Association of myocardial fibrosis detected by late gadolinium-enhanced MRI with clinical outcomes in patients with diabetes: a systematic review and meta-analysis

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INTRODUCTION

Diabetes is becoming a global healthcare problem, and it is estimated that there will be 693 million individuals with diabetes by 2045.¹ Patients with diabetes have a higher prevalence of ischaemic myocardial fibrosis and non-ischaemic myocardial fibrosis than their non-diabetic counterparts, and the mechanism has been confirmed extensively.²–⁵ The phenotype of unrecognised ischaemic myocardial fibrosis in patients with diabetes was well studied and was associated with 4–8 folds increase in the risk of major adverse cardiac events (MACEs).²–³ However, even without myocardial ischaemia, hyperglycaemia, oxidative stress and inflammation may lead to diffuse interstitial and non-ischaemic myocardial fibrosis in patients with diabetes.⁶–⁸ In addition, diffuse interstitial myocardial fibrosis can increase the risk of non-ischaemic myocardial fibrosis, and was associated with increased risk of left ventricular (LV) dysfunction in patients with diabetes.⁹ ¹⁰ However, non-ischaemic myocardial fibrosis, may be a biomarker for risk stratification, has not been systematically characterised.⁹ ¹¹

ABSTRACT

Objective This meta-analysis assessed the associations of myocardial fibrosis detected by late gadolinium-enhanced (LGE-MRI) with the risk of major adverse cardiac and cerebrovascular events (MACCEs) and major adverse cardiac events (MACEs) in patients with diabetes.

Design Systematic review and meta-analysis reported in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology statement.

Data sources We searched the Medline, Embase and Cochran databases for studies published up to 27 August 2021.

Eligibility criteria Prospective or retrospective cohort studies were included if they reported the HR and 95% CIs for MACCEs/MACEs in patients with either type 1 or 2 diabetes and LGE-MRI-detected myocardial fibrosis compared with patients without LGE-MRI-detected myocardial fibrosis and if the articles were published in the English language.

Data extraction and synthesis Two review authors independently extracted data and assessed the quality of the included studies. Pooled HRs and 95% CIs were analysed using a random effects model. Heterogeneity was assessed using forest plots and I² statistics.

Results Eight studies with 1121 patients with type 1 or type 2 diabetes were included in this meta-analysis, and the follow-up ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE-MRI was associated with an increased risk for MACCEs (HR: 2.58; 95% CI 1.42 to 4.71; p=0.002) and MACEs (HR: 5.28; 95% CI 3.20 to 8.70; p<0.001) in patients with diabetes. Subgroup analysis revealed that ischaemic fibrosis detected by LGE was associated with MACCEs (HR 3.80, 95% CI 2.38 to 6.07; p<0.001) in patients with diabetes.

Conclusions This study demonstrated that ischaemic myocardial fibrosis detected by LGE-MRI was associated with an increased risk of MACCEs/MACEs in patients with diabetes and may be an imaging biomarker for risk stratification. Whether LGE-MRI provides incremental prognostic information with respect to MACCEs/MACEs over risk stratification by conventional cardiovascular risk factors requires further study.

Strengths and limitations of this study

- This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology statement.
- All included studies were not community-based epidemiology research and came from developed countries.
- Reduced left ventricular ejection fraction and non-ischaemic subgroup analyses were not performed due to the limited number of related studies.

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Among detectors of myocardial fibrosis, late gadolinium-enhanced MRI (LGE-MRI) is the most reliable tool for identifying and quantifying focal myocardial fibrosis in vivo and allows discrimination between ischaemic and non-ischaemic fibrosis without ionising radiation.11–13 LGE-MRI, a promising technique, can provide more histological information than unenhanced cardiac MRI to illuminate the complex pathophysiological pathways of myocardial viability.3 While LGE-MRI is limited by its sensitivity and accuracy for detection of diffuse myocardial fibrosis, the role of T1-mapping MRI technique in quantifying myocardial fibrosis has been validated.12 13 Furthermore, recent guidelines suggested that LGE-MRI-detected myocardial fibrosis status, follow-up duration, outcome and HR (95% CI). Additionally, we extracted the adjusted HR if the study reported the HR with adjustment models.

This may highlight the role of LGE-MRI in the risk stratification of patients with diabetes.

Methods
This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology statement.22 23

Data sources and searches
We searched the Ovid Medline, Ovid Embase and Ovid Cochrane Library databases to find eligible studies published up to 27 August 2021. The search strategy included the following keywords: “diabetes”, “diabetes mellitus”, “MR”, “cardiac magnetic resonance”, “CMR”, “gadolinium”, “LGE”, “prognosis”, “diagnosed”, “predictor”, and “death”. The details of the search strategy used for Ovid are available in online supplemental tables S1–S3. In addition, only articles published in peer-reviewed journals and published in the English language were included.

Study selection
All articles were independently screened by two reviewers (ZY, RX), and any disagreement was resolved by consensus. The inclusion criteria were as follows: the design was a prospective or retrospective cohort study; the populations were patients with diabetes, and exposure to myocardial fibrosis was detected by LGE-MRI; the outcomes used composite endpoints including all-cause mortality, cardiac and cerebrovascular disease, late coronary revascularisation, and hospitalisation for unstable angina; the study reported the HR and 95% CIs and had ≥12 months of follow-up. We excluded reviews, abstracts, animal studies, case reports and cross-sectional studies. Additionally, if the cases were reported more than once, we included the study with the most comprehensive information. The reviewers independently screened the titles first, then the abstracts, and finally the full texts.

Data extraction and quality assessment
We extracted the following data from each included study: author, year of publication, sample size, study design, age, LGE-MRI-detected myocardial fibrosis status, follow-up duration, outcome and HR (95% CI). Additionally, we extracted the adjusted HR if the study reported the HR with adjustment models.

All of the included studies were prospective or retrospective cohort designs, and we used the Newcastle Ottawa Scale (NOS) to judge the quality of the studies, as this tool is usually used for evaluating the quality of cohort studies in meta-analyses.24 25 The scale uses a maximum of nine points involving three factors: patient selection (0–4 points), comparability (0–2 points) and outcome (0–3 points).26 We categorised the quality of studies as low (0–3 scores), moderate (4–6 scores) and high (7–9 scores).

Data synthesis and analysis
In this meta-analysis, the outcome measure was the prevalence of future adverse cardiac and/or cerebrovascular events among diabetes patients with LGE-MRI-detected myocardial fibrosis compared with those without LGE-MRI-detected myocardial fibrosis. We defined the primary endpoint as MACCEs, including myocardial infarction (MI), all-cause mortality, coronary and carotid revascularisation, heart failure, ventricular arrhythmias, unstable angina, cardiac and cerebrovascular death, and cerebrovascular disease. The secondary endpoints were MACEs, including all-cause mortality, cardiac death, MI, heart failure, unstable angina and ventricular arrhythmias. Additionally, the pattern of myocardial fibrosis was classified as ischaemic fibrosis or non-ischaemic fibrosis as described previously.3

We pooled the adjusted HRs with 95% CIs using a random effects model. In addition, we calculated the annualised event rates by dividing the total events by the median follow-up periods. To analyse the heterogeneity of the included studies, we used forest plots and the I² statistic.27 We assigned I² values of 0–25%, 25–50%, ~50% and 75–100% for low, medium and high heterogeneity of studies, respectively. Considering the heterogeneity of the included studies, we conducted sensitivity analyses by omitting one article to assess the influence of a single study. In particular, subgroup analyses were performed by outcome and the pattern of myocardial fibrosis. Additionally, a funnel plot was used to assess the publication bias of the included studies.28 The analyses were performed with Stata V.12 (StataCorp). P values were two sided, with a level of 0.05 considered significant.
Results

Patient and public involvement
No patient involved.

Literature search
Based on the selection strategy, we found 4520 citations. Of these, 349 duplicate studies were excluded. After screening the title and abstract, 14 articles remained for assessment of the full text. Six studies were excluded for the following reasons: studies without our outcome of interest, study populations did not meet our inclusion criteria, and studies did not report the HR. Ultimately, eight studies fulfilled our inclusion criteria and were included in this meta-analysis (figure 1).

Study characteristics
In aggregate, 8 studies were analysed, including a total of 1121 patients with diabetes (median age ranging from 52 to 67; 67% were men) who underwent LGE-MRI and whose follow-up duration ranged from 17 to 70 months. Across the 8 studies, 6 articles reported the duration of diabetes, and the mean duration of diabetes was 15 years. A total of 6 studies reported the LV ejection fraction, and the mean LV ejection fraction was 57.78%. The presence of LGE-MRI-detected myocardial fibrosis was evaluated by visual analysis in six studies. All of the included studies reported multiple clinical outcomes. The main characteristics of the included articles are shown in table 1.

Among the eight selected studies, six studies (75%) were conducted in a single centre (Germany, n=2; USA, n=2; Japan, n=2), and two studies were performed in multiple centres (USA, n=1; Europe, n=1). Five articles (62.5%) reported adjusted HR. Seven studies reported patients with ischaemic fibrosis, and the remaining one studies reported patients with ischaemic and non-ischaemic fibrosis.

Of the 8 eligible studies, 7 received NOS scores between 7 and 9, and the overall mean NOS score was 7.5. Overall, the aforementioned analysis showed that the included articles had high quality (table 1). Among the identified studies, there was no risk of publication bias according to a visual analysis of the funnel plot (online supplemental figure S1).

Prevalence of LGE-MRI-detected myocardial fibrosis and annualised event rates
Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE-MRI ranged from 15% to 62%, and the prevalence of LGE-MRI-detected myocardial fibrosis in the total sample was 38.09% (n=427). Furthermore, a total of 164 events occurred in the diabetes group (n=1121) during the median follow-up of 3.4 years. Patients with diabetes had annualised event rates for MACCEs of 4.3%.

Additionally, 3 studies reported a total of 301 patients with diabetes, and 19.27% (n=58) of patients with diabetes had LGE-MRI-detected myocardial fibrosis. Twenty-seven events occurred in these diabetic patients with LGE—MRI-detected myocardial fibrosis over a median follow-up of 3.9 years. The annualised event rate of patients with diabetes and LGE-MRI-detected myocardial fibrosis was 11.94%.

Major adverse cardiac and cerebrovascular events and major adverse cardiac events
A total of 8 studies reported the outcome of MACCEs or MACEs, and the presence of myocardial fibrosis detected...
Table 1  Description of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Journal</th>
<th>Patients</th>
<th>HbA1c, %</th>
<th>LGE definition</th>
<th>DM (type)</th>
<th>Mean age (years)</th>
<th>Duration of diabetes (years)</th>
<th>LVEF (%)</th>
<th>Follow-up duration (months)</th>
<th>Male</th>
<th>LGE(+)</th>
<th>Total events</th>
<th>Adjusted HR</th>
<th>Fibrosis type</th>
<th>Type design</th>
<th>Outcome</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertheau et al 2016</td>
<td>Eur Radiol</td>
<td>61</td>
<td>7.2 (6.5–7.9)</td>
<td>Visual</td>
<td>1 and 2</td>
<td>67.5 (56.7–71.8)</td>
<td>19 (14–28)</td>
<td>56 (46–61)</td>
<td>70 (57–72)</td>
<td>31</td>
<td>17</td>
<td>8</td>
<td>Yes</td>
<td>Ischaemic</td>
<td>Prospective, single centre</td>
<td>MACCES 7</td>
<td></td>
</tr>
<tr>
<td>Heydari et al 2016</td>
<td>Circ Cardiovasc Imaging</td>
<td>173</td>
<td>7.9±1.8</td>
<td>2 SD</td>
<td>NR</td>
<td>61.7±11.9</td>
<td>NR</td>
<td>51.8±17.6</td>
<td>34.8±30</td>
<td>109</td>
<td>88</td>
<td>21</td>
<td>No</td>
<td>Ischaemic</td>
<td>Prospective, single centre</td>
<td>MACCES 7</td>
<td></td>
</tr>
<tr>
<td>Elliott et al 2019</td>
<td>Diabetes Care</td>
<td>120</td>
<td>NR</td>
<td>Visual</td>
<td>1 and 2</td>
<td>52±13</td>
<td>17±11</td>
<td>63±9</td>
<td>46 (33–64)</td>
<td>65</td>
<td>23</td>
<td>19</td>
<td>Yes</td>
<td>Ischaemic</td>
<td>Prospective, two centres</td>
<td>MACES 9</td>
<td></td>
</tr>
<tr>
<td>Yoon et al 2013</td>
<td>Eur Radiol</td>
<td>120</td>
<td>7.4±1.5</td>
<td>Visual</td>
<td>2</td>
<td>67±9</td>
<td>11±11</td>
<td>63±6</td>
<td>27 (7–112)</td>
<td>83</td>
<td>18</td>
<td>10</td>
<td>No</td>
<td>Ischaemic</td>
<td>Retrospective, single centre</td>
<td>MACES 7</td>
<td></td>
</tr>
<tr>
<td>Giusca et al 2016</td>
<td>Eur Heart J Cardiovasc Imaging</td>
<td>328</td>
<td>NR</td>
<td>Visual</td>
<td>NR</td>
<td>67±11</td>
<td>NR</td>
<td>57.7±11.6</td>
<td>35 (23–51.6)</td>
<td>250</td>
<td>176</td>
<td>26</td>
<td>Yes</td>
<td>Ischaemic and nonischaemic</td>
<td>Prospective, multicentre</td>
<td>MACES 8</td>
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<tr>
<td>Bamberg et al 2013</td>
<td>Radiology</td>
<td>61</td>
<td>7.2 (6.5–7.9)</td>
<td>Visual</td>
<td>1 and 2</td>
<td>67.5 (56.7–71.8)</td>
<td>19 (14–28)</td>
<td>56 (46–61)</td>
<td>70 (57–72)</td>
<td>31</td>
<td>17</td>
<td>18</td>
<td>Yes</td>
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<td>Prospective, single centre</td>
<td>MACCES 7</td>
<td></td>
</tr>
<tr>
<td>Kwong et al 2008</td>
<td>Circulation</td>
<td>107</td>
<td>7.3±1.6</td>
<td>2 SD</td>
<td>NR</td>
<td>59±12</td>
<td>10.7±8.5</td>
<td>NR</td>
<td>17 (6–57)</td>
<td>67</td>
<td>30</td>
<td>38</td>
<td>Yes</td>
<td>Ischaemic</td>
<td>Prospective, single centre</td>
<td>MACCES 9</td>
<td></td>
</tr>
<tr>
<td>Yoon et al 2012</td>
<td>Radiology</td>
<td>151</td>
<td>7.4±1.6</td>
<td>Visual</td>
<td>NR</td>
<td>67±9</td>
<td>14±11</td>
<td>NR</td>
<td>30 (6–103)</td>
<td>113</td>
<td>58</td>
<td>24</td>
<td>No</td>
<td>Ischaemic</td>
<td>Retrospective, single centre</td>
<td>MACES 6</td>
<td></td>
</tr>
</tbody>
</table>

*Columns represent n (%) or mean±SD or median (IQR).
DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; NOS, Newcastle-Ottawa Scale; NR, not reported.
by LGE-MRI was a strong predictor of MACCEs and MACEs in patients with diabetes (random effects HR 3.87, 95% CI 2.58 to 5.80; p<0.0001) (figure 2). There was low heterogeneity (I²=15.1%, p=0.312) in the meta-analysis.

In addition, sensitivity analysis performed by excluding one study at a time did not reveal any significant changes in the HR values.

In the analysis of the outcome of MACCEs, 3 articles\textsuperscript{17, 20, 21} were included in this subgroup analysis, including 64 participants with LGE-MRI-detected myocardial fibrosis and 165 without LGE-MRI-detected myocardial fibrosis, with a total of 64 MACCEs during the follow-up period. Myocardial fibrosis detected by LGE-MRI was associated with an increased risk of MACCEs in patients with diabetes. The pooled HR obtained via the random effects model was 2.58 (95% CI 1.42 to 4.71; p=0.002), with no evidence of heterogeneity (I²=14.1%; p=0.312) (figure 2).

To further verify the robustness of the results, we grouped all included studies by adjusted or non-adjusted HR. In patients with diabetes, myocardial fibrosis detected by LGE-MRI was associated with an increased risk of MACCEs and MACEs in a subgroup analysis with or without adjusted HR. The pooled HRs obtained via a random effects model were 3.52 (95% CI 2.02 to 6.16; I²=35.8%) and 4.63 (95% CI 2.35 to 9.14; I²=0%), respectively. There was no significant heterogeneity among the studies (online supplemental figure S2).

To evaluate the effects of the myocardial fibrosis pattern, we further calculated a pooled HR by source of diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischaemic fibrosis detected

**Table 1** Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on the risk of MACCEs or MACEs. LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events.
by LGE-MRI was significantly associated with increased MACCEs and MACEs (random effects HR 3.80, 95% CI 2.38 to 6.07; I²=26.4%). No study in our meta-analysis reported the relationship between nonischaemic fibrosis and the risk of MACCEs and MACEs alone; hence, we cannot perform a meta-analysis to assess the relationship between nonischaemic fibrosis and MACCEs/MACEs (online supplemental figure S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup analysis with six studies. Among individuals with diabetes and LV ejection fraction >50%, the presence of myocardial fibrosis assessed by LGE-MRI was significantly associated with MACCEs and MACEs. The pooled HR obtained via the random effects model was 3.98 (95% CI 2.22 to 7.25; p<0.001), and there was a medium amount of heterogeneity among the studies (I²=37.9%; p=0.153) (figure 3).

### DISCUSSION

In this meta-analysis, the prevalence of myocardial fibrosis (mainly ischaemic fibrosis) assessed by LGE-MRI was increased in patients with diabetes, occurring in 38.09% of them, and it was associated with an increased risk for MACCEs and MACEs, even when the LV ejection fraction persisted. Moreover, ischaemic myocardial fibrosis detected by LGE-MRI has a higher predictive value for the occurrence of future MACEs than MACCEs in patients with diabetes. However, in this study, the relationship of non-ischaemic LGE-MRI-detected fibrosis and MACCEs/MACEs in patients with diabetes was not elucidated. Therefore, ischaemic myocardial fibrosis by LGE-MRI may be an imaging biomarker for predicting adverse outcomes in patients with diabetes.

In our meta-analysis, the results supported previous studies showing that participants with diabetes have a higher presence of myocardial fibrosis detected by LGE-MRI, especially ischaemic fibrosis. Importantly, in our included studies, the presence of myocardial fibrosis in symptomatic patients with diabetes was higher than that in asymptomatic patients with diabetes. Furthermore, unrecognised ischaemic myocardial fibrosis in patients with diabetes is considered as a biomarker which is responsible for poor outcomes, and maybe provides a stronger prognostic value than conventional cardiovascular risk factors. All studies included in our meta-analysis involved patients who had suffered a unrecognised MI, which implied they might represented a higher risk population. Current guidelines recommend that MRI may serve as a risk tool in patients with asymptomatic diabetes.

**Figure 3** Forest plots of six studies for pooled HR for MACCEs and MACEs in patients with diabetes with normal left ventricular ejection fraction and myocardial fibrosis detected by LGE. LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events.
with moderate or high risk of cardiovascular disease. However, it is unclear whether LGE-MRI-detected myocardial fibrosis would indicate an increased risk of MACEs in patients with diabetes at low cardiovascular risk. Notably, in our meta-analysis, focal ischaemic myocardial fibrosis detected by LGE-MRI did seem to predict a higher occurrence of MACCEs/MACEs, and the annualised event rate for MACCEs/MACEs in patients with diabetes and LGE-MRI-detected myocardial fibrosis was 11.94%. Additionally, the presence of ischaemic myocardial fibrosis indicated an eightfold higher risk for death/MI even in asymptomatic patients with diabetes. Notably, other techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than LGE-MRI. Thus, this finding may highlight the value of LGE-MRI for screening for cardiovascular risk in symptomatic patients with diabetes.

The risk of myocardial fibrosis in patients with diabetes is increased, and there are multiple factors that influence this relationship. First, patients with diabetes have a higher risk for coronary artery disease and myocardial dysfunction. Moreover, hyperglycaemic metabolism, microvascular disease and cardiac autonomic neuropathy are involved in the mechanisms of myocardial fibrosis. However, many studies have shown that patients with diabetes have a high incidence of obesity, visceral fat, hyperlipidaemia and insulin resistance, which may impair myocardial function. Furthermore, the multiple risk factors described above should increase the myocardial fibrosis burden. In addition, myocardial fibrosis is widespread in subjects with diabetes and may be associated with a high risk for cardiovascular disease.

Although focal myocardial fibrosis translates to an adverse outcome in the future and is not fully clear, several potential mechanisms may lead to MACCEs/MACEs. First, patients with diabetes are more inclined to develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia and heart failure. Second, patients with diabetes and myocardial fibrosis usually have a greater burden of microvascular complications, such as myocardial ischaemia, which confers an increased risk of MACCEs/MACEs. Additionally, the myocardial fibrosis detected by LGE-MRI, especially subendocardial fibrosis, indicates that patients with diabetes have had a subendocardial infarction in the past, which denotes a higher risk of MACEs in the future. Furthermore, subjects with diabetes had higher LV and left atrial remodelling due to myocardial fibrosis. For these reasons, the myocardial fibrosis detected by LGE-MRI has great potential to lead to adverse outcomes in the future.

As previously described, LGE-MRI has become a powerful non-invasive imaging method for the assessment of myocardial fibrosis. Although two studies included in our meta-analysis showed that ischaemic myocardial fibrosis detected by LGE-MRI did not increase the rate of MACCEs, our meta-analysis demonstrated that the presence of ischaemic myocardial fibrosis derived from LGE-MRI conferred an HR of 3.80 for future MACCEs/MACEs in individuals with diabetes. This might be explained by the following reasons: limited patient numbers and a higher prevalence of cardiovascular disease at patient enrolment. Indeed, detecting myocardial fibrosis can be used to clinically assess myocardial damage and to stratify cardiovascular risk in participants with diabetes. To date, only one study, which screened for asymptomatic diabetes by LGE-MRI, showed that diabetes with ischaemic myocardial fibrosis conferred an eightfold higher risk for all-cause mortality and MI. The prevalence of ischaemic myocardial fibrosis detected by LGE-MRI among patients with diabetes is higher than that among patients without diabetes. Although there were several studies that have reported the prognostic value of ischaemic myocardial fibrosis detected by LGE-MRI in patients with diabetes, the prognostic value of non-ischaemic myocardial fibrosis has not been studied. Therefore, patients with diabetes and ischaemic myocardial fibrosis might need aggressive management of cardiac and cerebrovascular risk factors. Given the scarcity of studies that focused on the prognosis of non-ischaemic myocardial fibrosis in patients with diabetes, more relevant studies are needed.
CONCLUSIONS

In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI, especially ischaemic lesions, was markedly associated with an important and increased risk of MACCEs/MACEs. This meta-analysis highlights the potential role of LGE-MRI in helping predict MACCEs/MACEs in complicated patients with diabetes, especially those with cardiac complications and a high risk for myocardial fibrosis. Although we reported that ischaemic myocardial fibrosis detected by LGE-MRI is a strong risk marker for improving risk stratification in patients with diabetes, whether LGE-MRI provides incremental prognostic information with respect to MACCEs/MACEs over risk stratification by conventional cardiovascular risk factors requires further study.

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Contributors Y-kG is the guarantor of the integrity of the entire study, ZY and RX conceived of this study, and participated in its design and coordination and drafted the manuscript. Contribution to the conceptualisation and design: J-W, H-YK, HF; L-jx and M-yx. Data analysis and interpretation: LZ, L-yW, HLL and H-lu. Obtaining funding: Z-gy and Y-kG. Z-gy and Y-kG interpreted the results, critically revised the manuscript, and helped to and approved the final version. All authors read and approved this manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Because this was a review, we did not do we did not apply for ethics approval for this article from the institutional ethics review board of West China Second University Hospital, exempted this study. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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REFERENCES


**Supplement legend**

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Table S2. The exact search strategy was used in PubMed.

Supplement Table S3. The exact search strategy was used in Cochrane Library.

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forest plots of pooled HR for MACCE and MACE in adjusted or not adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.

Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCE and MACE in patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.
Supplement Table S1-1

Search methodology

Search strategies

1 diabetes. ab, kw, ti.
2 diabetes mellitus. ab, kw, ti.
3 "diabetic*". ab, kw, ti.
4 1 or 2 or 3
5 mri. ab, kw, ti.
6 MR. ab, kw, ti.
7 "magnetic resonance imag*". ab, kw, ti.
8 cardiac magnetic resonance. ab, kw, ti.
9 cmr. ab, kw, ti.
10 late gadolinium enhancement. ab, kw, ti.
11 lge. ab, kw, ti.
12 delayed gadolinium enhancement. ab, kw, ti.
13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 prognosis. sh.
15 diagnosed. tw.
16 cohort:.mp.
17 predictor:.mp.
18 death.mp.
19 exp *models, statistical/
20 14 or 15 or 16 or 17 or 18 or 19
21 4 and 13 and 20
22 limit 21 to English language  [Limit not valid in CDSR, CCA, CLCMR; records were retained]
23 limit 22 to human  [Limit not valid in CDSR, CCA, CLCMR; records were retained]

24 limit 23 to journal article  [Limit not valid in CDSR, CCA, Embase; records were retained]

25 limit 24 to (embase or medline)  [Limit not valid in CDSR, CCA, CLCMR, Ovid MEDLINE(R); records were retained]

1 to 25 were performed in OvidSP platform.
**Supplement Table S1-2**

Search methodology

Search strategies

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>diabetes[Title/Abstract]</td>
</tr>
<tr>
<td>2</td>
<td>&quot;diabetes mellitus&quot;[Title/Abstract]</td>
</tr>
<tr>
<td>3</td>
<td>&quot;diabetic*&quot;[Title/Abstract]</td>
</tr>
<tr>
<td>4</td>
<td>1 or 2 or 3</td>
</tr>
<tr>
<td>5</td>
<td>mri[Title/Abstract]</td>
</tr>
<tr>
<td>6</td>
<td>MR[Title/Abstract]</td>
</tr>
<tr>
<td>7</td>
<td>&quot;magnetic resonance imag*&quot;[Title/Abstract]</td>
</tr>
<tr>
<td>8</td>
<td>&quot;Magnetic Resonance Imaging&quot;[MeSH Terms]</td>
</tr>
<tr>
<td>9</td>
<td>&quot;cardiac magnetic resonance&quot;[Title/Abstract]</td>
</tr>
</tbody>
</table>
10 cmr[Title/Abstract]
11 "late gadolinium enhancement" [Title/Abstract]
12 LGE[Title/Abstract]
13 "delayed gadolinium enhancement"[ Title/Abstract]
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 prognosis[ MeSH Terms]
16 diagnosed[Title/Abstract]
17 cohort:[MeSH Terms]
18 "predictor*"[Title/Abstract]
19 death[MeSH Terms]
20 models, statistical[MeSH Terms]
21 15 or 16 or 17 or 18 or 19 or 20
22 4 and 14 and 21
23 "english and humans"[Filter]

24 22 and 23

25 journal article[Filter]

26 24 and 25

1 to 26 were performed in PubMed.
Supplement Table S1-3

Search methodology

Search strategies

1 diabetes:ti,ab,kw
2 "diabetes mellitus":ti,ab,kw
3 "diabetic*":ti,ab,kw
4 1 or 2 or 3
5 mri:ti,ab,kw
6 MR:ti,ab,kw
7 "magnetic resonance imag*":ti,ab,kw
8 "Magnetic Resonance Imaging"[MeSH Terms]
9 "cardiac magnetic resonance":ti,ab,kw
10 cmr:ti,ab,kw

11 "late gadolinium enhancement":ti,ab,kw

12 LGE:ti,ab,kw

13 "delayed gadolinium enhancement":ti,ab,kw

14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15 prognosis[ MeSH Terms]

16 diagnosed:ti,ab,kw

17 cohort:[MeSH Terms]

18 "predictor*":ti,ab,kw

19 death[MeSH Terms]

20 models, statistical[MeSH Terms]

21 15 or 16 or 17 or 18 or 19 or 20

22 4 and 14 and 21
1 to 26 were performed in Cochrane Library.
Funnel plot with pseudo 95% confidence limits
Study

ID

HR (95% CI) Weight

Adjusted HR

Bertheau RC (2016) 2.25 (0.98, 5.38) 17.82
Elliott MD (2019) 8.08 (2.94, 22.22) 13.48
Giusca S (2016) 4.50 (1.50, 13.10) 11.99
Bamberg F (2013) 1.28 (0.35, 4.94) 8.44
Kwong RY (2008) 4.13 (1.75, 9.74) 17.60
Subtotal (I-squared = 35.8%, p = 0.183) 3.52 (2.02, 6.16) 69.33

Not adjusted HR

Heydari B (2016) 4.84 (1.06, 22.09) 6.57
Yoon YE (2013) 8.84 (2.48, 31.49) 9.09
Yoon YE (2012) 3.18 (1.23, 8.20) 15.01
Subtotal (I-squared = 0.0%, p = 0.449) 4.63 (2.35, 9.14) 30.67

Overall (I-squared = 15.1%, p = 0.311) 3.87 (2.58, 5.80) 100.00

NOTE: Weights are from random effects analysis

Supplemental material

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BMJ Open
doi: 10.1136/bmjopen-2021-055374:
e055374. 12 2022;BMJ Open, et al. Yang Z
<table>
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<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight</th>
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<tr>
<td><strong>Ischemic fibrosis</strong></td>
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<td>Bertheau RC (2016)</td>
<td>2.25 (0.98, 5.38)</td>
<td>17.82</td>
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<tr>
<td>Heydari B (2016)</td>
<td>4.84 (1.06, 22.09)</td>
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<tr>
<td>Yoon YE (2012)</td>
<td>3.18 (1.23, 8.20)</td>
<td>15.01</td>
</tr>
<tr>
<td><strong>Subtotal</strong> (I-squared = 26.4%, p = 0.227)</td>
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<tr>
<td><strong>Ischemic and nonischemic fibrosis</strong></td>
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<tr>
<td>Giusca S (2016)</td>
<td>4.50 (1.50, 13.10)</td>
<td>11.99</td>
</tr>
<tr>
<td><strong>Subtotal</strong> (I-squared = .%, p = .)</td>
<td>4.50 (1.52, 13.30)</td>
<td>11.99</td>
</tr>
<tr>
<td><strong>Overall</strong> (I-squared = 15.1%, p = 0.311)</td>
<td>3.87 (2.58, 5.80)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.