

# Prognostic value of late gadolinium enhancement in dilated cardiomyopathy patients

## A meta-analysis

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### ABSTRACT

**الأهداف:** تقييم أهمية الإنذار المبكر لزيادة فرصة ظهور العنصر الفلزي الجادليونيوم في المرضى الذين يعانون من تمدد وتوسع في عضلة القلب

**الطريقة:** قمنا بإجراء بحث في محركات البحث ومكتبة كوكرين وقاعدة بيانات Embase خلال الفترة من سبتمبر إلى ديسمبر 2012م. بمستشفى الشعب، وخان، الصين المرضى تمدد عضلة القلب التي يتواجد بها العنصر الفلزي الجاد. قمنا بدراسة العوامل الإكلينيكية التي تؤدي إلى الموت، كموت القلب والأوعية الدموية وذلك بسبب توقف وإجهاض القلب المفاجئ والفشل في علاج السكتة القلبية بالمستشفيات. وبعد الملاحظة الدقيقة لتحليل أشعة ميتا التي أجريت لحساب خلايا الدم المتجمدة بنسبة 95% للفترات الثقة والإنذار لعلاج المرضى السلبيين التي ثبت وجود العنصر الفلزي لديهم.

**النتائج:** أثبتت نتائج الدراسات للمرضى الذين يعانون من تمدد أو توسع عضلة القلب أنه لدى أجسام المرضى فرصة لزيادة العنصر الفلزي الجاد لينيوم المتأخر ومرتبطة ارتباطاً وثيقاً بالوفيات العالمية بأمراض القلب والأوعية الدموية (pooled OR: 2.67, 95% CI: 1.12 to 6.35; p=0.03)، توقف وإجهاض القلب المفاجئ (pooled OR: 5.26, 95% CI: 1.57 to 17.55; p=0.007)، وفشل علاج القلب في المستشفيات (pooled OR: 3.91, 95% CI: 1.99 to 7.69; p<0.001).

**خاتمة:** إن لدى مرضى القلب فرصة لزيادة العنصر الفلزي الجادليونيوم والذي يكون مرتبطاً ارتباطاً وثيقاً بظروف القلب والأوعية الدموية والإجهاض SCD وفشل علاج تمدد أو توسع عضلة القلب بالمستشفيات وأنه من المحتمل جداً موت المريض أثناء إنقاذه من تلك الأمراض.

**Objectives:** To evaluate the prognostic value of late gadolinium enhancement (LGE) in dilated cardiomyopathy (DCM) patients.

**Methods:** We searched PubMed, MEDLINE, the Cochrane library and EMBASE databases from September to December 2012 in the Renmin Hospital of Wuhan University, Wuhan, China for studies of LGE in DCM patients. We extracted the clinical outcomes (all-cause mortality, cardiovascular mortality, sudden cardiac death [SCD], aborted SCD, heart failure hospitalization) after carefully reviewed. A meta-analysis was performed to calculate pooled odds ratios (OR) with 95% confidence intervals (CIs) for prognostic outcomes in LGE positive versus LGE negative patients with DCM.

**Results:** Five studies for 545 DCM patients were contained in this meta-analysis. The results showed LGE positive patients was significantly associated with higher cardiovascular mortality (pooled OR: 2.67; 95% CI: 1.12-6.35; p=0.03), aborted SCD (pooled OR: 5.26; 95% CI: 1.57-17.55; p=0.007), and heart failure hospitalization (pooled OR: 3.91; 95% CI: 1.99-7.69; p<0.001).

**Conclusion:** Late gadolinium enhancement during cardiac MRI is significantly associated with cardiovascular mortality, aborted SCD and heart failure hospitalization in DCM patients. The LGE can be a potential stratification tool to predict the risk of cardiac events among patients with DCM.

*Saudi Med J 2013; Vol. 34 (7): 719-726*

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Received 14th April 2013. Accepted 9th June 2013.

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**D**ilated cardiomyopathy (DCM) is a primary myocardial disease which is characterized by enlarged heart chamber, single and/or both ventricular systolic dysfunction.<sup>1</sup> It is a severe heart disease which endangers people's health and usually identified at a late stage with multiple complications and adverse symptoms.<sup>2</sup> The incidence of DCM varies from 5 to 8/100,000/year, with a prevalence of 36 to 40/100,000/year in adults in Western countries.<sup>3</sup> Despite the routine use of angiotensin-converting enzyme (ACE) inhibitors,  $\beta$  blockers and diuretics in patients with DCM, the prognosis is still poor with a considerable mortality rate of 5-10% per year.<sup>3,4</sup> Sudden cardiac death (SCD) maybe the first manifestation of DCM that constitutes a considerable 30-50% of all deaths, due to rapid ventricular tachycardia (VT) or ventricular fibrillation (VF) more often.<sup>5,6</sup> Several clinical predictors, such as advanced age, QRS duration, QT interval dispersion, heart rate variability, fragmented QRS, natriuretic peptides are associated with an adverse prognosis in DCM patients.<sup>7,8</sup> However, risk stratification remains challenging because most trials of risk stratification for patients with DCM are unpowerful and non-randomized. Thus, better risk stratification prognostic factors are needed to be identified, and allowed earlier interventions in high-risk patients. Cardiac magnetic resonance (CMR) imaging is a non-invasive technique to assess myocardial morphology, structure and function.<sup>9</sup> The late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) imaging is originally used for the assessment of myocardial viability in myocardial infarction, subsequent studies reported LGE present in multiple ischemic or nonischemic cardiac diseases.<sup>10-12</sup> In addition to its diagnostic value, LGE-CMR has shown promising results in risk assessment in patients with cardiomyopathies. Recently, the prognostic value of LGE in clinical outcomes for hypertrophic cardiomyopathy has also been reviewed.<sup>13</sup> The prognostic value of the LGE in DCM patients has been assessed by several studies, but the findings have remained controversial and systematic review has not been performed. Thus, we conducted this meta-analysis to evaluate the prognostic value of LGE in patients with DCM.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

**Methods. Literature retrieval.** The PubMed, Medline, the Cochrane library and Embase databases were searched independently by 2 reviewers using the terms "magnetic resonance imaging", "MRI", "cardiac magnetic resonance", "CMR", "late gadolinium enhancement", "LGE", "delayed enhancement", "DE", "late enhancement", "LE", "Late gadolinium hyper-enhancement", "LHE", "contrast enhanced", "CE" and "dilated cardiomyopathy". The search has no country, language, race, or publication year limit. To identify any additional relevant studies, references cited by the retrieved studies were also searched.

**Inclusion/exclusion criteria.** Studies complying with the following criteria were enrolled: 1) cardiac magnetic resonance was performed in DCM patients; 2) the selected clinical outcomes(all-cause mortality, cardiovascular mortality, SCD, aborted SCD, heart failure hospitalization) were recorded in DCM patients; 3) the correlation between LGE and clinical outcomes of DCM patients explored; 4) sufficient information allows estimation of pooled odds ratios (ORs) and 95% confidence intervals (CIs). Studies were considered ineligible if: 1) the total patients were less than 20; 2) the patients underwent the cardiac resynchronization therapy or cardiac resynchronization therapy defibrillator therapy; 3) the same study population was assessed in more than 1 report(in this case, the study with the most details and / or the study published the most recently was chosen); 4) the selected clinical outcomes cannot be extracted.<sup>14</sup>

**Data extraction and validity assessment.** Study characteristics were collected, which include first author, study year, study design, number of patients, mean age, gender distribution, the New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), medication history, length of follow-up, clinical outcomes of all-cause mortality, cardiovascular mortality, SCD, aborted SCD, heart failure hospitalization. The 2 primary reviewers independently extracted data from each study. The exacted data were reviewed by one reviewer, disagreements were compromised and consensus were reached by discussions with a third reviewer.

**Statistical analysis.** We used Review Manager 5.0 software to perform the data analysis. The Cochrane Q statistic and inconsistency ( $I^2$ ) statistic was calculated to assess heterogeneity. For heterogeneity, we consider  $I^2$  values of 25 as low, 50 - moderate, and 75% - high.<sup>15</sup> If the  $p$ -value of heterogeneity tests was  $>0.1$  or  $I^2 <50\%$ , the fixed effect analysis of the Mantel-Haenszel model was chosen to calculate the pooled OR and its

corresponding 95% CI.<sup>16</sup> Otherwise, the random effect model based on the DerSimonian and Laird estimator was used.<sup>17</sup> A funnel plot was generated to evaluate the study bias. A  $p < 0.05$  was considered statistically significant.

### Results. Study selection and baseline characteristics.

The primary search retrieved 593 studies from PubMed, MEDLINE, the Cochrane library, EMBASE databases (Figure 1). After careful reviews, 31 studies were eligible for the inclusion criteria in this meta-analysis. Twenty-five studies which did not report the information regarding clinical outcomes (all-cause mortality, cardiovascular mortality, sudden cardiac death, heart failure hospitalization) were excluded. The adverse clinical outcomes could not be extracted in one study,<sup>18</sup> another 2 literature,<sup>19,20</sup> studied the patients with dilated cardiomyopathy after implantable cardiac defibrillator or cardiac resynchronization therapy. At last, 5 remaining studies with a total of 545 DCM patients (ranging from 32-184 patients per study) were identified in this systematic review and meta-analysis. The inclusion and exclusion criteria, quantity control and primary endpoints of these 5 studies are summarized in Table 1. All the DCM patients of the 5 studies were diagnosed according to World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) criteria.<sup>21</sup> The CMR was performed on a 1.5 T clinical scanner with 6-8 mm section thickness, and the LGE images were acquired 8-20 minutes after intravenous gadolinium-diethylenetriaminepentaacetate (DTPA) 0.1-0.2 mmol/kg.

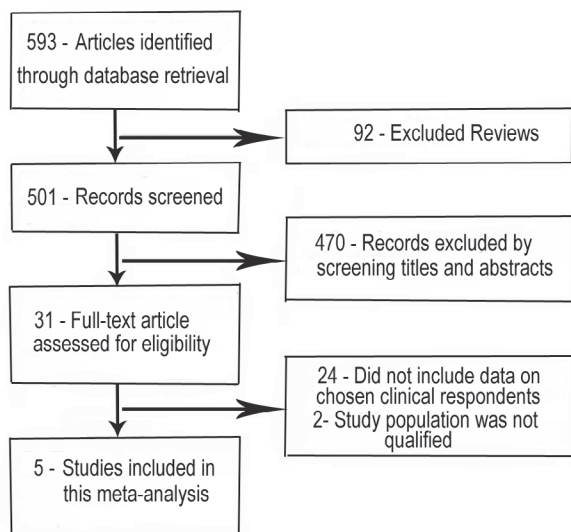
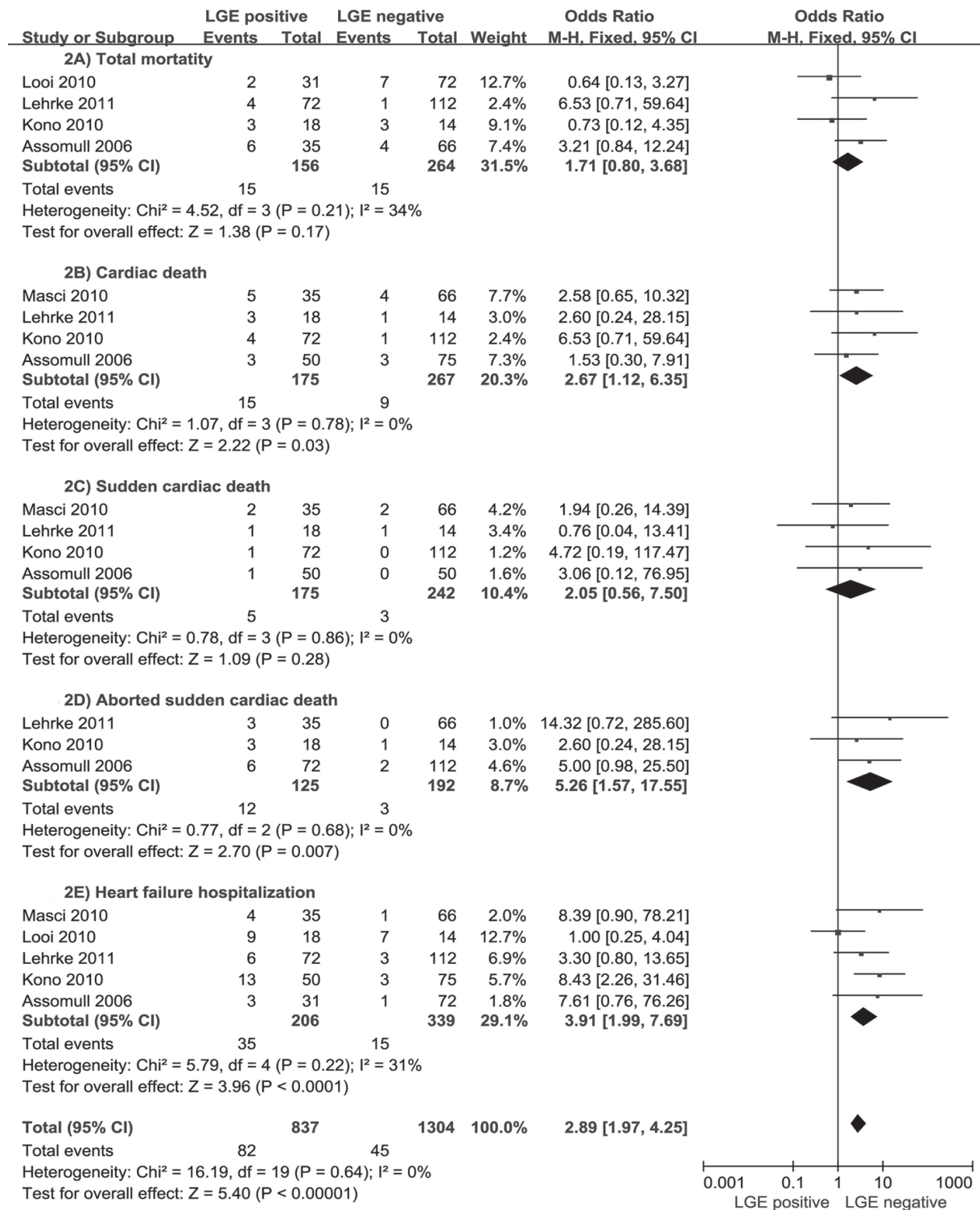


Figure 1 - Flowchart of the study selection.

**Clinical outcome analysis.** The average follow-up period of all 5 studies is 1.82 years. The cardiovascular mortality and sudden cardiac death data can be extracted in all 5 studies,<sup>8,22-25</sup> whereas the study by Kono<sup>24</sup> did not mention the all-cause mortality, likewise, the study by Masci<sup>23</sup> showed no sign of all-cause mortality and aborted SCD, and also Looi et al<sup>25</sup> did not mention the clinical outcomes such as cardiac death, SCD, and aborted SCD. Assomull et al<sup>22</sup> demonstrated that LGE positive patients had a significantly higher incidence of the all-cause mortality or hospitalization for cardiovascular causes (hazard ratio: 3.4; 95% CI: 1.4- 8.7;  $p < 0.01$ ) with a higher incidence of SCD/VT (hazard ratio: 5.2; 95% CI: 1.0-26.9;  $p = 0.03$ ). Thus, the study by Kono<sup>24</sup> suggested that no significant differences exist in the LGE positive and LGE negative groups regarding the survival rates of patients with DCM. Similarly, Lehrke<sup>8</sup> observed a trend towards higher cardiac mortality among LGE positive patients, but he failed to reach statistical significance perhaps due to the small total number ( $p = 0.08$ ). The clinical outcomes extracted from these studies for this meta-analysis are shown in Table 2. The meta-analysis indicated that LGE positive patients had a relatively higher all-cause mortality. However, this effect was not statistically significant (pooled OR: 1.71; 95% CI: 0.80-3.68;  $p = 0.17$ ) (Figure 2A). This analysis also showed that LGE positive was significantly associated with higher cardiovascular mortality in DCM patients (pooled OR: 2.67; 95% CI: 1.12-6.35;  $p = 0.03$ ) (Figure 2B). The result demonstrated LGE positive patients with DCM had a relatively higher risk of SCD, but the correlation was not statistically significant (pooled OR: 2.05; 95% CI: 0.56-7.50;  $p = 0.28$ ) (Figure 2C). Also, the result revealed that LGE positive was significantly associated with higher risk of aborted SCD (pooled OR: 5.26; 95% CI: 1.57-17.55;  $p = 0.0007$ ), and heart failure hospitalization (pooled OR: 3.91, 95% CI: 1.99-7.69;  $p < 0.001$ ) (Figure 2D, & Figure 2E). The LGE positive was significantly relevant with total adverse clinical outcomes (pooled OR: 2.89; 95% CI: 1.97-4.25;  $p < 0.001$ ). The pooled OR and 95% CI of adverse clinical outcomes are summarized in Table 3. Low heterogeneity was detected in the studies about all-cause mortality. In the sensitivity analysis, we removed one study<sup>24</sup> with relatively long time follow-up period and small amounts of DCM population, the heterogeneity was not found ( $p = 0.59$ ,  $I^2 = 0\%$ ). Moderate heterogeneity was detected in the studies about heart failure hospitalization, if the study described above is removed, the heterogeneity was not found ( $p = 0.60$ ,  $I^2 = 0\%$ ). In the final analysis, only 5 studies were included. Thus, we did not perform the funnel plot asymmetry test.



**Figure 2** - Forrest plot and pooled odds ratio for adverse clinical outcomes. The late gadolinium enhancement (LGE) positive by MRI predicts: A) total mortality, B) cardiac death, C) sudden cardiac death, D) aborted sudden cardiac death, and E) heart failure hospitalization.

**Table 1** - Studies included in the analysis in a study conducted at the Renmin Hospital of Wuhan University, Wuhan, China.

Study	Year	Inclusion criteria	Exclusion criteria	Quantity control	Primary endpoints
Lehrke <sup>8</sup>	2011	Referred to the Cardiomyopathy Center at the University Hospital Heidelberg	Patients initially diagnosed as having dilated cardiomyopathy (DCM) displaying a subendocardial or transmural pattern of late enhancement suggestive of myocardial infarction were excluded. Patients with a normal left ventricular ejection fraction (LVEF) on cardiac magnetic resonance (CMR) (>55%)	The presence and extent of late enhancement were evaluated by 2 independent observers experienced in contrast-enhanced (CE)-CMR, who were blinded to clinical data and outcome.	Cardiac death, hospitalization for decompensated heart failure, or appropriate implantable cardioverter defibrillator discharge
Assomull <sup>22</sup>	2006	From consecutive referrals from centers in southeast England	Patients with clinical evidence of left ventricular damage caused by coronary artery disease (CAD) with a normal CMR-derived ejection fraction (EF [>56%]), presence of any contraindications to CMR, significant valvular disease, hypertrophic cardiomyopathy	The late gadolinium enhancement (LGE) was assessed visually, and the volume was measured by manual planimetry by 2 independent readers blinded to all patient details.	Composite of all-cause mortality or hospitalization for a cardiovascular event
Masci <sup>23</sup>	2010	Nonischemic dilated cardiomyopathy patients without (stage B of heart failure [HF]) or with a history of mild HF symptoms (stage C of HF, New York Heart Association [NYHA] classes I-II)	Evidence of myocardial infarction or revascularization underwent invasive coronary angiography, active myocarditis, congenital heart disease, hypertrophic cardiomyopathy, infiltrative disease, moderate-to-severe valvular heart disease, substance abuse, untreated hypertension or any contraindication to CMR	An experienced cardiologist blinded to CMR and clinical data	The composite event of cardiac death and hospitalization
Kono <sup>24</sup>	2010	DCM who were referred to Hyogo Brain and Heart Center	Patients with persistent arrhythmias, presence of any contraindications for CMR, ischemic or hypertrophic cardiomyopathy, infiltrative heart disease, significant valvular disease	Cardiac MRI scans were visually evaluated on a commercially available workstation by a radiologist who was blinded to the clinical information of the patients	All-cause death and hospitalization for a cardiovascular event
Looi <sup>25</sup>	2010	DCM patients with (A) a clinical presentation of heart failure (B) an echocardiogram demonstrating impaired (LVEF<50%) (C) successfully completed a CE-CMR	Patients with (A) significant coronary artery disease (>50% diameter luminal stenosis in any coronary artery) documented on angiography (B) significant valvular disease (C) cardiomyopathy of known cause including hypertrophic, alcohol- or chemotherapy induced or infiltrative myopathies	Areas of LGE were defined as subendocardial, mid-myocardial or transmural on visual analysis by a consensus of 2 independent cardiologists	Death, infarction, ventricular arrhythmias or rehospitalization

**Table 2** - Adverse clinical outcomes of the included studies.

Study	Total	LGE+ (n)	Follow-up, (year)	All-cause mortality		All cardiac deaths		Sudden cardiac death		Aborted sudden cardiac death		Heart failure hospitalization	
				LGE+	LGE-	LGE+	LGE-	LGE+	LGE-	LGE+	LGE-	LGE+	LGE-
Lehrke <sup>8</sup>	184	72	1.80	4	1	4	1	1	0	6	2	6	3
Assomull <sup>22</sup>	101	35	1.80	6	4	5	4	3	2	3	0	3	1
Masci <sup>23</sup>	125	50	1.08	NA	NA	3	3	1	0	NA	NA	13	3
Kono <sup>24</sup>	32	18	2.57	3	3	3	1	1	1	3	1	9	7
Looi <sup>25</sup>	103	31	1.86	2	7	NA	NA	NA	NA	NA	NA	3	1

LGE - late gadolinium enhancement

**Table 3** - Pooled odds ratios (OR) of adverse clinical outcomes.

Adverse clinical outcomes	Pooled OR	95% confidence interval	P-value
Total mortality	1.71	0.80-3.68	1.38
Cardiac death	2.67	1.12-6.35	0.03
Sudden cardiac death (SCD)	2.05	0.56-7.50	0.28
Aborted SCD	5.26	1.57-17.55	0.007
Heart failure hospitalization	3.91	1.99-7.69	<0.001
Total adverse clinical outcomes	2.89	1.97-4.25	<0.001

**Discussion.** This meta-analysis combining results from 5 studies of 545 patients highlighted that LGE positive in DCM patients was significantly associated with a higher cardiovascular mortality (pooled OR: 2.67, 95% CI: 1.12-6.35;  $p=0.03$ ), aborted SCD (pooled OR: 5.26; 95% CI: 1.57-17.55;  $p=0.0007$ ) and heart failure hospitalization (pooled OR: 3.91; 95% CI: 1.99-7.69;  $p<0.001$ ) (Table 3, Figure 2A-2E).

Why is LGE can be present in patients with DCM? First of all, the definition of LGE needs to be clarified. Gadolinium is a rare-earth element with low molecular weight (<1000 Da). It is hydrophilic that can penetrate into the extracellular space and increase in water-containing tissues easily.<sup>26</sup> Myocardial fibrosis or edema could lead to gadolinium accumulation. Thus, the focus of myocardial fibrosis can accumulate gadolinium without delay and can be reflected by LGE imaging. The LGE has multiple morphological types:<sup>27</sup> myocarditis typically leads to a spotty-focal occurrence of LGE that frequently disappears over time (reversible nature of LGE). Increased left ventricular wall stress in dilated cardiomyopathy typically leads to a streaky-like midwall LGE predominantly located in the interventricular septum or at the hinge points of the right ventricle. In patients with DCM, the renin-angiotensin-aldosterone system (RAAS) is activated and several neurohumoral factors such as angiotensin-II (Ang-II), endothelin-1 (ET-1), norepinephrine (NE), aldosterone, fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), and transforming growth factor-alpha (TGF-alpha), and type I/III collagen increase at the protein level, thus the myocardial fibrosis can be observed pathologically.<sup>28,29</sup>

The LGE is closely related to clinical outcomes in DCM patients. Wu et al<sup>9</sup> studied NIDCM patients with LVEF <35% and an ICD implantation found that patients with LGE had an 8 times greater risk of experiencing the primary outcome. Sasaki et al<sup>30</sup> concluded that mid-wall LGE was an indicator to predict SCD/VT in an electrophysiological study. The presence of LGE is also closely related with adverse clinical outcomes. One important reason could be the promotion of re-entry mechanisms by cardiac focal fibrosis.<sup>8</sup> A study<sup>31</sup> showed that approximately 30% of patients with DCM have midwall fibrosis observed LGE. Cardiac fibrosis can lead to ventricular remodeling such as LV stiffness, reduced LV compliance, and diastolic and systolic function impairment, resulting in cardiac output decrease and heart failure exacerbation.<sup>23</sup> Basaran et al<sup>32</sup> has recently reported an association between the extent of fibrosis revealed by LGE in DCM patients and intra-left ventricular dyssynchrony. Similarly, Alter

et al<sup>33</sup> demonstrated that the occurrence of LGE in non-ischaemic dilated cardiomyopathy is associated with increased LV wall stress and mass. Therefore, more severe cardiac fibrosis, worse cardiac function in DCM patients. Other potential mechanisms include: pathogens exposure, microvascular ischaemia or edema, abnormal immune and genetic factors.<sup>8</sup>

The iron overload in the cardiac muscle can be reversed, indicates that any such fibrosis would be reversible, which is one compensatory mechanisms occurred in injured heart muscle.<sup>34</sup> Also, there are some other reversible causes of LGE such as transient myocarditis or increased ventricular wall stress that leads to prolonged interstitial contrast agent deposition or an impaired redistribution into the vasculature, which could explain the CMR findings that LGE has lower sensitivity and LGE has multiple morphological types, as we mentioned above. The hypothesis does not hold true in the pathological entities, which may be recognized by multiple diffuse necrosis and could be the cause of myocarditis. Our findings also revealed that LGE imaging may have important applications in the clinical management of DCM patients. The DCM has great advantage in detecting small subendocardial infarction, which raises the patient's risk of cardiac event. Leong et al<sup>35</sup> demonstrated an inverse correlation between the LGE extent and improvement in LVEF in DCM patients. Primary prevention LGE positive NIDCM patients may have a similar risk for appropriate ICD therapy to ICM patients.<sup>36</sup> Thus, appropriate medical therapy such as medication therapy, device-based therapy (cardiac resynchronization therapy or cardiac resynchronization therapy defibrillator) is needed for the patients with DCM according to LGE imaging to prevent cardiac events. In addition, LGE-CMR can reflect cardiac function and disease etiology with unique image quality.<sup>19</sup> We can also be inspired by this finding that more high quality imaging technique are helpful for the prognostic stratification of patients with DCM.

Some inherent limitations should be considered in this meta-analysis. Firstly, there has been a few studies with relatively small amounts of patients analyzed the precise value of LGE by CMR in the clinical outcomes of DCM patients, which can be reflect by the width of the pooled OR and confidence intervals. Secondly, some other traditional risk factors of DCM patients may influence the clinical outcome of the DCM patients, adjusted OR taking into account the risk factors could not be calculated due to the raw data. Finally, because of renal toxicity of gadolinium contrast agents, DCM patients with chronic renal failure were not analyzed in included studies, that may hinder the interpreting of our results.

In conclusion, the findings of this study support that LGE by CMR could be used as a novel risk-stratification tool measuring the clinical endpoints in dilated cardiomyopathy patients, it can be independent of QRS duration, NYHA class, LVEF, and mechanical dyssynchrony and so on. The LGE may prove more promising and can be applied in the patients clinically with better user comfort and less adverse reaction. However, more larger, prospective trials with longer follow-up period are needed to confirm these findings and to evaluate the prognostic value of LGE in DCM patients.

**Acknowledgment.** *The authors gratefully acknowledge all the colleagues working in the Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, China for their help and kind support. Special thanks to Pro. Rongjian Li and Mr. Long Cheng for their help during the language proofing process.*

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