostic value of different locations and patterns of LGE needs to be confirmed in future studies, and the combined predictive value of these predictors warrants further exploration.

FOOTNOTES

Co-first authors: Xin-Yi Feng and Wen-Feng He.

Author contributions: Feng XY participated in the study design, contributed to data analysis and interpretation, and drafted the manuscript; He WF contributed to the preparation, editing and review of the manuscript; Zhang TY carried out data acquisition, performed data analysis and interpretation and edited the manuscript; Wang LL, Feng YL, and Li CP carried out data acquisition and performed data analysis and interpretation; Li R contributed to quality control of data and algorithm, and editing and review of the manuscript; All authors read and approved the final manuscript.

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