

# Left ventricular midwall fibrosis as a predictor of sudden cardiac death in non-ischaemic dilated cardiomyopathy: a meta-analysis

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## Abstract

Identification of patients with non-ischaemic dilated cardiomyopathy (NICM) who are at risk of sudden cardiac death (SCD) and could benefit from an implantable cardioverter defibrillator (ICD) is challenging. The study aims to systematically assess the prognostic value of left ventricular (LV) midwall late gadolinium enhancement (LGE) pattern in patients with NICM and further explore its value on predicting SCD events. The study was prospectively registered in PROSPERO (CRD42019138468). We systematically searched PubMed, Ovid Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov to identify studies that evaluated the association between LV midwall LGE and clinical outcomes (all-cause mortality, cardiovascular mortality, and SCD or aborted SCD endpoint) in NICM patients. A meta-analysis was performed to determine pooled odds ratio (OR) for these adverse events. Seven studies including 1827 NICM patients over a mean follow-up duration of  $36.1 \pm 19.3$  months were included. The presence of LV midwall LGE pattern was observed in 562 (30.8%) patients. The pooled OR was 3.37 [95% confidence intervals (CIs): 1.35–8.42] for all-cause mortality, 5.56 (95% CI: 1.23–25.22) for cardiovascular mortality, and 2.25 (95% CI: 1.16–3.16) for SCD or aborted SCD. In a subgroup analysis with mean ejection fraction cut-off point of 35%, the pooled OR for SCD or aborted SCD was 2.06 (95% CI: 1.32–3.22) for LV ejection fraction (LVEF)  $> 35\%$  and 2.49 (95% CI: 1.48–4.20) for LVEF  $\leq 35\%$ . In addition, our study indicated that LV midwall LGE showed an excellent negative predictive value in identifying high-risk NICM patients and that the number needed to treat with ICD implantation in NICM patients with midwall LGE is 7. The presence of LV midwall on LGE is a significant prognosticator of adverse events in NICM patients. Additionally, patients with LV midwall LGE may be considered for ICD therapy irrespective of LVEF.

**Keywords** Late gadolinium enhancement (LGE); Midwall; Dilated cardiomyopathy; Meta-analysis

Received: 17 October 2019; Revised: 26 May 2020; Accepted: 9 June 2020

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## Introduction

Non-ischaemic dilated cardiomyopathy (NICM) is a myocardial disorder characterized by ventricular chamber dilation and progressive systolic dysfunction in the absence of obstructive coronary artery disease and has a prevalence of 1:250.<sup>1,2</sup> Once diagnosed, it predisposes affected individuals to life-threatening cardiac arrhythmias, heart failure, and sudden cardiac death (SCD).<sup>3</sup> Therefore, early identification of high-risk patients, especially for SCD, to receive appropriate therapy in the form of an implantable cardioverter defibrillator

(ICD) is important. To date, the therapeutic recommendation for ICD in patients with NICM is solely based on left ventricular (LV) ejection fraction (LVEF) with a cut-off value of 35%. Although LVEF remains the primary prognosticator in NICM,<sup>4</sup> studies have indicated that the value of LVEF in identifying high-risk patients with NICM is limited, particularly in the following patient groups: (i) NICM patients with mild-to-moderate LV systolic dysfunction but at high risk of SCD<sup>5</sup> and (ii) NICM patients with significant LVEF impairment but still at low risk for SCD.<sup>6</sup> Therefore, it is imperative to identify better prognosticators for accurate risk stratification in NICM.

Recently, several studies have proposed that the presence of LV midwall late gadolinium enhancement (LGE) pattern has an incremental prognostic value over LVEF in NICM.<sup>7,8</sup> Additionally, midwall LGE also has a good prognostic value in patients with NICM having an LVEF > 40%<sup>7</sup> or undergoing cardiac resynchronization therapy (CRT) implantation.<sup>8</sup> However, its validity is limited by the small sample size and low number of events. In addition, a study also reported that LV midwall LGE pattern was not an independent prognosticator for the risk of major arrhythmic events such as sustained ventricular tachycardia, appropriate ICD or CRT-D intervention, ventricular fibrillation, and SCD.<sup>9</sup> Therefore, it is important to clarify these inconsistencies and provide stronger evidence to assess the prognostic performance of LV midwall LGE pattern. In this study, we performed a random-effects meta-analysis to estimate the relationship between the presence of LV midwall LGE pattern and subsequent all-cause mortality, cardiovascular mortality, and SCD or aborted SCD events. Subgroup meta-analyses were carried out to assess the performance of LV midwall LGE in predicting SCD or aborted SCD events in NICM patients with different mean ejection fraction values.

## Methods

### Eligibility criteria

The study was registered in PROSPERO (CRD42019138468). We included studies that met the following criteria: (i) observational cohort studies (both prospective and retrospective) from patients with NICM; (ii) mean follow-up duration was more than 12 months; (iii) all studies had been published in peer-reviewed journals with complete analysis; (iv) English-language publications; (v) studies that explicitly assessed a midwall LGE pattern; and (vi) the definition of NICM used fulfils the World Health Organization/International Society and Federation of Cardiology<sup>10</sup> criteria—(a) a clinical presentation of heart failure based on Framingham criteria, (b) an echocardiogram or cardiovascular magnetic resonance (CMR) demonstrating impaired LV systolic function (ejection fraction < 50%) without regional wall motion abnormalities, (c) an LV diastolic dimension of >55 mm, and (d) absence of significant coronary artery disease on angiography (to ensure exclusion of >50% obstruction of one or more coronary arteries). Exclusion criteria included population composed of patients in disease-specific subpopulations of NICM (e.g. hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy) and studies using *in vitro* or animal models. Editorials, reviews, commentaries, conference abstracts, case reports, and meta-analysis were also excluded. If two or more studies included the same participants, we selected the study with the larger sample size. LV midwall fibrosis was considered

present if there was linear midmyocardial high signal, generally in the basal septal segments. LV non-midwall LGE was defined as patients who do not have midwall LGE, including patients with LV positive non-midwall LGE patterns and patients who have no LGE.

### Search strategy

Meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>11</sup> We performed a systematic search of PubMed, Ovid Embase, the Cochrane Library, Web of Science, and ClinicalTrials.gov, and the references of the included studies were also thoroughly checked for additional studies that may have been missed during the literature search. The last search was performed on 31 May 2019. The keywords used in the search were [(DCM) OR (dilated cardiomyopathy) OR (nonischemic dilated cardiomyopathy) OR (idiopathic dilated cardiomyopathy)] AND [(CMR) OR (cardiac magnetic resonance imaging)] AND [(LGE) OR (late gadolinium enhancement) OR (delayed gadolinium enhancement) OR (contrast enhancement) OR (gadolinium enhancement) OR (delayed enhancement)] AND [prognosis OR risk assessment OR predictive value OR outcome].

### Data extraction

Two researchers independently screened the title and abstract according to the inclusion and exclusion criteria after eliminating duplicate studies and further reviewed the full text of the selected articles for eligibility. Any disagreement was resolved by a third reviewer. The data of eligible studies were independently extracted by the two researchers. The recorded data included first author, year of publication, study design, country of the study, major inclusion criteria, sample size, mean follow-up period, age, sex, CMR parameters, and field strength. Data extraction focused on the prognostic endpoint: all-cause mortality, cardiovascular mortality or transplantation, SCD events, and aborted SCD.

### Quality assessment

The quality of the selected articles was assessed by the Newcastle–Ottawa Quality Assessment Scale and was evaluated based on three aspects: selection of patients, comparability, and outcome. Studies with a score of  $\geq 6$  were considered high-quality studies.

## Data analysis

Statistical analyses were performed using STATA software version 15.0 (Stata Corp LP, College Station, Texas USA). The  $I^2$  statistics were used to assess heterogeneity among studies, with  $I^2$  values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Based on the  $I^2$  value, pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model according to the Mantel–Haenszel method. A ‘one study removed’ sensitivity analysis was performed to determine the sensitivity of the meta-analysis of each result and inter-study variability. Begg’s funnel plot and Egger’s test were performed to evaluate publication bias. In addition, we compared the ORs in different subgroups via meta-analysis. The subgroups included LV midwall LGE, LV non-midwall LGE (non-midwall LGE + no LGE), LV positive non-midwall LGE (excluding midwall LGE), LV positive LGE (the presence of LGE), and LV negative LGE (the absence of LGE) groups. All statistical tests were two-tailed, and a  $P$  value of  $<0.05$  was considered statistically significant.

For evaluating an individual NICM patient in clinic to determine risk and need for ICD, sensitivity, specificity, the positive and negative predictive values, and number of ICDs needed to prevent one major event (NNT) and number of individuals with a major event without an ICD (NNH) were calculated to evaluate the performance of LV midwall LGE in the identification of SCD or aborted SCD events on the basis of extracted information from each individual study.

## Results

### Study inclusion and exclusion

In all, 766 citations were shortlisted based on the search strategy; of these, 583 remained after duplicates were

removed. According to the inclusive and exclusive criteria, 558 were excluded by title or abstract, and 25 were retrieved for full-text evaluation. Two studies were then excluded because of repetition of cohort,<sup>7,15</sup> and a further 16 studies were excluded because of lack of raw data or otherwise ineligible comparison of study design with selection criteria. Finally, seven studies<sup>8,9,12–14,16,17</sup> enrolling 1827 patients were included for the meta-analysis. *Figure 1* provides further details regarding the identification and selection process.

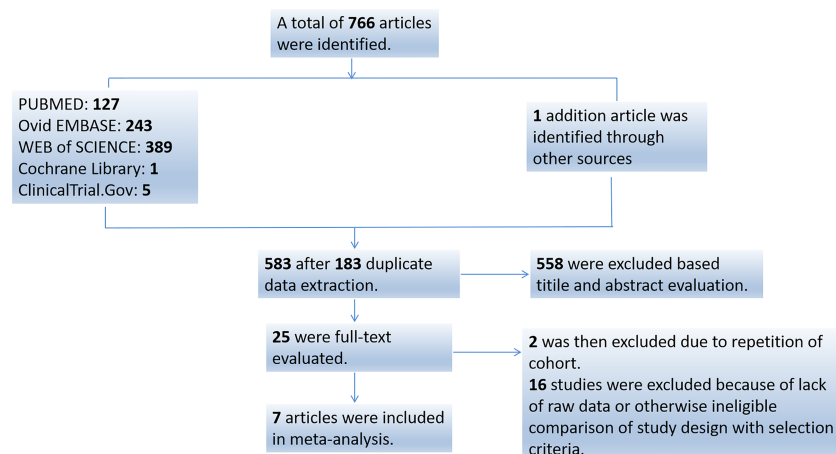
### Study characteristics

The population characteristics of recruited studies are shown in *Table 1*. The median age of the cohorts was 53 (inter-quartile range: 51–63) years; the median size of the cohorts was 175 (inter-quartile range: 98–320). The mean follow-up duration was  $36.1 \pm 19.3$  months. All participants underwent CMR on 1.5 Tesla scanners. The mean LVEF in recruited patients was  $29.7 \pm 8.2\%$ . The presence of LV midwall LGE pattern was observed in 562 (30.8%) patients with NICM.

### Comparison of all-cause death in non-ischaeamic dilated cardiomyopathy with left ventricular midwall late gadolinium enhancement versus non-midwall late gadolinium enhancement

During a mean follow-up of  $36.1 \pm 19.3$  months, 183 (14.6%) all-cause death events occurred in 1287 patients with NICM. Pooled OR and rates of all-cause death events are presented in *Figure 2A* and *Table 2*. The presence of LV midwall LGE predicted all-cause death endpoints with a pooled OR of 3.37 (95% CI: 1.35–8.42,  $P < 0.001$ ). The

**Figure 1** Flow diagram of literature search.



**Table 1** Characteristics of included studies

Article	Region	Patients (n)	Age (years)	Sex (male, %)	LVEF (%)	Duration of follow-up (months)	Family history of SCD (n, %)	Medical therapy				
								DM (n, %)	HTN (n, %)	ACEI/ARB	Beta-blocker	Diuretics
Lehrke <i>et al.</i> (2010)	Germany	184	51.6 ± 1.1	138 (75)	38.9	21.2 ± 1	27 (14.7)	22 (12)	71 (38.6)	149 (81.0)	159 (86.4)	78 (42.4)
Gulati <i>et al.</i> (2013) <sup>a</sup>	England	472	51.1 ± 14.7	324 (68.6)	37.2 ± 13.1	63.6 (range, 1.0 to 132.0)	36 (7.6)	35 (7.4)	N	472 (90.5)	322 (68.2)	243 (51.5)
Halliday <i>et al.</i> (2018) <sup>a</sup>	UK	874	52	588 (67.3)	39.0 (IQR: 29.0 to 50.0)	58.8 (IQR: 42.0 to 84.0)	63 (7.2)	79 (9.0)	190 (21.7)	625 (71.5)	637 (72.9)	387 (44.3)
Chimura <i>et al.</i> (2015)	Japan	175	60 ± 15	110 (62.9)	29.0 ± 5.4	61.2 ± 39.6	14 (8)	N	N	166 (94.9)	165 (94.3)	131 (74.9)
Shin <i>et al.</i> (2016)	Republic of Korea	365	54.1 ± 14.5	226 (61.9)	26.5 ± 10.9	44.3 ± 36.4	N	114 (31.2)	173 (47.4)	338 (92.6)	279 (76.4)	241 (66.0)
Leyva <i>et al.</i> (2012)	UK	97	66.1	60 (61.9)	22.3	34.1	N	13 (13.4)	26 (26.8)	90 (92.8)	50 (55.6)	81 (83.5)
Assomull <i>et al.</i> (2006)	UK	101	50.5 ± 13.5	35 (34.7)	34.5 ± 12	21.2 ± 11.5	17 (16.8)	5 (5.0)	14 (13.9)	79 (78.2)	72 (71.3)	48 (47.5)
Venero <i>et al.</i> (2015)	USA	31	45.4	21 (67.7)	17.6	12.0	N	13 (41.9)	3 (9.7)	30 (96.8)	25 (80.6)	21 (67.7)

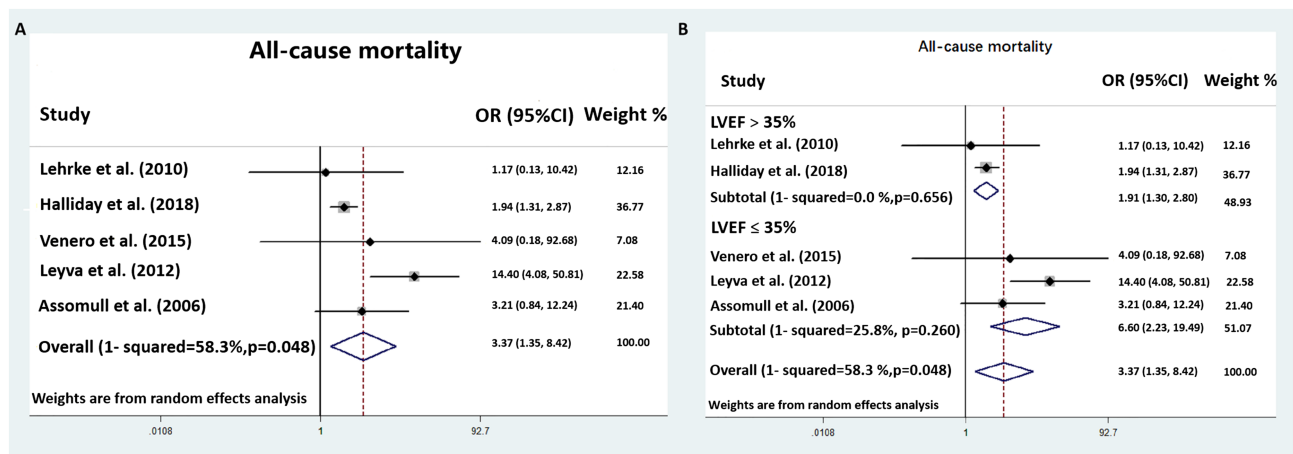
DM, diabetes mellitus; HTN, hypertension; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death. <sup>a</sup>Gulati *et al.* (2013) recruited patients between 2000 and 2008 at the Royal Brompton, and the Halliday *et al.* (2018) study recruited patients between 2000 and 2011 at the same institution; thus, we selected the study with the larger sample size of Halliday *et al.* (2018) for the meta-analysis of all-cause mortality and SCD events (or aborted SCD). However, we included the study of Gulati *et al.* (2013) for the meta-analysis of cardiovascular mortality or transplantation because we could not extract any statistics of cardiovascular mortality in the study of Halliday *et al.* (2018).

pooled OR results for the five articles did not exhibit significant inter-study heterogeneity ( $I^2 = 58.3\%$ ,  $P = 0.05$ ). In the subgroup analysis by mean LVEF, the inter-study heterogeneity significantly decreased and the predictive ability of the presence of LV midwall LGE remained higher in the subgroup with LVEF ≤ 35% (OR = 6.60, 95% CI: 2.23–19.49;  $I^2 = 25.8\%$ ,  $P = 0.26$ ) than the subgroup with LVEF > 35% (OR = 1.91, 95% CI: 1.30–2.80;  $I^2 = 0.0\%$ ,  $P = 0.66$ ). Egger’s test and Begg’s funnel plot showed no significant publication bias ( $t = 0.92$ ;  $P = 0.41$  and  $P = 0.85$ , respectively).

### Comparison of cardiovascular death in non-ischaemic dilated cardiomyopathy with left ventricular midwall late gadolinium enhancement versus non-midwall

Pooled OR for the combined endpoint of cardiovascular mortality was 5.56 (95% CI: 1.23–25.22,  $P = 0.026$ ) (Table 2 and Figure 3A), with a significant heterogeneity of 70.4% ( $P = 0.03$ ). In the subgroup analysis by mean LVEF, the predictive ability of the presence of LV midwall LGE remained higher in the subgroup with LVEF ≤ 35% (OR = 30.68, 95%

**Figure 2** Forest plot of pooled OR for all-cause mortality by the presence of left ventricular midwall LGE (A). Subgroup meta-analysis of pooled OR based on LVEF cut-off value of 35% (B). CI, confidence interval; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OR, odds ratio.



**Table 2** Distribution of all-cause cardiovascular mortality endpoints in non-*ischaemic* dilated cardiomyopathy subgroup with left ventricular midwall late gadolinium enhancement and non-midwall late gadolinium enhancement

Article	All patients (n)	Midwall LGE (n)		Non-midwall LGE (n)		Midwall LGE (n)		Non-midwall LGE (n)	
		All-cause mortality (n)	Total (n)	All-cause mortality (n)	Total (n)	Cardiovascular mortality (n)	Total (n)	Cardiovascular mortality (n)	Total (n)
Lehrke <i>et al.</i> (2010)	184	1	27	5	157	1	27	5	157
Gulati <i>et al.</i> (2013)	Excluded	Excluded	Excluded	Excluded	Excluded	34	142	24	330
Halliday <i>et al.</i> (2018)	874	47	185	103	689	N	N	N	N
Leyva <i>et al.</i> (2012)	97	10	20	5	77	9	20	2	77
Assomull <i>et al.</i> (2006)	101	6	35	4	66	N	N	N	N
Venero <i>et al.</i> (2015)	31	2	18	0	13	N	N	N	N

LGE, late gadolinium enhancement.

LV non-midwall LGE was defined as patients without midwall LGE, including patients with LV positive non-midwall LGE patterns and no LGE.

CI: 5.85–161.00, *Figure 3B*) than the subgroup with LVEF > 35% (OR = 3.47, 95% CI: 1.59–7.58, *Figure 3B*). Egger's test ( $t = 0.25$ ,  $P = 0.84$ ) and Begg's funnel plot showed no significant publication bias ( $P = 0.60$ ).

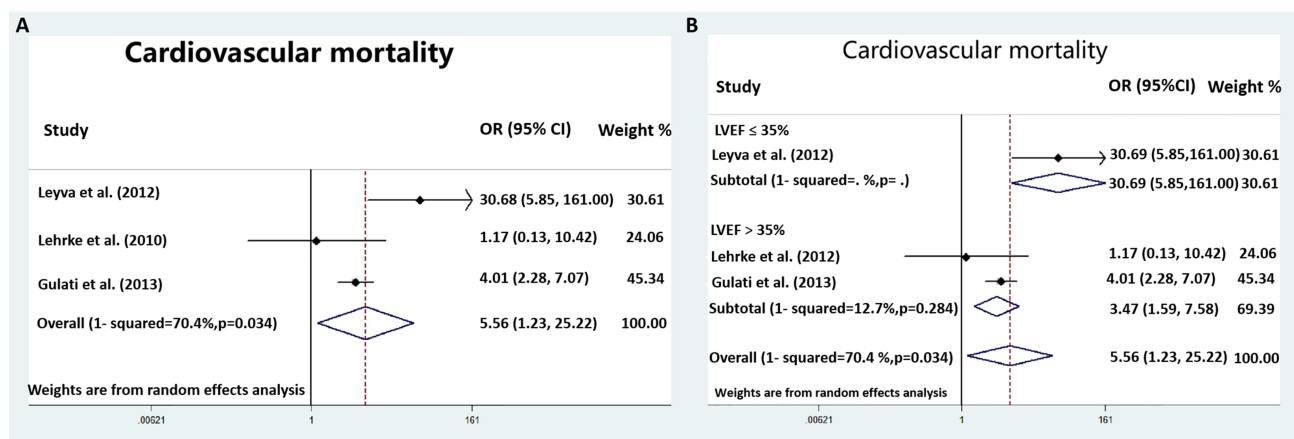
### Comparison of sudden cardiac death and aborted sudden cardiac death in non-*ischaemic* dilated cardiomyopathy with left ventricular midwall late gadolinium enhancement versus non-midwall late gadolinium enhancement

For the combined endpoint of SCD and aborted SCD, the presence of LV midwall LGE had a significant pooled OR of 2.25 (95% CI: 1.61–3.16,  $P < 0.001$ ), without a significant heterogeneity between included studies ( $I^2 = 41.1\%$ ,  $P = 0.13$ ) (*Table 3* and *Figure 4A*). In the subgroup analysis by mean

LVEF with a point of 35%, the SCD or aborted SCD could still be predicted by the presence of LV midwall LGE pattern on CMR in the subgroup with LVEF > 35% (OR = 2.06; 95% CI: 1.32–3.22, *Figure 4B*) and LVEF ≤ 35% (OR = 2.49; 95% CI: 1.48–4.20, *Figure 4B*). Additionally, when studies with mean LVEFs > 35% or ≤ 35% were considered separately, there was a similar percentage of SCD or aborted SCD events (9.73% vs. 9.80%). Egger's test ( $t = 0.96$ ,  $P = 0.38$ ) and Begg's funnel plot showed no significant publication bias ( $P = 0.18$ ).

### The power of left ventricular midwall late gadolinium enhancement to detect sudden cardiac death and aborted sudden cardiac death endpoints

The sensitivity, specificity, positive and negative predictive values, and NNT and NNH of LV midwall LGE for the

**Figure 3** Forest plot of pooled OR for cardiovascular death by the presence of left ventricular midwall LGE (A). Subgroup meta-analysis of pooled OR based on LVEF cut-off value of 35% (B). CI, confidence interval; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OR, odds ratio.

**Table 3** The performance of left ventricular midwall late gadolinium enhancement in predicting sudden cardiac death endpoints in non-ischaemic dilated cardiomyopathy

Article	All patients (n)	Midwall LGE (n)		Non-midwall LGE (n)		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	NNT	NNH
		Events	Total	Events	Total						
Lehrke et al. (2010)	184	4	27	15	157	21.1 (7.0, 46.1)	86.1 (79.6, 90.8)	14.8 (4.9, 34.6)	90.4 (84.5, 94.4)	7	11
Halliday et al. (2018)	874	29	185	55	689	34.5 (24.7, 45.8)	80.3 (77.3, 82.9)	15.7 (10.9, 21.9)	92.0 (89.7, 93.9)	6	13
Chimura et al. (2015)	175	17	114	1	61	94.4 (70.6, 99.7)	38.2 (30.7, 46.3)	14.9 (9.2, 23.1)	85.1 (76.9, 90.8)	7	61
Shin et al. (2016)	365	23	163	21	202	52.3 (36.9, 67.3)	56.4 (50.8, 61.9)	14.1 (9.3, 20.6)	89.6 (84.3, 93.3)	7	10
Leyva et al. (2012)	97	3	20	0	77	100 (31.0, 100)	81.9 (72.3, 88.8)	15 (4.0, 38.9)	100 (94.1, 100)	7	∞
Assomull et al. (2006)	101	5	35	2	66	71.4 (30.3, 94.9)	68.1 (57.6, 77.1)	14.3 (5.4, 31.0)	97.0 (88.5, 99.4)	7	33

LGE, late gadolinium enhancement; NNH, number of individuals with a major event without implantable cardioverter defibrillators (ICDs); NNT, number of ICDs needed to prevent one major event.

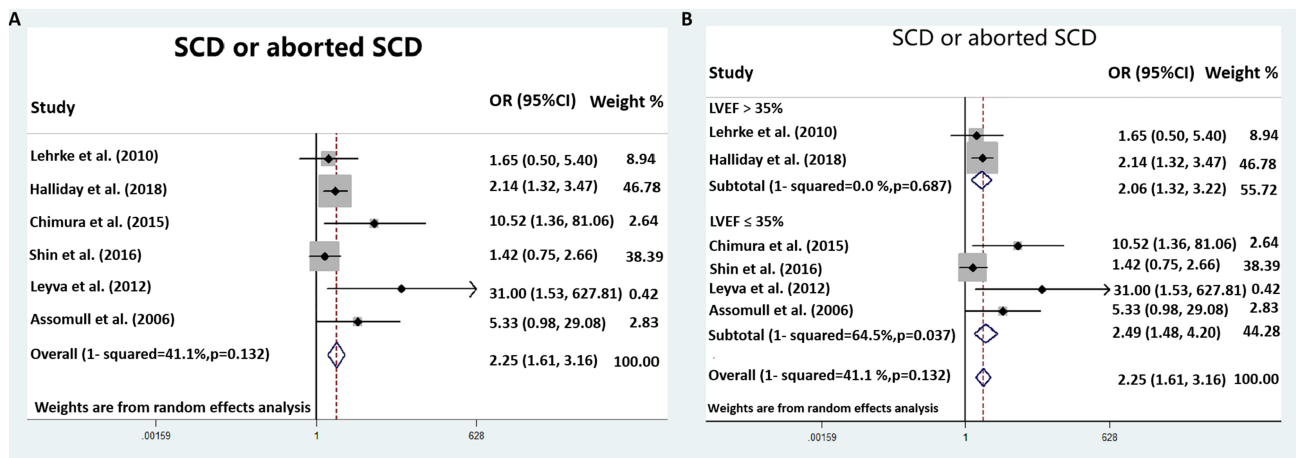
prediction of SCD or aborted SCD events are shown in Table 3. In particular, the negative predictive value showed excellent performance in all recruited studies, ranging from 85.1% to 100%, regardless of LVEF (Table 3). Furthermore, NNH in all included studies was low, ranging from 6 to 7, also regardless of LVEF (Table 3).

### The sudden cardiac death predictive value of left ventricular late gadolinium enhancement pattern in non-ischaemic dilated cardiomyopathy

In included six studies, we could extract data for further analysis on the basis of different LGE patterns (Table 4 and Supporting Information, Figures S1 and S2) in four studies. For the combined endpoint of SCD and aborted SCD, the presence of LV LGE had a significant pooled OR of 4.55 (95% CI: 3.01–6.88,  $P < 0.001$ ; Supporting Information, Figure S1), without a significant heterogeneity between included

studies ( $I^2 = 0.0\%$ ,  $P = 0.70$ ). In addition, the presence of LV midwall LGE had a significant increased OR of 4.04 (95% CI: 2.54–6.42, Supporting Information, Figure S2A) compared with the absence of LGE in NICM patients without a significant heterogeneity between included studies ( $I^2 = 0.0\%$ ,  $P = 0.48$ ), while OR of the presence of positive non-midwall LGE patterns is 5.60 (95% CI: 3.44–9.10; Supporting Information, Figure S2B) without a significant heterogeneity between included studies ( $I^2 = 0.0\%$ ,  $P = 0.88$ ). Furthermore, OR of the midwall LGE pattern is 1.94 (95% CI: 1.23–3.06; Supporting Information, Figure S3A) compared with non-midwall LGE in NICM patients. Owing to the existence of significant heterogeneity between included studies ( $I^2 = 77.2\%$ ,  $P = 0.004$ ), we further conducted the subgroup analysis by mean LVEF with a cut-off point of 35%. In the subgroup with LVEF > 35%, the patients with midwall LGE retained a significant OR as compared with the patients with non-midwall LGE (OR = 2.06, 95% CI: 1.32–3.23; Supporting Information, Figure S3B), with decreased heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.687$ ).

**Figure 4** Forest plot of pooled OR for SCD or aborted SCD endpoint by the presence of left ventricular midwall LGE (A). Subgroup meta-analysis of pooled OR based on LVEF cut-off value of 35% (B). CI, confidence interval; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OR, odds ratio; SCD, sudden cardiac death.



**Table 4** The performance of left ventricular midwall late gadolinium enhancement, non-midwall late gadolinium enhancement, late gadolinium enhancement positive and late gadolinium enhancement negative in sudden cardiac death or aborted sudden cardiac death prediction in non-ischaemic dilated cardiomyopathy

Article	All patients (n)	Midwall LGE (n)		Positive non-midwall LGE patterns (n)		LGE positive (n)		LGE negative (n)	
		Events (n)	Total (n)	Events	Total (n)	Events (n)	Total (n)	Events (n)	Total (n)
Lehrke <i>et al.</i> (2010)	184	4	27	4	45	8	72	2	112
Halliday <i>et al.</i> (2018)	874	29	185	26	115	55	300	29	574
Shin <i>et al.</i> (2016)	365	23	163	17	98	40	261	4	104
Chimura <i>et al.</i> (2015)	175	17	114	1	8	18	122	0	53

LGE, late gadolinium enhancement.

## Sensitivity analysis

The overall effect size remained robust when each study was removed in turn (Supporting Information, *Figure S4*).

## Discussion

This meta-analysis summarized seven different published studies evaluating the prognostic value of LV midwall LGE in patients with NICM. The main findings are as follows. First, the presence of LV midwall LGE pattern could predict all-cause death, cardiovascular death endpoint, and SCD (or aborted SCD) events. Second, the presence of LV midwall LGE may be able to predict SCD or aborted SCD in patients with NICM irrespective of LVEF. Third, the LV midwall LGE pattern had an excellent negative predictive value, and the numbers of ICDs needed to prevent one major event in included studies are low. NICM patients with midwall LGE could benefit from primary prevention ICDs regardless of LVEF.

The histological basis for LV midwall LGE in dilated cardiomyopathy (DCM) is focal replacement fibrosis as a result of reparative microscopic scarring following myocyte death. This has been seen at autopsy in up to one-third of patients with DCM, a prevalence similar to that of midwall fibrosis on LGE-CMR.<sup>18</sup> Consistent with histopathological reports, our study reported the prevalence of LV midwall LGE pattern to be 30.8% in 1827 patients with NICM. Previous studies have indicated that NICM patients with midwall LGE had a higher ventricular stiffness index and more impaired ventriculoarterial coupling than other NICM patients.<sup>19</sup> Additionally, midwall LGE pattern may play an important role in the evaluation of reverse remodelling in NICM.<sup>20</sup>

Furthermore, several studies have reported the added prognostic value of LV midwall LGE in NICM. In the Gulati *et al.* study of 472 patients with NICM, the presence of midwall fibrosis had a 2.43-fold, 3.22-fold, and 4.61-fold increase in the risk of all-cause mortality, cardiovascular death, and the secondary composite of SCD or aborted SCD, respectively.<sup>15</sup> Additionally, Halliday *et al.* reported that the adjusted hazard ratio (HR) for NICM patients with linear midwall pattern were 1.70 (95% CI: 1.17–2.49;  $P = 0.006$ )

for all-cause mortality and 3.21 (95% CI: 1.82–5.66;  $P < 0.0001$ ) for SCD or aborted SCD in 874 patients.<sup>13</sup> Similarly, Leyva *et al.* included 97 patients with NICM undergoing CRT and found that midwall fibrosis could predict cardiovascular mortality (HR: 18.5; 95% CI: 3.93–87.3;  $P = 0.0002$ ).<sup>8</sup> In contrast, Shin *et al.* reported in a study of 365 patients that the midwall LGE pattern did not increase HR in the major arrhythmic events risk including sustained ventricular tachycardia, appropriate ICD or CRT-D intervention, ventricular fibrillation, and SCD ( $P = 0.74$ ) after adjusting for clinical variables including LVEF.<sup>9</sup> However, all these were single-centre studies with limited sample size. Moreover, the event rate in most previous studies such as those by Leyva *et al.* and Venero *et al.* was lower than 10%, suggesting that there may be insufficient data to accurately assess the prognostic value of midwall LGE. Therefore, a systemic review and meta-analysis was necessary to clarify the current indication on the prediction value by the presence of midwall LGE pattern.

Previously conducted meta-analyses have confirmed that the presence or quantitative burden of LGE in CMR could provide important prognostic information regarding all-cause mortality, cardiovascular mortality, ventricular arrhythmia, and SCD in NICM.<sup>21–25</sup> However, there were no recent meta-analyses exploring the prognostic value of specific midwall LGE pattern in NICM. Becker *et al.* summarized 34 studies and reported that the OR in NICM patients with LGE showed a 3.40-fold increase for cardiovascular mortality and a 4.52-fold increase for ventricular arrhythmic events as compared with those without LGE.<sup>20</sup> Our study indicated that the pattern of midwall LGE had a high prognostic value and that considerations should be given to the presence of LV midwall LGE in future risk stratification in NICM patients.

In addition, current studies have generally reported that the higher amount of fibrosis shown by CMR as LGE showed more advanced damage to myocyte and hence poorer prognosis. However, owing to technique limitation and very thin myocardium in NICM patients, it is hard to quantify the extent of fibrosis by LGE. Therefore, when we analysed the SCD predictive value on the basis of the presence of LGE patterns, we found that the LV midwall LGE patterns seem to have an independent association with the combined endpoint of SCD and aborted SCD, which indicated that the

location of LGE may be associated with SCD. Additionally, previous studies have indicated that LGE is not always irreversible fibrosis, and in some situations, LGE could regress. In the setting of inflammation, LGE could represent oedema. However, the 'reversible' LGE changes are generally associated with acute processes such as myocarditis and myocardial infarction, which are excluded from the current selected studies.

Risk stratification, especially in identifying SCD candidates among patients with NICM, remains inadequate and challenging in clinical practice. Not all SCDs can be prevented by ICDs, and an appropriate ICD therapy cannot be translated to lower all-cause mortality.<sup>26</sup> Currently, LVEF remains the main criterion used to identify high-risk patients for ICD implantation. Kadish *et al.* reported that LVEF had low sensitivity and low specificity for the prediction of SCD,<sup>27</sup> and indeed, only about 20% of patients with DCM who have ICDs for primary prevention subsequently received appropriate therapies during follow-up.<sup>28</sup> Therefore, it is important to find a better prognosticator for NICM. In our study, patients with midwall LGE had a similar proportion of SCD or aborted SCD endpoint in studies with mean LVEF  $\leq 35\%$  and  $>35\%$ , and the SCD or aborted SCD could be predicted by the presence of LV midwall LGE pattern in NICM patients regardless of LVEF. In addition, the numbers of ICDs required to prevent one major event based on the presence of LV midwall LGE were low, thereby implying that NICM patients with midwall LGE could benefit from primary prevention ICDs irrespective of their LVEF.

Our study has limitations. All included studies were single centred, and LGE-CMR protocols were not standardized. Additionally, all analyses performed were based on the presented data.

In conclusion, this meta-analysis showed that the presence of LV midwall LGE pattern is a significant predictor of all-cause mortality, cardiovascular mortality, and SCD or aborted SCD events in NICM patients. In particular, midwall LGE in NICM patients has an excellent negative predictive value and low NNT regardless of LVEF. The assessment of midwall LGE may improve the appropriateness of ICD implantation in patients with depressed ejection fraction by identifying a lower-risk group unlikely to benefit from ICD.

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## Acknowledgement

J.W. acknowledges support from the China Scholarship Council.

## Conflict of interest

All authors have no potential conflicts of interest in connection with the submitted article. All authors had access to the data and participated in the writing of the manuscript.

## Funding

This work was supported by grants from Sichuan province science and technology support grant, China (2012JZ0002), 1-3-5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC18013) and China Scholarship Council.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Forest plot of pooled OR for SCD or aborted SCD by the presence of left ventricular LGE.

**Figure S2.** Forest plot of pooled ORs for SCD or aborted SCD endpoints by the presence of left ventricular midwall LGE (A) and LV non-midwall LGE patterns (B) compared to the absence of LGE.

**Figure S3.** Forest plot of pooled ORs for SCD or aborted SCD endpoints by the presence of left ventricular midwall LGE compared to non-midwall LGE (A) and subgroup meta-analysis of pooled OR based on LVEF cut-off value of 35% (B).

**Figure S4.** Sensitivity analysis of the pooled OR for all-cause mortality (A) and for SCD or aborted SCD (B).



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