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Complete List of Authors:	Yang, Zhi; Chengdu Fifth People's Hospital, Department of Radiology Xu, Rong; Sichuan University West China Second University Hospital Wang, Jia-rong; Sichuan University West China Second University Hospital Xu, Hua-yan; Sichuan University West China Second University Hospital Fu, Hang; Sichuan University West China Second University Hospital Xie, Ling-jun; Sichuan University West China Second University Hospital Yang, Meng-xi Zhang, Lu; Sichuan University West China Second University Hospital Wen, Ling-yi; Sichuan University West China Second University Hospital Liu, Hui; Sichuan University West China Second University Hospital Li, Hong; Sichuan University West China Second University Hospital Yang, Zhi-gang; Sichuan University, Guo, Ying-kun ; Sichuan University West China Second University Hospital, 3. Department of Radiology
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Title page：

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Zhi Yang[1,2*], MS; Rong Xu[1*], MS; Jia-rong Wang[1], MD; Hua-yan Xu[1], MD; Hang Fu[1], MS; Ling-jun Xie[1], MS; Meng-xi Yang[4], MS; Lu Zhang[1], MS; Ling-yi Wen[1], MD; Hui Liu[1], MS; Hong Li[3], MD; Zhi-gang Yang[4†], MD; Ying-kun Guo[1†], MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China.
4. Department of Radiology, West China Hospital, Sichuan University, Chengdu, China.

*** These authors contributed equally to this work and should be considered the co-first authors.**

† Guarantor and correspondent:

These two authors contributed equally to this work and should be considered corresponding authors.

Zhigang Yang, PhD, MD

Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University，No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)

E-mail: yangzg666@163.com

Yingkun Guo, MD

Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China

Tel: +86-28-85503275(O)

E-mail: gykpanda@163.com

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ABSTRACT

Aim/Introduction: Prior studies demonstrated that myocardial fibrosis assessed by late gadolinium-enhanced (LGE) MRI is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes. However, the results of these studies were controversial and limited. Therefore, we performed this meta-analysis assessing the associations of myocardial fibrosis detected by LGE with the risk of MACCE and MACE in patients with diabetes.

Materials And Methods: We selected studies using MEDLINE, EMBASE and Cochrane by Ovid on December 2019. Pooled hazard ratios (HR), and 95% confidence intervals (CI) by random-effects model to assess the relationship of myocardial fibrosis and risk of MACCE or MACE in patients with diabetes. Results: Eight studies with 1121 patients were included in this meta-analysis, and follow-up of patients ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE was associated with an increased risk for MACCE (HR: 2.58; 95%CI 1.42-4.71; P=0.002) and MACE (HR: 5.28; 95%CI 3.20-8.70; P=0.000) in patients with diabetes. In a subgroup meta-analysis, ischemic fibrosis detected by LGE was associated with MACCE/MACE (HR 3.75, 95%CI 2.11-6.69; P=0.000) in patients with diabetes. In diabetic patients with preserved ejection fraction, the association between myocardial fibrosis detected by LGE and MACCE/MACE remained significant (HR: 3.98; 95%CI 2.22-7.25; P=0.000).

Conclusions: This study demonstrated that myocardial fibrosis detected by LGE conferred an increase in the risk of MACCE/MACE in patients with diabetes and may be an imaging biomarker for risk stratification.

Keywords: Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

Strengths and limitations of this study:

The presence of myocardial fibrosis detected by LGE-MRI in patients with diabetes was markedly associated with an important and increased risk of MACCE/MACE.

The prevalence of myocardial fibrosis detected by LGE among patients with diabetes is higher than that among nondiabetic patients.

Diabetes duration plays a central role in the assessment of cardiovascular risk, but the incremental value of diabetes duration to the prevalence and incidence of LGE was not revealed in this article.

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 myocardial fibrosis

than their nondiabetic counterparts as a result of microvascular and macrovascular dysfunction, even when asymptomatic.[2-5] Moreover, the presence of myocardial fibrosis is associated with diabetic cardiomyopathy.[6-8] In addition, myocardial fibrosis can increase the risk of left ventricular (LV) dysfunction and heart failure with preserved ejection fraction in patients with diabetes.[9 10] Therefore, it is important to detect myocardial fibrosis by noninvasive imaging technology for risk stratification in the clinical routine.

Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) is the most reliable tool for identifying and quantifying myocardial fibrosis in vivo.[11-13] Furthermore, LGE-MRI is noninvasive and can easily discriminate between ischemic and nonischemic fibrosis without ionizing radiation.[3] Furthermore, recent guidelines suggested that MRI may be considered an imaging technique for stratifying cardiovascular risk in patients with diabetes.[14 15] This highlights the role of LGE-MRI in risk stratification of patients with diabetes.

Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.[2] Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.[2 3 16-21] In addition, most previous studies were single-center studies and have been limited by small numbers of events. Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected by late gadolinium enhancement (LGE) with future MACCE and MACE in patients with diabetes.

METHODS

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[22 23]

Patient and Public Involvement

No patient involved.

Data Sources and Searches

We searched the Ovid MEDLINE, Ovid EMBASE and Ovid Cochrane Library databases to find eligible studies in December 2019. 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 Supplemental Table S1. In addition, only articles published in peer-reviewed journals and in the English language were included.

Study Selection

All articles were independently screened by two reviewers using the following inclusion criteria, and any disagreement was resolved by consensus. The inclusion criteria were as follows: the design was prospective or retrospective cohort study; the populations were patients with diabetes, and exposure of myocardial fibrosis was detected by LGE-MRI; the outcomes used composite endpoints including all-cause mortality, cardiac and cerebrovascular disease, late coronary revascularization, and hospitalization for unstable angina; the study reported the hazard ratio (HR) and 95% confidence intervals (CI) 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. Moreover, to obtain eligible studies, two reviewers independently

screened the title first, then the abstract, and finally the full text.

Data Extraction and Quality Assessment

We extracted the following demographic data from each included study: author, year of publication, sample size, study design, age, LGE status, follow-up duration, outcome, and HR (95% CI). Additionally, we extracted the adjustment 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 study quality, which is usually used for evaluating the quality of cohort studies in meta-analyses.[24 25] The scale uses a maximum of 9 points involving 3 factors: patient selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).[26] We delimited the quality of studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 9 scores).

Data Synthesis and Analysis

In this meta-analysis, the outcome measure was the occurrence of future adverse cardiac and/or cerebrovascular events among diabetes patients with LGE compared to those without LGE. We defined the primary endpoint as MACCE, including myocardial infarction (MI), all-cause mortality, coronary and carotid revascularization, heart failure, ventricular arrhythmias, unstable angina, cardiac and cerebrovascular death, and cerebrovascular disease. The secondary end points were MACE, including all-cause mortality, cardiac death, MI, heart failure, unstable angina, and ventricular arrhythmias. Additionally, the pattern of myocardial fibrosis was classified as ischemic fibrosis or nonischemic fibrosis as described previously.[3]

We pooled the adjusted HR with its 95% CI using a random-effects model. In addition, we calculated the annualized event rates (AERs) by dividing the total events by the median follow-up periods. To analyze the heterogeneity of the included studies, we used forest plots and the I^2 statistic.[27] We assigned

I^2 values of 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively.

Considering the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 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 version 12 (StataCorp). *P* values were two sided, with a level of 0.05 considered significant.

RESULTS

Literature Search

Based on the selection strategy, we found 2134 citations. Of these, 151 duplicate studies were excluded. After screening the title and abstract, 12 articles remained for assessment of the full text. Four studies[29-32] 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, 8 studies[2 3 16-21] fulfilled our inclusion criteria and were included in this meta-analysis (Fig. 1).

Study Characteristics

In aggregate, 8 studies included 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 ranged from 17 to 70 months. Across the 8 studies, 6 articles[2 17-21] reported the duration of diabetes, and the mean duration of diabetes was 15 years. A total of 6 studies[2 3 16 19-21] reported the LV ejection fraction, and the mean LV ejection fraction was 57.78%. The presence of LGE was evaluated by visual analysis in 6 publications.[2 3 18-21] All of the included studies reported multiple clinical outcomes. The main characteristics of the included

articles are shown in Table 1.

Among the 8 selected studies, 6 studies[16-21] (75%) were conducted in a single center (Germany, n=2; USA, n=2; Japan, n=2), and 2 studies[2 3] were performed in multiple centers (USA, n=1; Europe, n=1). Five articles[2 3 17 20 21] (62.5%) reported adjusted HR. Six studies[2 16 18-21] reported patients with ischemic fibrosis, and the remaining 2 studies[3 17] reported patients with ischemic and nonischemic fibrosis.

Of the 8 eligible studies, 7 received 7 to 9 scores, and the 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 assessed by visual analysis of the funnel plot (Supplemental Fig. S1).

Prevalence of LGE and AERs

Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE ranged from 15% to 62%, and the prevalence of LGE 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 AERs for MACCE of 4.3%. However, only 3 studies[2 19 21] reported a total of 301 patients with diabetes. Among these patients, 19.27% (n=58) had myocardial fibrosis detected by LGE, with 27 events occurring over a median follow-up of 3.9 years. The AERs of patients with diabetes and LGE was 11.94%.

MACCE and MACE

A total of 8 studies reported the outcome of MACCE or MACE, and the presence of myocardial fibrosis detected by LGE was a strong predictor of MACCE and MACE in patients with diabetes (random-effects HR 3.87, 95% CI 2.58-5.80; P=0.000) (Fig. 2). Low heterogeneity (I^2=15.1%, P=0.311) existed in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study each time found that the HR values were not significantly changed.

In the analysis of the outcome of MACCE, 3 articles[17 20 21] were included in this subgroup meta-analysis, including 64 participants with LGE and 165 diabetes without LGE, with a total of 64 MACCE outcomes during the follow-up period. Myocardial fibrosis detected by LGE was associated with an increased risk of MACCE in patients with diabetes. The pooled random-effects HR was 2.58 (95% CI 1.42-4.71; P=0.002), with no evidence of heterogeneity (I^2=14.1%; P=0.312) (Fig. 2).

To explore the association between myocardial fibrosis and the outcome of MACE in patients with diabetes, we included 5 articles[2 3 16 18 19] that provided a subgroup meta-analysis. The results showed that the presence of LGE in diabetes was associated with a significantly higher risk of MACE. As in the discovery analyses, the pooled HR was 5.28 (95% CI 3.20-8.70; P=0.000) with no significant heterogeneity (I^2=0%; P=0.643) from random effects (Fig. 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 was associated with an increased risk of MACCE and MACE in a subgroup meta-analysis with or without adjusted HR. The pooled HRs were 3.52 (random-effects, 95% CI 2.02-6.16; I^2=35.8%) and 4.63 (random-effects, 95% CI 2.35-9.14; I^2=0%), respectively. There was no significant heterogeneity among the studies (Supplemental Fig. S2).

To evaluate the pattern of myocardial fibrosis effects, we further calculated a pooled HR by source of diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischemic fibrosis detected by LGE was significantly associated with increased MACCE and MACE (random-effects HR 3.75, 95% CI 2.11-6.69; I^2=38.3%). Furthermore, all myocardial fibrosis detected by LGE in patients with diabetes may increase the risk of MACCE and MACE (random-effects HR 4.27, 95% CI 2.17-8.37; I^2=0%) (Supplemental Fig. S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup meta-analysis with 6 studies. Among individuals with diabetes and LV ejection fraction > 50%, the presence of myocardial fibrosis assessed by LGE was significantly associated with MACCE and MACE. The pooled HR was 3.98 (95% CI 2.22-7.25; P=0.000) with random effects, and there was medium heterogeneity among the studies (I^2=37.9%; P=0.153) (Fig. 3).

DISCUSSION

In this meta-analysis, the prevalence of myocardial fibrosis assessed by LGE was increased in patients with diabetes, occurring in 38.09% of them. In addition, the presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted. Specifically, myocardial fibrosis detected by LGE has a higher predictive value for the occurrence of future MACE than MACCE in patients with diabetes. Furthermore, myocardial fibrosis by LGE 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. Importantly, in our included studies, the presence of myocardial fibrosis in symptomatic patients with diabetes was higher than that in asymptomatic patients with diabetes.[2 3 17] Given that more than 38.09% of patients with diabetes have myocardial fibrosis detected by LGE in our meta-analysis, it indicated that LGE is very important for screening myocardial fibrosis in diabetes. Current guidelines recommend that MRI may be a risk tool in asymptomatic patients with diabetes at moderate or high risk of cardiovascular disease.[14] However, the value of MRI in routine clinical stratification of cardiovascular risk is unclear. Notably, in our meta-analysis, focal myocardial fibrosis detected by LGE did seem to predict a higher occurrence MACCE/MACE in the future, and the AERs for MACCE/MACE in patients with diabetes and LGE was 11.94%. Additionally, the presence of myocardial fibrosis indicated a 8-fold higher risk for death/MI even in asymptomatic patients with diabetes.[2] It must be noted that other techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than LGE.[33 34] Thus, this finding highlighted the value of LGE for screening for cardiovascular risk in patients with diabetes.

The risk of myocardial fibrosis in patients with diabetes is increased and likely multifactorial. First, patients with diabetes have a higher risk for coronary artery disease and myocardial dysfunction.[35-37] Moreover, hyperglycemic metabolism, microvascular disease, and cardiac autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.[4 38 39] However, many studies have shown that patients with diabetes have a high incidence of obesity, visceral fat, hyperlipidemia, and insulin resistance, which may impair myocardial function.[6 40 41] 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 the focal myocardial fibrosis translates to an adverse outcome in future is not fully clear, several potential mechanisms may lead to MACCE/MACE. First, patients with diabetes are more inclined to develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia and heart failure.[3 42-44] Second, patients with diabetes and myocardial fibrosis usually have a greater burden of microvascular complications, such as myocardial ischemia, which confers an increased risk of MACCE/MACE.[16 45] Additionally, the myocardial fibrosis detected by LGE, especially subendocardial fibrosis, indicates more severe coronary calcium and atherosclerotic disease, which denotes a higher risk of MACE.[46 47] Furthermore, subjects with diabetes had higher LV and left atrial remodeling due to myocardial fibrosis.[9 43 48] For these reasons, the myocardial fibrosis detected by LGE indeed has clinical relevance.

As previously described, LGE-MRI has become a powerful noninvasive imaging method for the assessment of myocardial fibrosis.[11] Unfortunately, our meta-analysis demonstrated that the presence of myocardial fibrosis derived from LGE conferred an HR of 3.87 for future MACCE/MACE in individuals with diabetes, and the risk increased with ischemic myocardial fibrosis. It must be indicated that two studies[20 21] were included in our meta-analysis, which showed that ischemic myocardial fibrosis detected by LGE did not increase the rate of MACCE. This might be explained by the following reasons, such as limited patients and the patients having a high prevalence of cardiovascular disease. 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, showed that diabetes with ischemic myocardial fibrosis conferred an 8-fold higher risk for all-cause mortality and MI.[2] The prevalence of myocardial fibrosis detected by LGE among patients with diabetes is higher than that among nondiabetic patients.[3 30] Therefore, patients with diabetes and myocardial fibrosis might need aggressive management of cardiac and cerebrovascular risk factors.

However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies[20 21] were from the same group of patients but reported different outcomes. However, when we excluded either of the above articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of myocardial fibrosis in patients with diabetes was not community-based epidemiology research. The prevalence of myocardial fibrosis, therefore, may be higher in this study, which pooled studies including high-risk or average-risk populations with diabetes. Third, a previous study found that women with diabetes had a higher risk for MACCE than men with diabetes.[49] However, this study was not designed to evaluate sex differences in the effect of myocardial fibrosis on MACCE/MACE in patients with diabetes. Fourth, most studies selected in this meta-analysis reported adjusted HRs, and various adjustments for adverse outcomes among the selected studies may affect the pooled results. However, the heterogeneity among the selected studies was low, and publication bias did not exist. This might strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration to the prevalence and incidence of LGE was not revealed. However, diabetes duration plays a central role in the assessment of cardiovascular risk.[14 50] Hence, a prospective study that evaluates the association between diabetes duration and myocardial fibrosis and determines the best time to screen myocardial fibrosis by LGE-CMR for risk stratification in patients with diabetes is needed.

CONCLUSIONS

In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI was markedly associated with an important and increased risk of MACCE/MACE. Myocardial fibrosis may be a risk marker for improving risk stratification in patients with diabetes. This meta-analysis highlights the role of LGE-MRI in helping identify high-risk diabetic patients in routine clinical practice.

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Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on the risk of MACCE or MACE. LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.

Figure 3. Forrest plots of 6 studies for pooled HR for MACCE and MACE in patients with diabetes with normal LV ejection fraction and 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.

Table legend

Table 1. Description of the Studies Included in the Meta-Analysis

Supplement legend

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

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Supplement Figure S3. Forrest 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.

Notes

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Compliance with ethical standards

Not applicable.

Conflict of interest

The authors report no conflicts of interest.

Authors' contributions

Zhi Yang and Rong Xu conceived of this study, and participated in its design and coordination and drafted the manuscript, Zhi-gang Yang and Ying-kun Guo helped to draft the manuscript. Other participated in the design of the study and helped with the statistical analysis. All authors read and approved this manuscript.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

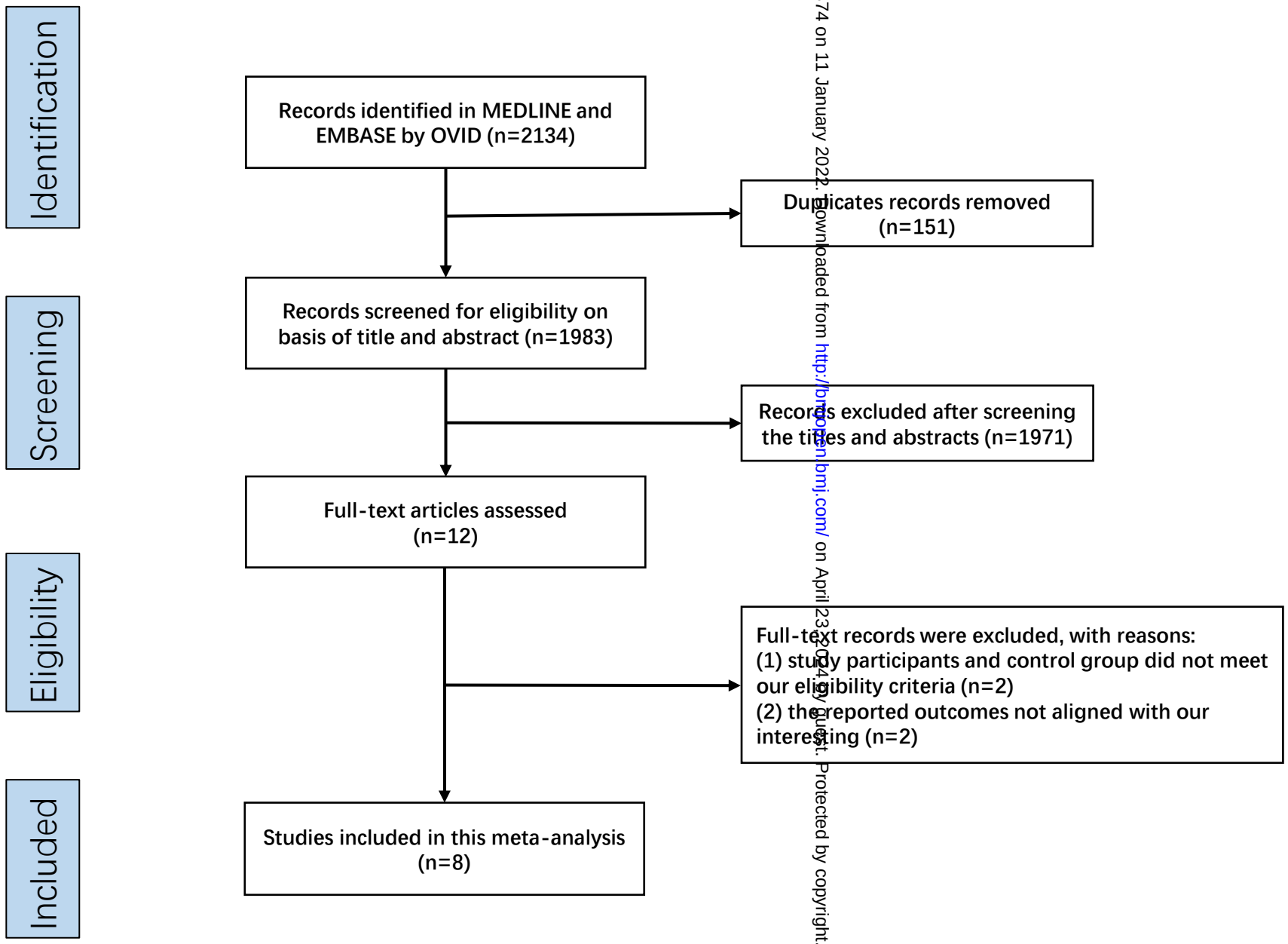
Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

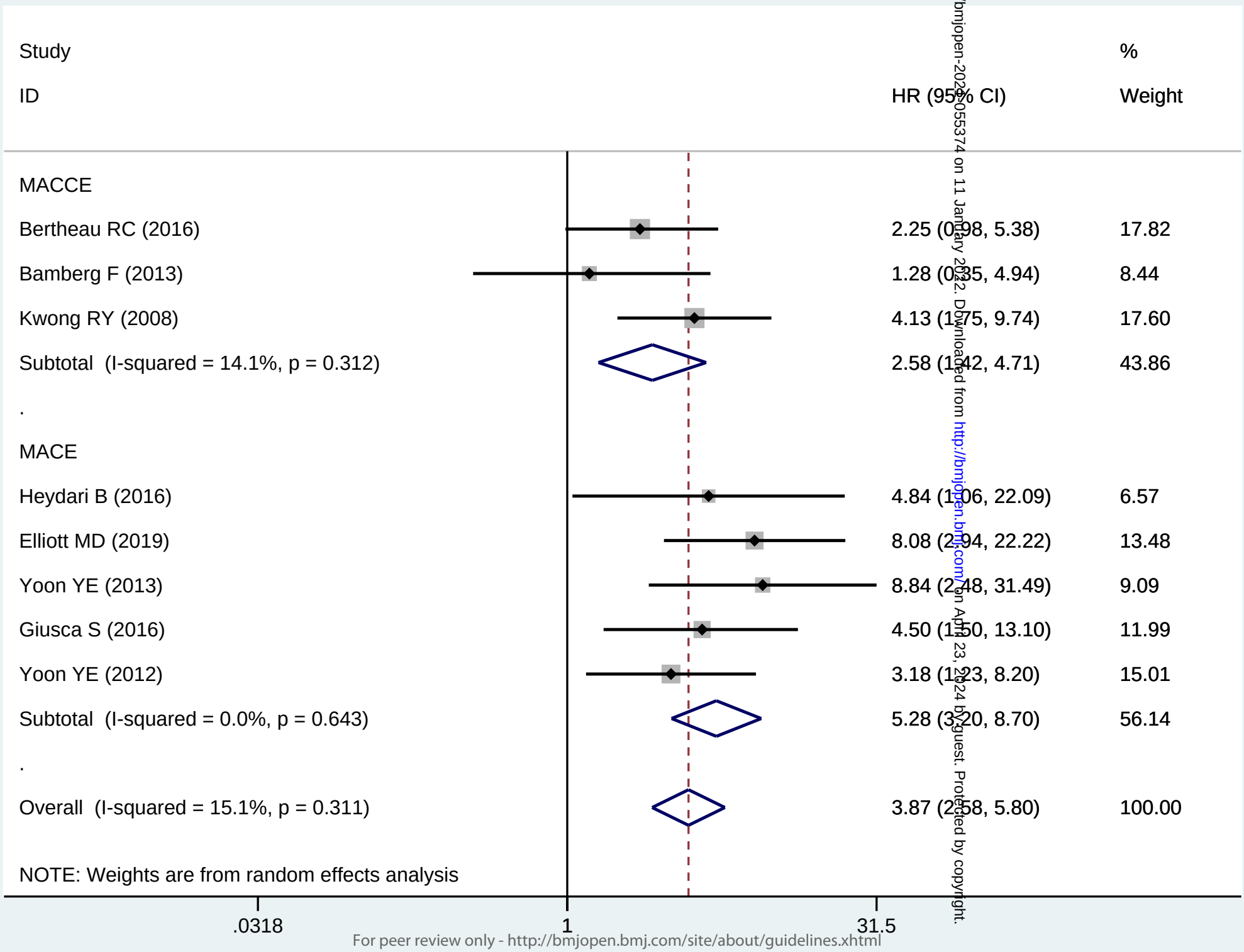
Table 1 Description of the Studies Included in the Meta-Analysis

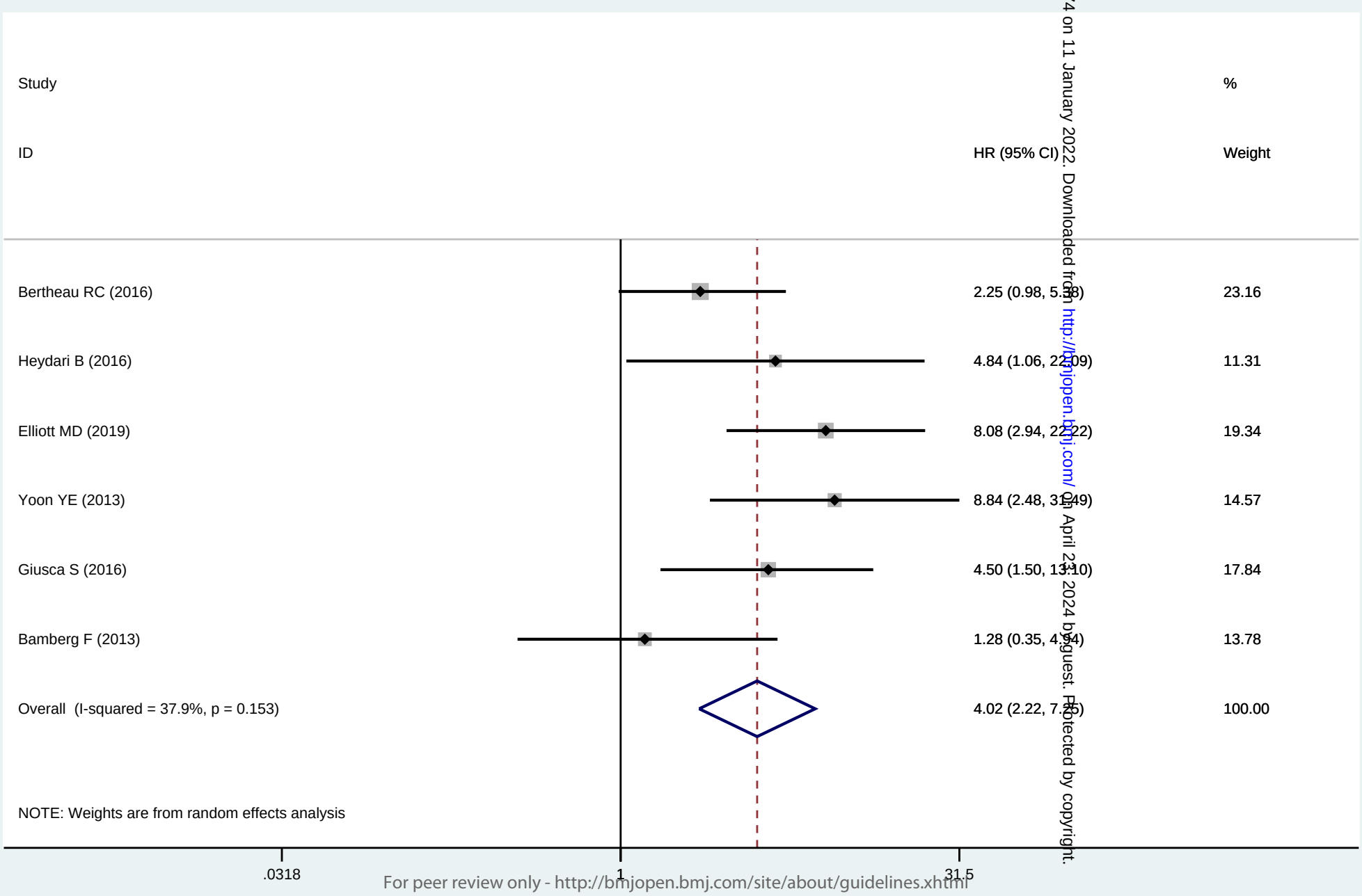
First Author, Year	Journal	patients	Hblc, %	LGE Definition	DM (type)	Mean age (years)	Duration of Diabetes (years)	LVEF (%)	Follow-up duration (months)	male	LGE(+)	Total events	Adjusted HR	Fibrosis type	Type design	outcome	NOS
Berthe au RC,2016	Eur Radiol	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischemic	Prospective, single-centre	MACCE	7
Heydari B,2016	Circ Cardiovasc Imaging	173	7.9±1.8	2 SD	NA	61.7±11.9	NA	51.8±17.6	34.8±30	109	88	21	NO	Ischemic	Prospective, single-centre	MACE	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischemic	Prospective, two-centre	MACE	9
Yoon YE,2013	Eur Radiol	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischemic	Retrospective, single-centre	MACE	7
Giusca S,2016	Eur Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±11.6	35 (23-51.6)	250	176	26	YES	Ischemic and nonischemic	Prospective, multicentre	MACE	8

	sc Imaging															
Bamberg F,2013	Radiology	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischemic	Prospective, single-centre	MACCE	7
Kwong RY,2008	Circulation	107	7.3±1.6	2 SD	NA	59±12	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischemic and nonischemic	Prospective, single-centre	MACCE	9
Yoon YE,2012	Radiology	151	7.4±1.6	visual	NA	67±9	14±11	NA	30(6-103)	113	58	24	NO	Ischemic	Retrospective, single-centre	MACE	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle-Ottawa Scale; HR, hazard ratio; NR, not reported; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events.







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Supplement Tabe S1

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/

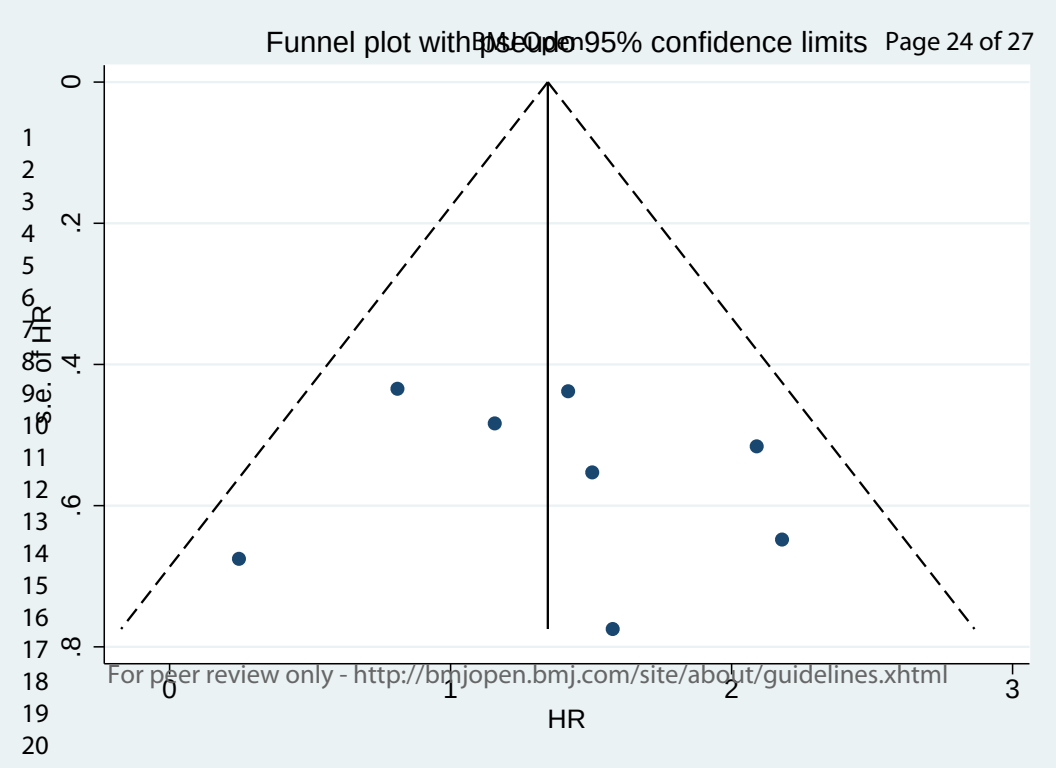
20 14 or 15 or 16 or 17 or 18 or 19

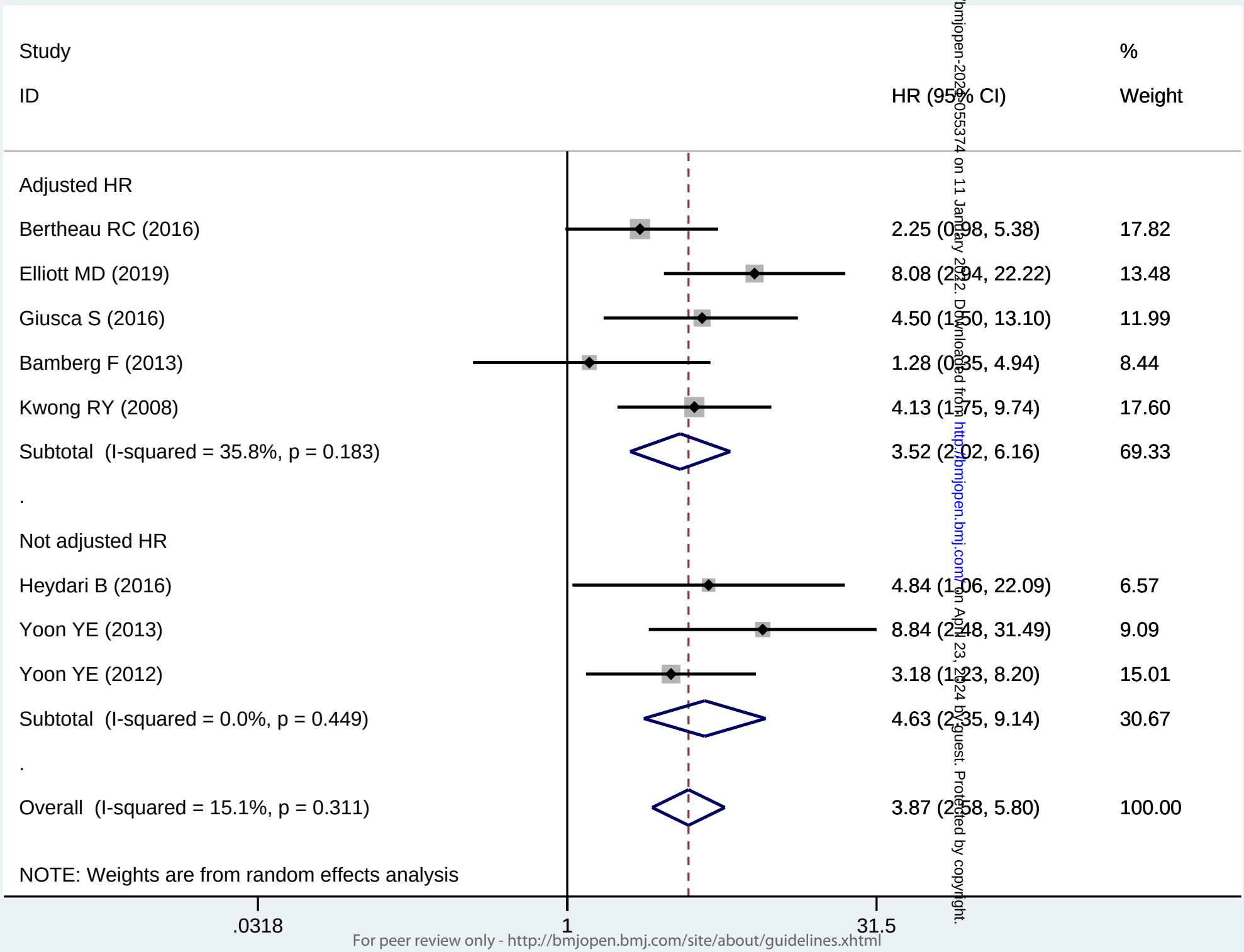
21 4 and 13 and 20

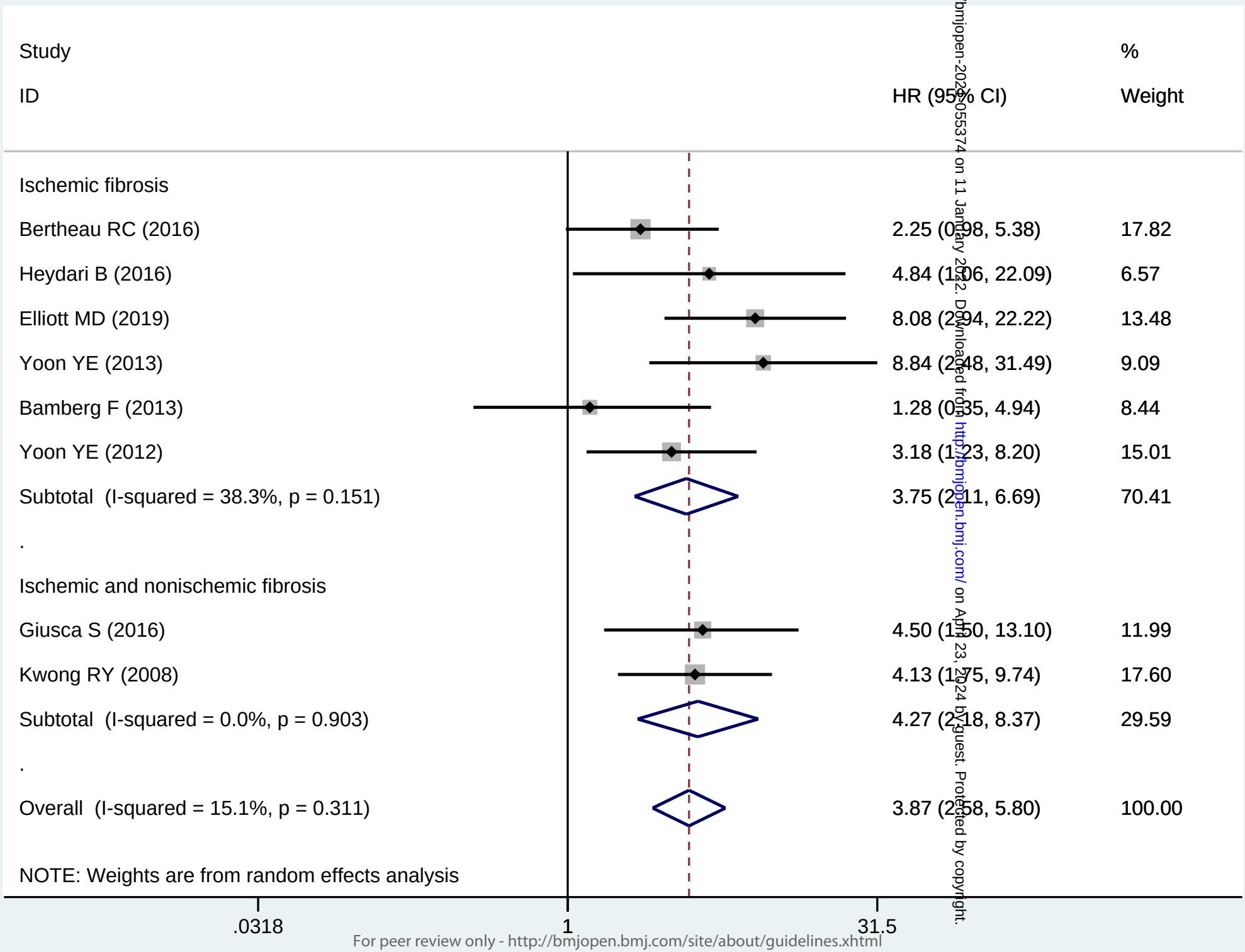
22 limit 21 to English language [Limit not valid in CDSR, CCA, CLCMR; records were retained]

23 limit 22 to human [Limit not valid in CDSR, CCA, CLCMR; records were retained]
24 limit 23 to clinical study [Limit not valid in CDSR, CCA, CLCMR, Embase; records were retained]
25 limit 24 to journal article [Limit not valid in CDSR, CCA, Embase; records were retained]
26 limit 25 to (embase or medline) [Limit not valid in CDSR, CCA, CLCMR, Ovid MEDLINE(R); records were retained]

1 to 26 were performed in OvidSP platform.







PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2,3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2,3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3,4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4,5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5,6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5,6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4,5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5,6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4,5,6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	4,5,6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	5,6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	5,6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	5,6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	5,6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	6,7
	23b	Discuss any limitations of the evidence included in the review.	7
	23c	Discuss any limitations of the review processes used.	7
	23d	Discuss implications of the results for practice, policy, and future research.	7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	11,12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	12

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

BMJ Open

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

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Complete List of Authors:	Yang, Zhi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education; Chengdu Fifth People's Hospital, Department of Radiology Xu, Rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Wang, Jia-rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Xu, Hua-yan; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Fu, Hang; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Xie, Ling-jun; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Yang, Meng-xi ; Sichuan University West China Hospital, Department of Radiology Zhang, Lu; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Wen, Ling-yi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Liu, Hui; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Li, Hong; Sichuan University West China Second University Hospital, Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education Yang, Zhi-gang; Sichuan University West China Hospital, Department of Radiology Guo, Ying-kun ; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and

	Related Diseases of Women and Children of Ministry of Education
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diabetes and endocrinology, Cardiovascular medicine
Keywords:	RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, DIABETES & ENDOCRINOLOGY

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Title page：

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Zhi Yang[1,2*], MS; Rong Xu[1*], MS; Jia-rong Wang[1], MD; Hua-yan Xu[1], MD; Hang Fu[1], MS; Ling-jun Xie[1], MS; Meng-xi Yang[4], MS; Lu Zhang[1], MS; Ling-yi Wen[1], MD; Hui Liu[1], MS; Hong Li[3], MD; Zhi-gang Yang[4†], MD; Ying-kun Guo[1†], MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

*** These authors contributed equally to this work and should be considered the co-first authors.**

† Guarantor and correspondent:
These two authors contributed equally to this work and should be considered corresponding authors.

Zhigang Yang, PhD, MD
Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University，No.37 Guoxue Xiang, Chengdu, 610041, China
Tel: +86-28-85423817(O)
E-mail: yangzg666@163.com

Yingkun Guo, MD
Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China
Tel: +86-28-85503275(O)
E-mail: gykpanda@163.com

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

ABSTRACT

Objective To performed this meta-analysis assessing the associations of myocardial fibrosis detected by late gadolinium-enhanced (LGE) MRI with the risk of major adverse cardiac and cerebrovascular events (MACCE) and major adverse cardiac events (MACE) in patients with diabetes.

Design Systematic review and meta-analysis u the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

Data sources We selected studies using MEDLINE, EMBASE and Cochrane by Ovid on 27 August 2021.

Eligibility criteria for selecting studies Prospective or respective cohort studies if they reported the hazard ratio (HR) and 95% confidence intervals (CI) for MACCE/MACE in patients with both type 1 and 2 diabetes and LGE compared with those without LGE, and articles published in the English language.

Data extraction and synthesis Two review authors independently extracted data and assessed the quality of study. Pooled hazard ratios (HR), and 95% confidence intervals (CI) by random-effects model. Heterogeneity were assessed using forest plots and the I^2 statistic.

Results Eight studies with 1121 patients with both type 1 and type 2 diabetes were included in this meta-analysis, and follow-up of patients ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE was associated with an increased risk for MACCE (HR: 2.58; 95%CI 1.42-4.71; P=0.002) and MACE (HR: 5.28; 95%CI 3.20-8.70; P=0.000) in patients with diabetes. In a subgroup meta-analysis, ischemic fibrosis detected by LGE was associated with MACCE (HR 3.75, 95%CI 2.11-6.69; P=0.000) in patients with diabetes. In diabetic patients with preserved ejection fraction, the association between myocardial fibrosis detected by LGE and MACCE remained significant (HR: 3.98; 95%CI 2.22-7.25; P=0.000).

Conclusions This study demonstrated that myocardial fibrosis detected by LGE conferred an increase in the risk of MACCE/MACE in patients with diabetes and may be an imaging biomarker for risk stratification.

Keywords: Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

Strengths and limitations of this study:

This meta-analysis focuses on the relationship between LGE and MACCE/MACE in patients with diabetes, and the distribution of ischemic LGE seems to increase the unfavorable prognosis.

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

All included studies were not community-based epidemiology research, and came from developed

countries.

Additionally, most studies selected in this meta-analysis reported adjusted HRs may lead to bias.

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 myocardial fibrosis than their nondiabetic counterparts as a result of microvascular and macrovascular dysfunction, even when asymptomatic.[2-5] Moreover, the presence of myocardial fibrosis is associated with diabetic cardiomyopathy.[6-8] In addition, myocardial fibrosis can increase the risk of left ventricular (LV) dysfunction and heart failure with preserved ejection fraction in patients with diabetes.[9 10] Therefore, it is important to detect myocardial fibrosis by noninvasive imaging technology for risk stratification in the clinical routine.

Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) is the most reliable tool for identifying and quantifying myocardial fibrosis in vivo that allows discriminate between ischemic and nonischemic fibrosis without ionizing radiation.[11-13] LGE-MRI, a promising technique, can provides more histological information over with unenhanced cardiac MRI, to illuminate the complex pathophysiologic pathways of myocardial viability.[3] Furthermore, recent guidelines suggested that MRI may be considered an imaging technique for stratifying cardiovascular risk in patients with diabetes.[14 15] This maybe highlights the role of LGE-MRI in risk stratification of patients with diabetes.

Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.[2] Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.[2 3 16-21] In addition, most previous studies were single-center studies and have been limited by small numbers of events. Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected by late gadolinium enhancement (LGE) with future MACCE and MACE in patients with diabetes.

METHODS

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[22 23]

Data Sources and Searches

We searched the Ovid MEDLINE, Ovid EMBASE and Ovid Cochrane Library databases to find eligible studies in December 2019. 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 Supplemental Table S1-S3. In addition, only articles published in peer-reviewed journals and in the English language were included.

Study Selection

All articles were independently screened by two reviewers (ZY, RX) using the following inclusion criteria, and any disagreement was resolved by consensus. The inclusion criteria were as follows: the design was prospective or retrospective cohort study; the populations were patients with diabetes, and

exposure of myocardial fibrosis was detected by LGE-MRI; the outcomes used composite endpoints including all-cause mortality, cardiac and cerebrovascular disease, late coronary revascularization, and hospitalization for unstable angina; the study reported the hazard ratio (HR) and 95% confidence intervals (CI) 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. Moreover, to obtain eligible studies, two reviewers independently screened the title first, then the abstract, and finally the full text.

Data Extraction and Quality Assessment

We extracted the following demographic data from each included study: author, year of publication, sample size, study design, age, LGE status, follow-up duration, outcome, and HR (95% CI). Additionally, we extracted the adjustment 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 study quality, which is usually used for evaluating the quality of cohort studies in meta-analyses.[24 25] The scale uses a maximum of 9 points involving 3 factors: patient selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).[26] We delimited the quality of studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 9 scores).

Data Synthesis and Analysis

In this meta-analysis, the outcome measure was the occurrence of future adverse cardiac and/or cerebrovascular events among diabetes patients with LGE compared to those without LGE. We defined the primary endpoint as MACCE, including myocardial infarction (MI), all-cause mortality, coronary and carotid revascularization, heart failure, ventricular arrhythmias, unstable angina, cardiac and cerebrovascular death, and cerebrovascular disease. The secondary end points were MACE, including all-cause mortality, cardiac death, MI, heart failure, unstable angina, and ventricular arrhythmias. Additionally, the pattern of myocardial fibrosis was classified as ischemic fibrosis or nonischemic fibrosis as described previously.[3]

We pooled the adjusted HR with its 95% CI using a random-effects model. In addition, we calculated the annualized event rates by dividing the total events by the median follow-up periods. To analyze the heterogeneity of the included studies, we used forest plots and the I^2 statistic.[27] We assigned I^2 values of 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively. Considering the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 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 version 12 (StataCorp). *P* values were two sided, with a level of 0.05 considered significant.

Patient and Public Involvement

No patient involved.

RESULTS

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. Four studies[29-32] 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, 8 studies[2 3 16-21] fulfilled

our inclusion criteria and were included in this meta-analysis (Fig. 1).

Study Characteristics

In aggregate, 8 studies included 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 ranged from 17 to 70 months. Across the 8 studies, 6 articles[2 17-21] reported the duration of diabetes, and the mean duration of diabetes was 15 years. A total of 6 studies[2 3 16 19-21] reported the LV ejection fraction, and the mean LV ejection fraction was 57.78%. The presence of LGE was evaluated by visual analysis in 6 publications.[2 3 18-21] All of the included studies reported multiple clinical outcomes. The main characteristics of the included articles are shown in Table 1.

Among the 8 selected studies, 6 studies[16-21] (75%) were conducted in a single center (Germany, n=2; USA, n=2; Japan, n=2), and 2 studies[2 3] were performed in multiple centers (USA, n=1; Europe, n=1). Five articles[2 3 17 20 21] (62.5%) reported adjusted HR. Six studies[2 16 18-21] reported patients with ischemic fibrosis, and the remaining 2 studies[3 17] reported patients with ischemic and nonischemic fibrosis.

Of the 8 eligible studies, 7 received 7 to 9 scores, and the 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 assessed by visual analysis of the funnel plot (Supplemental Fig. S1).

Prevalence of LGE and annualized event rates

Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE ranged from 15% to 62%, and the prevalence of LGE 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 annualized event rates for MACCE of 4.3%.

Additionally, 3 studies[2 19 21] reported a total of 301 patients with diabetes, and 19.27% (n=58) patients with diabetes had LGE. These patients which with patients and LGE, with 27 events occurring over a median follow-up of 3.9 years. The annualized event rates of patients with diabetes and LGE was 11.94%.

MACCE and MACE

A total of 8 studies reported the outcome of MACCE or MACE, and the presence of myocardial fibrosis detected by LGE was a strong predictor of MACCE and MACE in patients with diabetes (random-effects HR 3.87, 95% CI 2.58-5.80; P=0.000) (Fig. 2). Low heterogeneity (I^2=15.1%, P=0.311) existed in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study each time found that the HR values were not significantly changed.

In the analysis of the outcome of MACCE, 3 articles[17 20 21] were included in this subgroup meta-analysis, including 64 participants with LGE and 165 diabetes without LGE, with a total of 64 MACCE outcomes during the follow-up period. Myocardial fibrosis detected by LGE was associated with an increased risk of MACCE in patients with diabetes. The pooled random-effects HR was 2.58 (95% CI 1.42-4.71; P=0.002), with no evidence of heterogeneity (I^2=14.1%; P=0.312) (Fig. 2).

To explore the association between myocardial fibrosis and the outcome of MACE in patients with diabetes, we included 5 articles[2 3 16 18 19] that provided a subgroup meta-analysis. The results showed that the presence of LGE in diabetes was associated with a significantly higher risk of MACE. As in the

discovery analyses, the pooled HR was 5.28 (95% CI 3.20-8.70; P=0.000) with no significant heterogeneity (I^2=0%; P=0.643) from random effects (Fig. 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 was associated with an increased risk of MACCE and MACE in a subgroup meta-analysis with or without adjusted HR. The pooled HRs were 3.52 (random-effects, 95% CI 2.02-6.16; I^2=35.8%) and 4.63 (random-effects, 95% CI 2.35-9.14; I^2=0%), respectively. There was no significant heterogeneity among the studies (Supplemental Fig. S2).

To evaluate the pattern of myocardial fibrosis effects, we further calculated a pooled HR by source of diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischemic fibrosis detected by LGE was significantly associated with increased MACCE and MACE (random-effects HR 3.75, 95% CI 2.11-6.69; I^2=38.3%). There is no study in our meta-analysis reported the relationship between non-ischemic fibrosis and risk of MACCE and MACE; hence, we cannot permed a meta-analysis to assess the relationship between non-ischemic fibrosis and MACCE/MACE. Furthermore, all myocardial fibrosis detected by LGE in patients with diabetes may increase the risk of MACCE and MACE (random-effects HR 4.27, 95% CI 2.17-8.37; I^2=0%) (Supplemental Fig. S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup meta-analysis with 6 studies. Among individuals with diabetes and LV ejection fraction > 50%, the presence of myocardial fibrosis assessed by LGE was significantly associated with MACCE and MACE. The pooled HR was 3.98 (95% CI 2.22-7.25; P=0.000) with random effects, and there was medium heterogeneity among the studies (I^2=37.9%; P=0.153) (Fig. 3).

DISCUSSION

In this meta-analysis, the prevalence of myocardial fibrosis assessed by LGE was increased in patients with diabetes, occurring in 38.09% of them. In addition, the presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted. Moreover, the distribution of ischemic LGE seems to increase the unfavorable prognosis; however, in this study, non-ischemic LGE and MACCE/MACE in patients who with diabetes were not obtained. Specifically, ischemic myocardial fibrosis detected by LGE has a higher predictive value for the occurrence of future MACE than MACCE in patients with diabetes. Furthermore, myocardial fibrosis by LGE 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. Importantly, in our included studies, the presence of myocardial fibrosis in symptomatic patients with diabetes was higher than that in asymptomatic patients with diabetes.[2 3 17] Current guidelines recommend that MRI may be a risk tool in asymptomatic patients with diabetes at moderate or high risk of cardiovascular disease.[14] However, the value of MRI in routine clinical stratification of cardiovascular risk is unclear. Notably, in our meta-analysis, focal myocardial fibrosis detected by LGE did seem to predict a higher occurrence MACCE/MACE in the future, and the annualized event rates for MACCE/MACE in patients with diabetes and LGE was 11.94%. Additionally, the presence of myocardial fibrosis indicated a 8-fold

higher risk for death/MI even in asymptomatic patients with diabetes.[2] It must be noted that other techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than LGE.[33 34] Thus, this finding maybe highlighted the value of LGE for screening for cardiovascular risk in symptomatic patients with diabetes.

The risk of myocardial fibrosis in patients with diabetes is increased and likely multifactorial. First, patients with diabetes have a higher risk for coronary artery disease and myocardial dysfunction.[35-37] Moreover, hyperglycemic metabolism, microvascular disease, and cardiac autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.[4 38 39] However, many studies have shown that patients with diabetes have a high incidence of obesity, visceral fat, hyperlipidemia, and insulin resistance, which may impair myocardial function.[6 40 41] 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 the focal myocardial fibrosis translates to an adverse outcome in future is not fully clear, several potential mechanisms may lead to MACCE/MACE. First, patients with diabetes are more inclined to develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia and heart failure.[3 42-44] Second, patients with diabetes and myocardial fibrosis usually have a greater burden of microvascular complications, such as myocardial ischemia, which confers an increased risk of MACCE/MACE.[16 45] Additionally, the myocardial fibrosis detected by LGE, especially subendocardial fibrosis, indicates patients with diabetes has had a subendocardial infarction in the past, which denotes a higher risk of MACE in the future.[46 47] Furthermore, subjects with diabetes had higher LV and left atrial remodeling due to myocardial fibrosis.[9 43 48] For these reasons, the myocardial fibrosis detected by LGE indeed has clinical relevance.

As previously described, LGE-MRI has become a powerful noninvasive imaging method for the assessment of myocardial fibrosis.[11] Unfortunately, our meta-analysis demonstrated that the presence of myocardial fibrosis derived from LGE conferred an HR of 3.87 for future MACCE/MACE in individuals with diabetes, and the risk increased with ischemic myocardial fibrosis. It must be indicated that two studies[20 21] were included in our meta-analysis, which showed that ischemic myocardial fibrosis detected by LGE did not increase the rate of MACCE. This might be explained by the following reasons, such as limited patients and the patients having a high prevalence of cardiovascular disease. 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, showed that diabetes with ischemic myocardial fibrosis conferred an 8-fold higher risk for all-cause mortality and MI.[2] The prevalence of myocardial fibrosis detected by LGE among patients with diabetes is higher than that among nondiabetic patients.[3 30] Therefore, patients with diabetes and myocardial fibrosis might need aggressive management of cardiac and cerebrovascular risk factors.

However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies[20 21] were from the same group of patients but reported different outcomes. However, when we excluded either of the above articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of myocardial fibrosis in patients with diabetes was not community-based epidemiology research. The prevalence of myocardial fibrosis, therefore, may be higher in this study, which pooled studies including

high-risk or average-risk populations with diabetes. Third, a previous study found that non-ischemic LGE is associated with increased myocardial mass, increased myocardial extracellular volume and impaired diastolic parameters.[49] However, this study was not designed to evaluate the effect of non-ischemic myocardial fibrosis on MACCE/MACE in patients with diabetes. Further studies are needed to establish those non-ischemic LGE lesions and their prognosis. Fourth, most studies selected in this meta-analysis reported adjusted HRs, and various adjustments for adverse outcomes among the selected studies may affect the pooled results. However, the heterogeneity among the selected studies was low, and publication bias did not exist. This might strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration to the prevalence and incidence of LGE was not revealed. However, diabetes duration plays a central role in the assessment of cardiovascular risk.[14 50] Hence, a prospective study that evaluates the association between diabetes duration and myocardial fibrosis and determines the best time to screen myocardial fibrosis by LGE-CMR for risk stratification in patients with diabetes is needed.

CONCLUSIONS

In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI was markedly associated with an important and increased risk of MACCE/MACE. Myocardial fibrosis may be a risk marker for improving risk stratification in patients with diabetes. This meta-analysis highlights the role of LGE-MRI in helping identify high-risk diabetic patients in clinical practice.

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Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on the risk of MACCE or MACE. LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, hazard ratios; CI,

confidence interval.

Figure 3. Forest plots of 6 studies for pooled HR for MACCE and MACE in patients with diabetes with normal LV ejection fraction and 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.

Table legend

Table 1. Description of the Studies Included in the Meta-Analysis

Supplement legend

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

Supplement Figure S1. Funnel plots of 8 eligible stuides.

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.

Notes

Author affiliations

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.

2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.

3. Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.

4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

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Compliance with ethical standards

Not applicable.

Conflict of interest

The authors report no conflicts of interest.

Authors' contributions

Zhi Yang and Rong Xu conceived of this study, and participated in its design and coordination and drafted the manuscript. Contribution to the conceptualization and design: Jia-rong Wang, Hua-yan Xu, Hang Fu, Ling-jun Xie and Meng-xi Yang. Data analysis and interpretation: Lu Zhang, Ling-yi Wen, Hui Liu and Hong Li. Obtaining funding: Zhi-gang Yang and Ying-kun Guo. Zhi-gang Yang and Ying-kun Guo interpreted the results, critically revised the manuscript, and helped to and approved the final version. All authors read and approved this manuscript.

Patient consent for publication

Not required.

Ethics approval

Ethics approval was not required for this meta-analysis.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

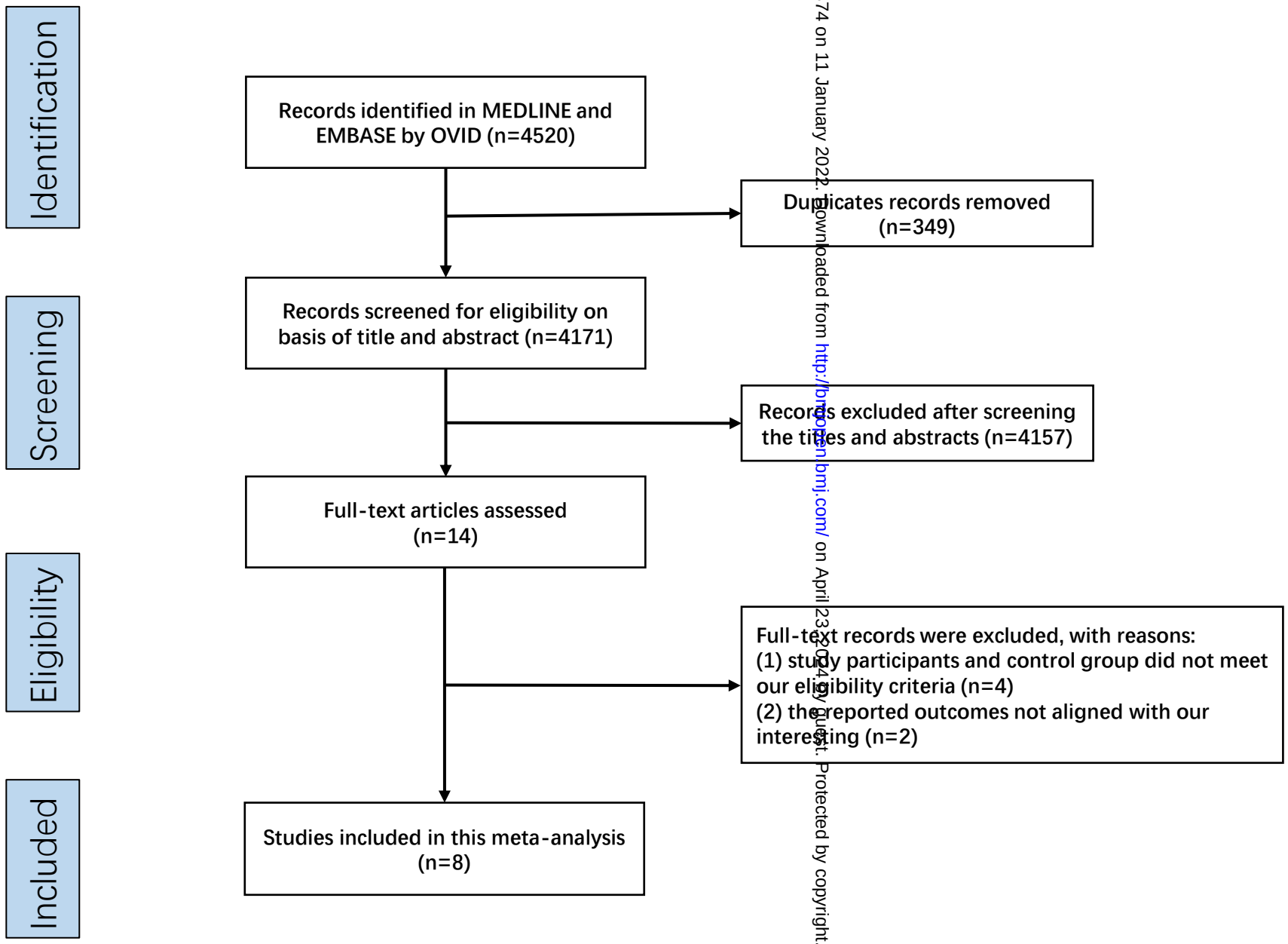
No additional data are available.

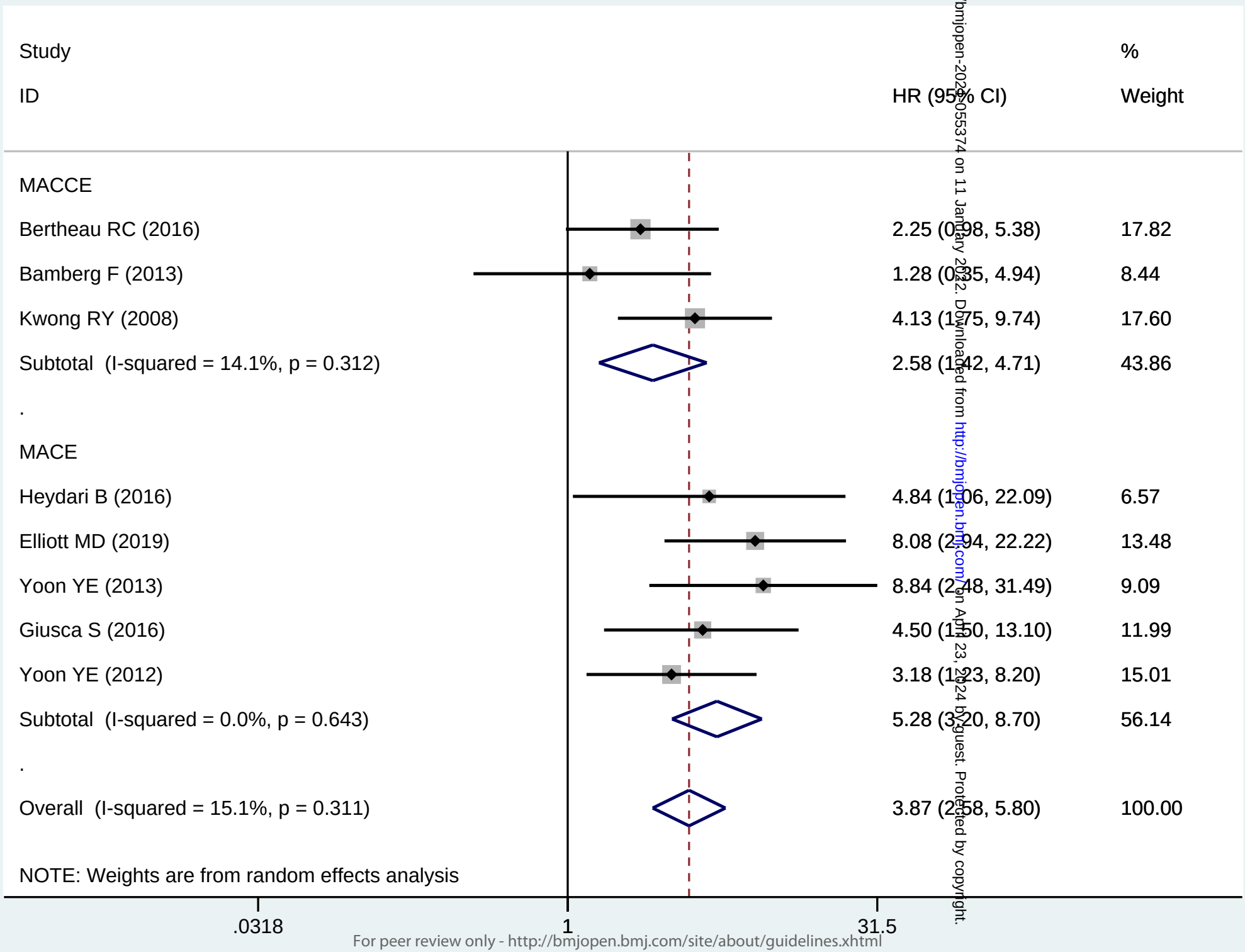
Table 1 Description of the Studies Included in the Meta-Analysis

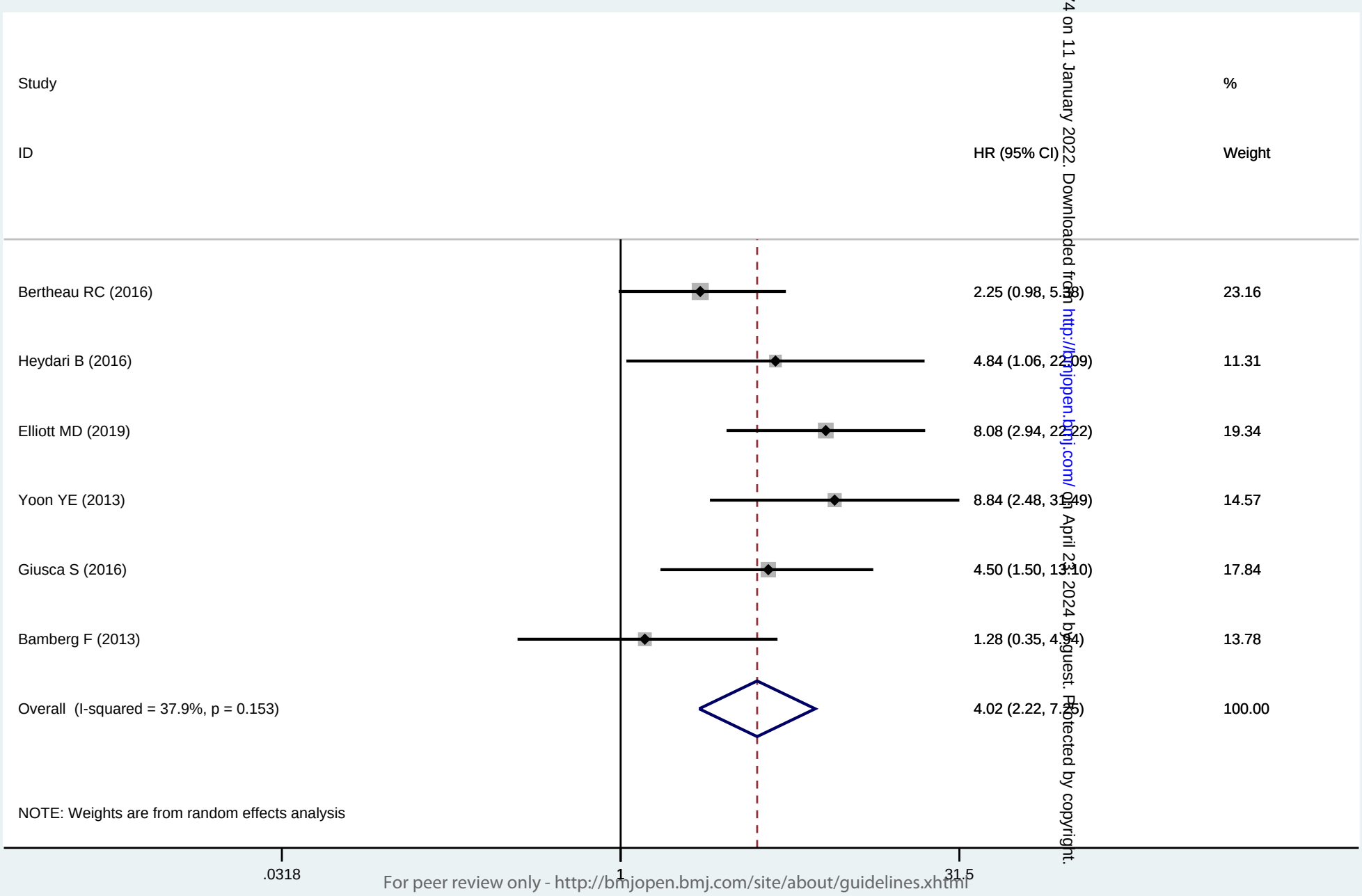
First Author, Year	Journal	patients	Hblc, %	LGE Definition	DM (type)	Mean age (years)	Duration of Diabetes (years)	LVEF (%)	Follow-up duration (months)	male	LGE(+)	Total events	Adjusted HR	Fibrosis type	Type design	outcome	NOS
Berthe au RC,2016	Eur Radiol	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischemic	Prospective, single-centre	MACCE	7
Heydari B,2016	Circ Cardiovasc Imaging	173	7.9±1.8	2 SD	NA	61.7±11.9	NA	51.8±17.6	34.8±30	109	88	21	NO	Ischemic	Prospective, single-centre	MACE	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischemic	Prospective, two-centre	MACE	9
Yoon YE,2013	Eur Radiol	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischemic	Retrospective, single-centre	MACE	7
Giusca S,2016	Eur Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±11.6	35 (23-51.6)	250	176	26	YES	Ischemic and nonischemic	Prospective, multicentre	MACE	8

	sc Imaging															
Bamberg F,2013	Radiology	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischemic	Prospective, single-centre	MACCE	7
Kwong RY,2008	Circulation	107	7.3±1.6	2 SD	NA	59±12	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischemic and nonischemic	Prospective, single-centre	MACCE	9
Yoon YE,2012	Radiology	151	7.4±1.6	visual	NA	67±9	14±11	NA	30(6-103)	113	58	24	NO	Ischemic	Retrospective, single-centre	MACE	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle-Ottawa Scale; HR, hazard ratio; NR, not reported; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events.







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 Tabe 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 Tabe S1-2

Search methodology

Search strategies

1 diabetes[Title/Abstract]
2 "diabetes mellitus"[Title/Abstract]
3 "diabetic*"[Title/Abstract]
4 1 or 2 or 3
5 mri[Title/Abstract]
6 MR[Title/Abstract]
7 "magnetic resonance imag*"[Title/Abstract]
8 "Magnetic Resonance Imaging"[MeSH Terms]
9 "cardiac magnetic resonance"[Title/Abstract]

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 Tabe S1-3

Search methodolog

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

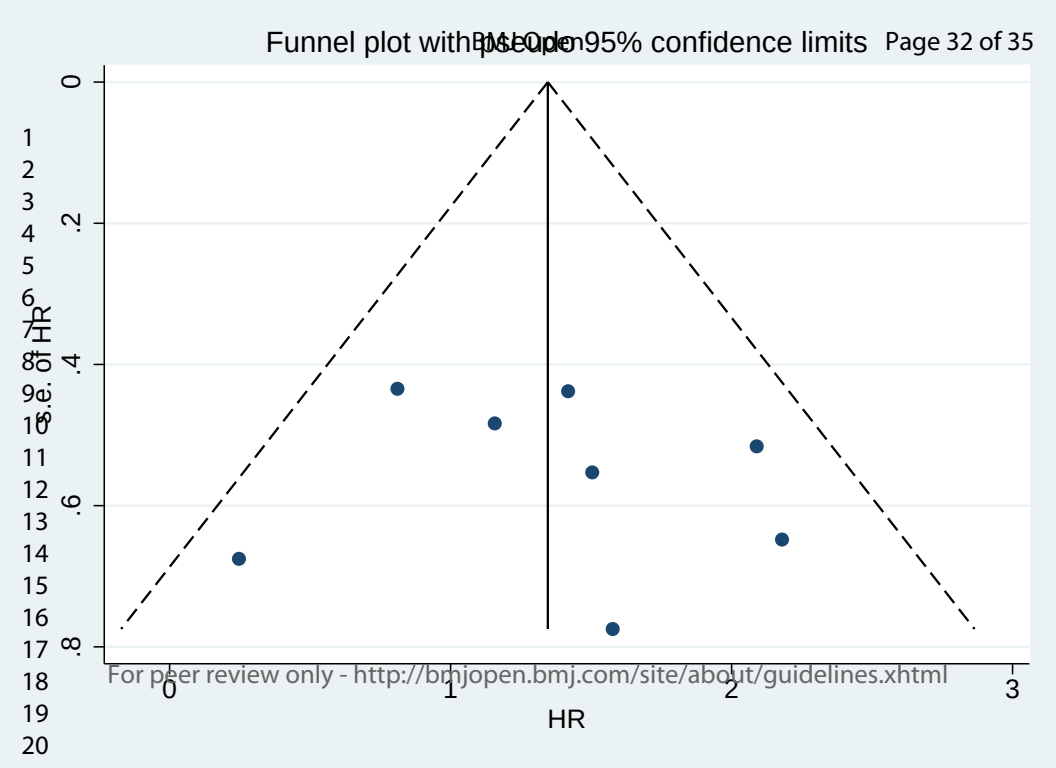
19 death[MeSH Terms]

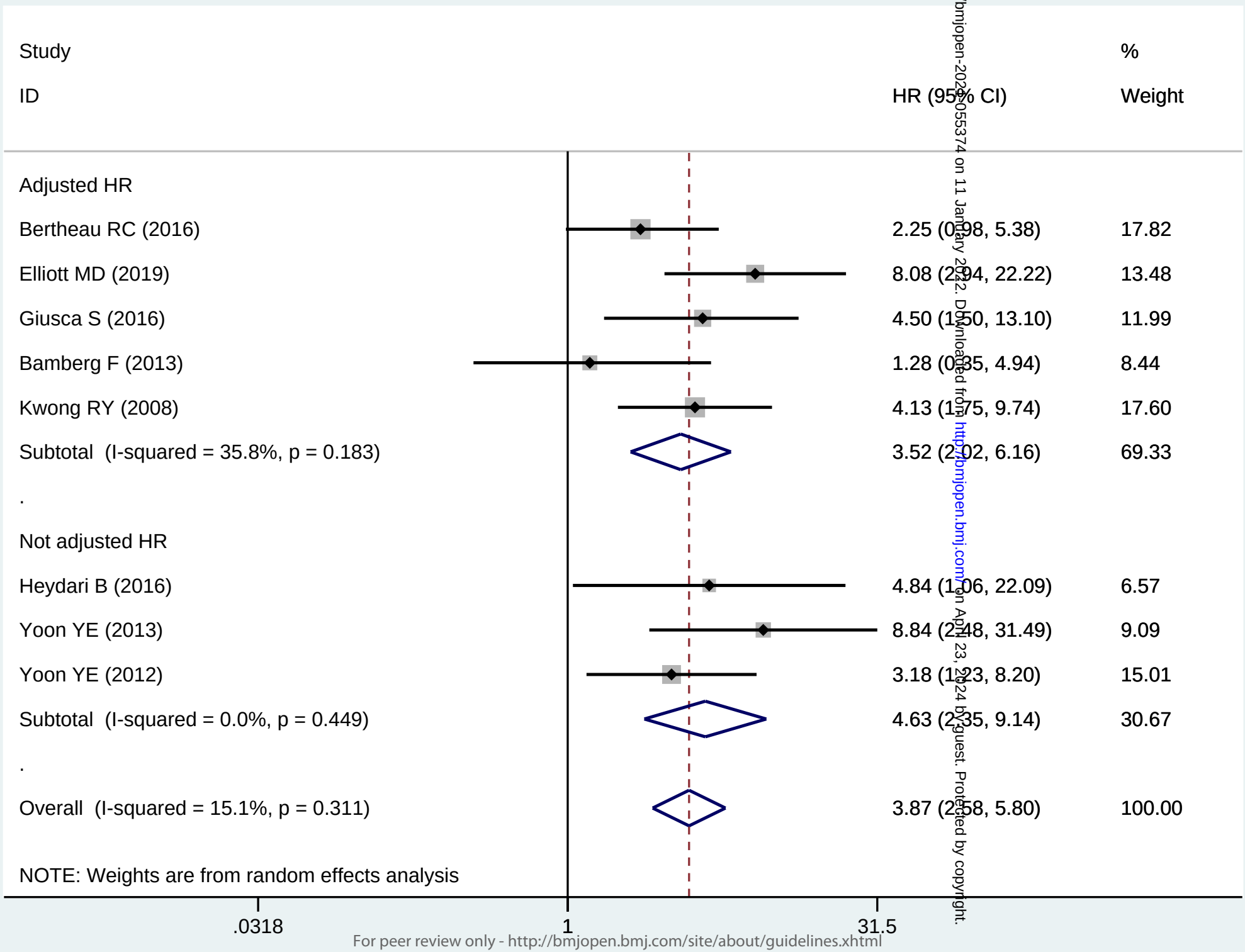
20 models, statistical[MeSH Terms]

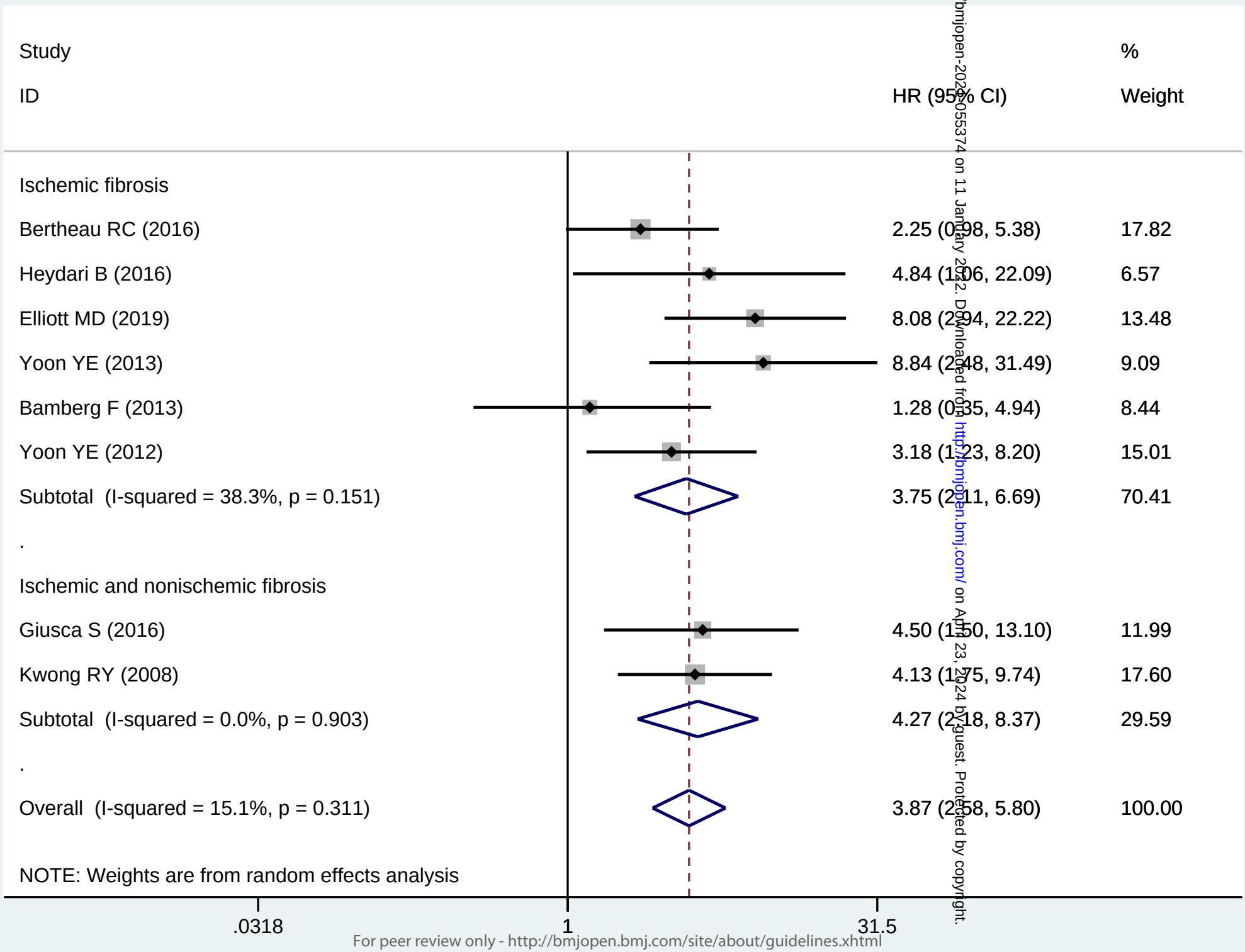
21 15 or 16 or 17 or 18 or 19 or 20

22 4 and 14 and 21

1 to 26 were performed in Cochrane Library.







MOOSE Checklist

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Corresponding Author :

Yingkun Guo, MD, PHD

Department of Radiology, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education; West China Second University Hospital, Sichuan University,

Address: 20# South Renmin Road, Chengdu, Sichuan 610041, China.

Phone No: +86-18980006572

Fax No: +86 28-85502946(H)

Email Address: gykpanda@163.com

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.
√	Hypothesis statement	LGE is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes.
√	Description of study outcomes	MACCE/MACE
√	Type of exposure or intervention used	LGE-MRI
√	Type of study designs used	We included case-control studies, prospective cohort studies, retrospective studies, and randomized controlled studies.
√	Study population	Patients with diabetes.

Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators ZY and RX are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	See the section of "Data Sources and Searches" in the article.
√	Databases and registries searched	PubMed and EMBASE, Cochrane Library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	Articles published in the English language were included.
√	Method of handling abstracts and unpublished studies	Only studies published in peer-reviewed journals were included.
√	Description of any contact with authors	Not.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and HR (95% CI).
√	Assessment of confounding	We extracted the adjustment HR if the study reported the HR with adjustment models.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
√	Assessment of heterogeneity	To analyze the heterogeneity of the included studies, we used forest plots and the I^2 statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 summary table detailing the search strategy used for database search, 1 flow chart,1 summary

		table, 4 forest plots, 1 funnel plots.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 1
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses.
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.
√	Assessment of quality of included studies	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	In this article, we discussed the potential reasons that patients with diabetes have more myocardial fibrosis than who without diabetes. In addition, we discussed the myocardial fibrosis detected by LGE-MRI may increase the risk of MACCE/MACE, and the limitations of our study.
√	Generalization of the conclusions	The presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted.
√	Guidelines for future research	Myocardial fibrosis detected by LGE-MRI may be a risk marker for improving risk stratification in patients with diabetes.
√	Disclosure of funding source	This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586，81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).

BMJ Open

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

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Complete List of Authors:	Yang, Zhi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education; Chengdu Fifth People's Hospital, Department of Radiology Xu, Rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Wang, Jia-rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Xu, Hua-yan; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Fu, Hang; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Xie, Ling-jun; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Yang, Meng-xi ; Sichuan University West China Hospital, Department of Radiology Zhang, Lu; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Wen, Ling-yi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Liu, Hui; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Li, Hong; Sichuan University West China Second University Hospital, Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education Yang, Zhi-gang; Sichuan University West China Hospital, Department of Radiology Guo, Ying-kun ; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and

	Related Diseases of Women and Children of Ministry of Education
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diabetes and endocrinology, Cardiovascular medicine
Keywords:	RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, DIABETES & ENDOCRINOLOGY

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Title page：

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Zhi Yang[1,2*], MS; Rong Xu[1*], MS; Jia-rong Wang[1], MD; Hua-yan Xu[1], MD; Hang Fu[1], MS; Ling-jun Xie[1], MS; Meng-xi Yang[4], MS; Lu Zhang[1], MS; Ling-yi Wen[1], MD; Hui Liu[1], MS; Hong Li[3], MD; Zhi-gang Yang[4†], MD; Ying-kun Guo[1†], MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

*** These authors contributed equally to this work and should be considered the co-first authors.**

† Guarantor and correspondent:
These two authors contributed equally to this work and should be considered corresponding authors.

Zhigang Yang, PhD, MD
Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University，No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)
E-mail: yangzg666@163.com

Yingkun Guo, MD
Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China
Tel: +86-28-85503275(O)
E-mail: gykpanda@163.com

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

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 This systematic review and meta-analysis was performed in accordance with accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

Data sources We retrieved studies from the MEDLINE, Embase and Cochrane by Ovid databases on 27 August 2021.

Eligibility criteria for selecting studies Prospective or respective cohort studies were included if they reported the hazard ratio (HR) and 95% confidence intervals (CI) for MACCEs/MACEs in patients with either type 1 or 2 diabetes and LGE compared with patients without LGE 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 hazard ratios (HRs) and 95% confidence intervals (CIs) were analysed using a random effects model. Heterogeneity was assessed using forest plots and the I^2 statistic.

Results Eight studies with 1121 patients with type 1 or type 2 diabetes were included in this meta-analysis, and the follow-up of patients ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE was associated with an increased risk for MACCEs (HR: 2.58; 95% CI 1.42-4.71; P=0.002) and MACEs (HR: 5.28; 95% CI 3.20-8.70; P<0.0001) in patients with diabetes. Subgroup analysis revealed that ischaemic fibrosis detected by LGE was associated with MACCEs (HR 3.75, 95% CI 2.11-6.69; P<0.0001) in patients with diabetes. In diabetic patients with preserved ejection fraction, the association between myocardial fibrosis detected by LGE and MACCEs remained significant (HR: 3.98; 95% CI 2.22-7.25; P<0.0001).

Conclusions This study demonstrated that ischaemic myocardial fibrosis detected by LGE conferred an increased risk of MACCEs/MACEs in patients with diabetes and may be an imaging biomarker for risk stratification.

Keywords: Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

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 (MOOSE) statement.

Myocardial fibrosis was a proven to be a reliable prognostic predictor via subgroup analyses based on preserved left ventricular ejection fraction (LVEF), ischaemic LGE, MACCEs or MACEs.

All included studies were not community-based epidemiology research and came from developed countries.

Reduced LVEF and nonischaemic subgroup analyses were not performed due to the limited number of related studies.

INTRODUCTION

Diabetes is becoming a global health care 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 myocardial fibrosis than their nondiabetic counterparts as a result of macrovascular dysfunction, even when they are asymptomatic.[2-5] Moreover, the presence of myocardial fibrosis is associated with diabetic cardiomyopathy.[6-8] In addition, myocardial fibrosis can increase the risk of left ventricular (LV) dysfunction and heart failure with preserved ejection fraction in patients with diabetes.[9 10] Therefore, it is important to detect myocardial fibrosis by noninvasive imaging technology for risk stratification.

Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) is the most reliable tool for identifying and quantifying myocardial fibrosis in vivo and allows discrimination between ischaemic and nonischaemic fibrosis without ionizing radiation.[11-13] LGE-MRI, a promising technique, can provide more histological information than unenhanced cardiac MRI to illuminate the complex pathophysiologic pathways of myocardial viability.[3] Furthermore, recent guidelines suggested that MRI may be considered an imaging technique for stratifying cardiovascular risk in patients with diabetes.[14 15] This may highlight the role of LGE-MRI in the risk stratification of patients with diabetes.

Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.[2] Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACEs) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCEs) is unclear.[2 3 16-21] In addition, most previous studies were single-centre studies and have been limited by small numbers of events. Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected by late gadolinium enhancement (LGE) with future MACCEs and MACEs in patients with diabetes.

METHODS

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[22 23]

Data Sources and Searches

We searched the Ovid MEDLINE, Ovid Embase and Ovid Cochrane Library databases to find eligible studies on August 27, 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 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 revascularization, and hospitalization for unstable angina; the

study reported the hazard ratio (HR) and 95% confidence intervals (CI) 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 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 9 points involving 3 factors: patient selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).[26] We categorized the quality of studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 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 compared to those without LGE. We defined the primary endpoint as MACCEs, including myocardial infarction (MI), all-cause mortality, coronary and carotid revascularization, 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 nonischaemic fibrosis as described previously.[3]

We pooled the adjusted HRs with 95% CIs using a random effects model. In addition, we calculated the annualized 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 I^2 statistic.[27] We assigned I^2 values of 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively. Considering the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 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 version 12 (StataCorp). *P* values were two sided, with a level of 0.05 considered significant.

Patient and Public Involvement

No patient involved.

RESULTS

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[29-34] 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, 8 studies[2 3 16-21] fulfilled our inclusion criteria and were included in this meta-analysis (Fig. 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[2 17-21] reported the duration of diabetes, and the mean duration of diabetes was 15 years. A total of 6 studies[2 3 16 19-21] reported the LV ejection fraction, and the mean LV ejection fraction was 57.78%. The presence of LGE was evaluated by visual analysis in 6 studies.[2 3 18-21] All of the included studies reported multiple clinical outcomes. The main characteristics of the included articles are shown in Table 1.

Among the 8 selected studies, 6 studies[16-21] (75%) were conducted in a single centre (Germany, n=2; USA, n=2; Japan, n=2), and 2 studies[2 3] were performed in multiple centres (USA, n=1; Europe, n=1). Five articles[2 3 17 20 21] (62.5%) reported adjusted HRs. Six studies[2 16 18-21] reported patients with ischaemic fibrosis, and the remaining 2 studies[3 17] reported patients with ischaemic and nonischaemic 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 (Supplemental Fig. S1).

Prevalence of LGE and annualized event rates

Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE ranged from 15% to 62%, and the prevalence of LGE 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 annualized event rates for MACCEs of 4.3%.

Additionally, 3 studies[2 19 21] reported a total of 301 patients with diabetes, and 19.27% (n=58) of patients with diabetes had LGE. Twenty-seven events occurred in these diabetic patients with LGE over a median follow-up of 3.9 years. The annualized event rate of patients with diabetes and LGE was 11.94%.

MACCEs and MACEs

A total of 8 studies reported the outcome of MACCEs or MACEs, and the presence of myocardial fibrosis detected by LGE was a strong predictor of MACCEs and MACEs in patients with diabetes (random effects HR 3.87, 95% CI 2.58-5.80; P<0.0001) (Fig. 2). There was low heterogeneity (I^2=15.1%, P=0.311) in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study at a time did not reveal any significant changes in the HR values.

In the analysis of the outcome of MACCEs, 3 articles[17 20 21] were included in this subgroup analysis, including 64 participants with LGE and 165 diabetes without LGE, with a total of 64 MACCEs during the follow-up period. Myocardial fibrosis detected by LGE 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 1.42-4.71; P=0.002), with no evidence of heterogeneity (I^2=14.1%; P=0.312) (Fig. 2).

To explore the association between myocardial fibrosis and the outcome of MACEs in patients with diabetes, we included 5 articles[2 3 16 18 19] that provided a subgroup outcome analysis of MACEs. The results showed that the presence of LGE in diabetes was associated with a significantly higher risk of MACEs. As in the discovery analyses, the pooled HR obtained via the random effects model was 5.28 (95% CI 3.20-8.70; P<0.0001), with no significant heterogeneity (I^2=0%; P=0.643) (Fig. 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 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 2.02-6.16; I^2=35.8%) and 4.63 (95% CI 2.35-9.14; I^2=0%), respectively. There was no significant heterogeneity among the studies (Supplemental Fig. 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 by LGE was significantly associated with increased MACCEs and MACEs (random effects HR 3.75, 95% CI 2.11-6.69; I^2=38.3%). 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. Furthermore, two studies reported that ischaemic and nonischaemic myocardial fibrosis detected by LGE in patients with diabetes may increase the risk of MACCEs and MACEs, and the pooled HR obtained via the random effects model was 4.27 (95% CI 2.17-8.37; I^2=0%) (Supplemental Fig. S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup analysis with 6 studies. Among individuals with diabetes and LV ejection fraction > 50%, the presence of myocardial fibrosis assessed by LGE was significantly associated with MACCEs and MACEs. The pooled HR obtained via the random effects model was 3.98 (95% CI 2.22-7.25; P=0.000), and there was a medium amount of heterogeneity among the studies (I^2=37.9%; P=0.153) (Fig. 3).

DISCUSSION

In this meta-analysis, the prevalence of myocardial fibrosis (mainly ischaemic fibrosis) assessed by LGE 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 has a higher predictive value for the occurrence of future MACEs than MACCEs in patients with diabetes. However, in this study, the relationship of nonischaemic LGE and MACCEs/MACEs in patients with diabetes was not elucidated. Therefore, ischaemic myocardial fibrosis by LGE 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, 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.[2 3 17] Current guidelines recommend that MRI may be a risk tool in asymptomatic patients with diabetes at moderate or high risk of cardiovascular disease.[14] However, the value of MRI in routine clinical stratification of cardiovascular risk is unclear. Notably, in our meta-analysis, focal ischaemic myocardial fibrosis detected by LGE did seem to predict a higher occurrence of MACCEs/MACEs in the future, and the annualized event rate for MACCEs/MACEs in patients with diabetes and LGE was 11.94%. Additionally, the presence of

ischaemic myocardial fibrosis indicated an 8-fold higher risk for death/MI even in asymptomatic patients with diabetes.[2] It must be noted that other techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than LGE.[35 36] Thus, this finding may highlight the value of LGE 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.[37-39] Moreover, hyperglycaemic metabolism, microvascular disease, and cardiac autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.[4 40 41] 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.[6 42 43] 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.[3 44-46] 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.[16 47] Additionally, the myocardial fibrosis detected by LGE, 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.[48 49] Furthermore, subjects with diabetes had higher LV and left atrial remodelling due to myocardial fibrosis.[9 45 50] For these reasons, the myocardial fibrosis detected by LGE has great potential to lead to adverse outcomes in the future.

As previously described, LGE-MRI has become a powerful noninvasive imaging method for the assessment of myocardial fibrosis.[11] Although two studies[20 21] included in our meta-analysis showed that ischaemic myocardial fibrosis detected by LGE did not increase the rate of MACCEs, our meta-analysis demonstrated that the presence of ischaemic myocardial fibrosis derived from LGE conferred an HR of 3.75 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, showed that diabetes with ischaemic myocardial fibrosis conferred an 8-fold higher risk for all-cause mortality and MI.[2] The prevalence of ischaemic myocardial fibrosis detected by LGE among patients with diabetes is higher than that among nondiabetic patients.[3 30] Therefore, patients with diabetes and ischaemic myocardial fibrosis might need aggressive management of cardiac and cerebrovascular risk factors.

However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies[20 21] were from the same group of patients but reported different outcomes. However, when we excluded either of the above articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of myocardial fibrosis in patients with diabetes was not obtained via community-based epidemiology

research. Therefore, the prevalence of myocardial fibrosis may be higher in this study, which pooled studies including high-risk or average-risk populations with diabetes. Third, a previous study found that nonischaemic LGE is associated with increased myocardial mass, increased myocardial extracellular volume and impaired diastolic parameters.[51] However, subgroup analysis was not conducted to evaluate the effect of nonischaemic myocardial fibrosis on MACCEs/MACEs in patients with diabetes due to a lack of information. Further studies are needed to establish nonischaemic LGE lesions and their prognosis. Fourth, most studies selected in this meta-analysis reported adjusted HRs, and various adjustments for adverse outcomes among the selected studies may affect the pooled results. However, the heterogeneity among the selected studies was low, and publication bias did not exist. This might strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration to the prevalence and incidence of LGE was not revealed. However, diabetes duration plays a central role in the assessment of cardiovascular risk.[14 52] Hence, prospective studies that evaluate the association between diabetes duration and myocardial fibrosis and determine the best time to screen myocardial fibrosis by LGE-CMR for risk stratification in patients with diabetes 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. Ischaemic myocardial fibrosis is a strong risk marker for improving risk stratification in patients with diabetes. The value of nonischaemic myocardial fibrosis in predicting MACCEs/MACEs in diabetes needs to be verified in future studies. This meta-analysis highlights the role of LGE-MRI in helping predict MACCEs/MACEs in complicated diabetic patients, especially those with cardiac complications and a high risk for myocardial fibrosis.

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Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. 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; HR, hazard ratios; CI, confidence interval.

Figure 3. Forest plots of 6 studies for pooled HR for MACCEs and MACEs in patients with diabetes with normal LV ejection fraction and myocardial fibrosis detected by LGE. HR, hazard ratio; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.

Table legend

Table 1. Description of the Studies Included in the Meta-Analysis

Supplement legend

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

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forest plots of pooled HRs for MACCEs and MACEs in adjusted or not

adjusted HR studies. HR, hazard ratios; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.

Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCEs and MACEs in patients with diabetes and different patterns of myocardial fibrosis detected by LGE. HR, hazard ratios; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.

Notes

Author affiliations

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.

2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.

3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.

4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

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Compliance with ethical standards

Not applicable.

Conflict of interest

The authors report no conflicts of interest.

Authors' contributions

Zhi Yang and Rong Xu conceived of this study, participated in its design and coordination and drafted the manuscript. Contribution to the conceptualization and design: Jia-rong Wang, Hua-yan Xu, Hang Fu, Ling-jun Xie and Meng-xi Yang. Data analysis and interpretation: Lu Zhang, Ling-yi Wen, Hui Liu and Hong Li. Obtaining funding: Zhi-gang Yang and Ying-kun Guo. Zhi-gang Yang and Ying-kun Guo interpreted the results, critically revised the manuscript, and helped to and approved the final version. All authors read and approved this manuscript.

Patient consent for publication

Not required.

Ethics approval

Ethics approval was not required for this meta-analysis.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

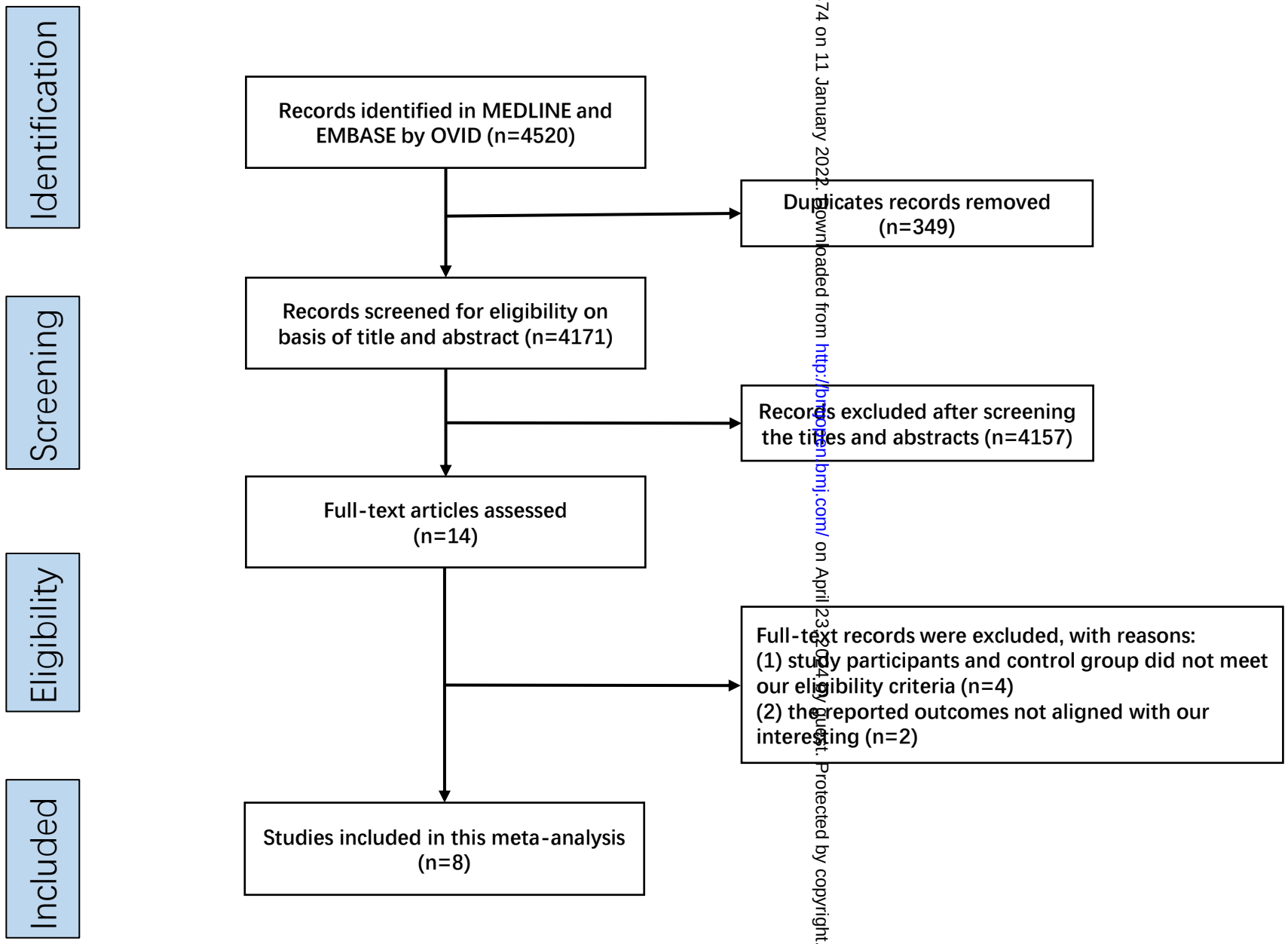
No additional data are available.

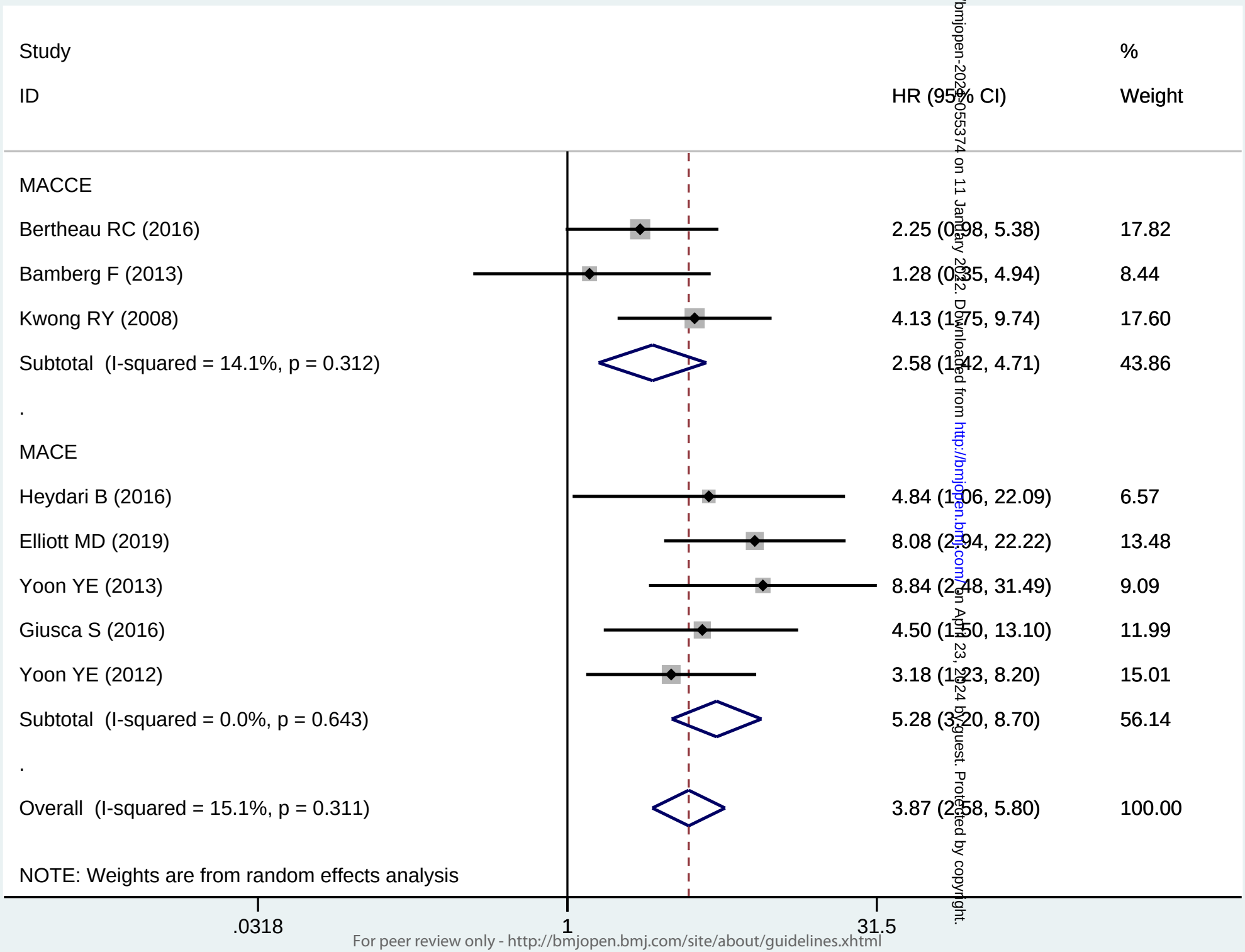
Table 1 Description of the Studies Included in the Meta-Analysis

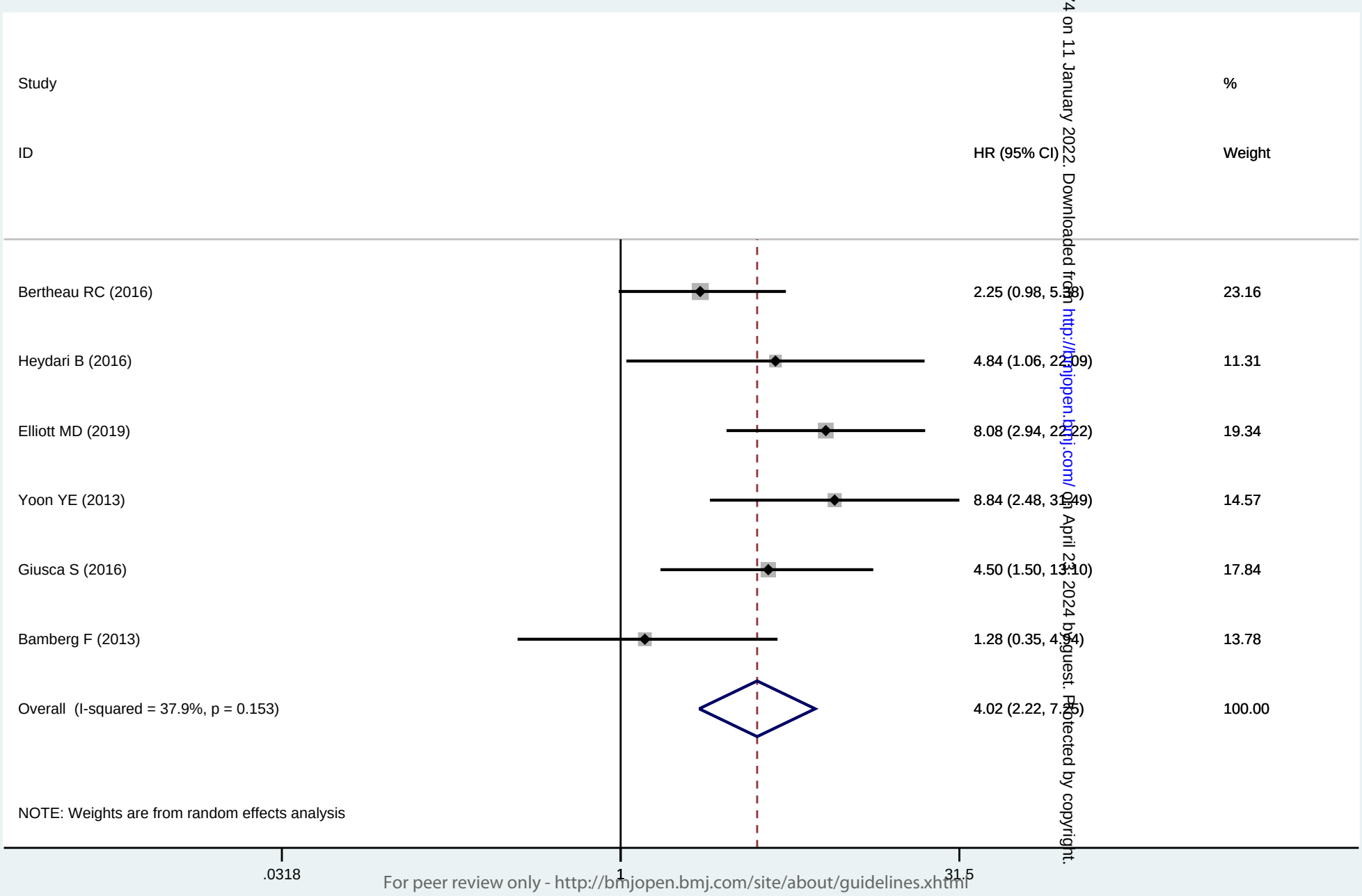
First Author, Year	Journal	patients	HbAlc, %	LGE Definition	DM (type)	Mean age (years)	Duration of Diabetes (years)	LVEF (%)	Follow-up duration (months)	male	LGE(+)	Total events	Adjusted HR	Fibrosis type	Type design	Outcome	NOS
Berthe au RC,2016	Eur Radiol	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischaemic	Prospective, single-centre	MACCES	7
Heyda ri B,2016	Circ Cardiovasc Imaging	173	7.9±1.8	2 SD	NA	61.7±11.9	NA	51.8±7.6	34.8±30	109	88	21	NO	Ischaemic	Prospective, single-centre	MACES	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischaemic	Prospective, two-centre	MACES	9
Yoon YE,2013	Eur Radiol	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischaemic	Retrospective, single-centre	MACES	7
Giusca S,2016	Eur Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±11.6	35 (23-51.6)	250	176	26	YES	Ischaemic and	Prospective,	MACES	8

	sc Imaging												nonischaemic	multicentre		
Bamberg F,2013	Radiology	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischaemic	Prospective, single-centre	MACCES	7
Kwong RY,2008	Circulation	107	7.3±1.6	2 SD	NA	59±12	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischaemic and nonischaemic	Prospective, single-centre	MACCES	9
Yoon YE,2012	Radiology	151	7.4±1.6	visual	NA	67±9	14±11	NA	30(6-103)	113	58	24	NO	Ischaemic	Retrospective, single-centre	MACES	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle–Ottawa Scale; HR, hazard ratio; NR, not reported; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events.







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.

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Supplement Tabe 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 Tabe S1-2

Search methodology

Search strategies

1 diabetes[Title/Abstract]
2 "diabetes mellitus"[Title/Abstract]
3 "diabetic*"[Title/Abstract]
4 1 or 2 or 3
5 mri[Title/Abstract]
6 MR[Title/Abstract]
7 "magnetic resonance imag*"[Title/Abstract]
8 "Magnetic Resonance Imaging"[MeSH Terms]
9 "cardiac magnetic resonance"[Title/Abstract]

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

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1 to 26 were performed in PubMed.

Supplement Tabe S1-3

Search methodolog

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

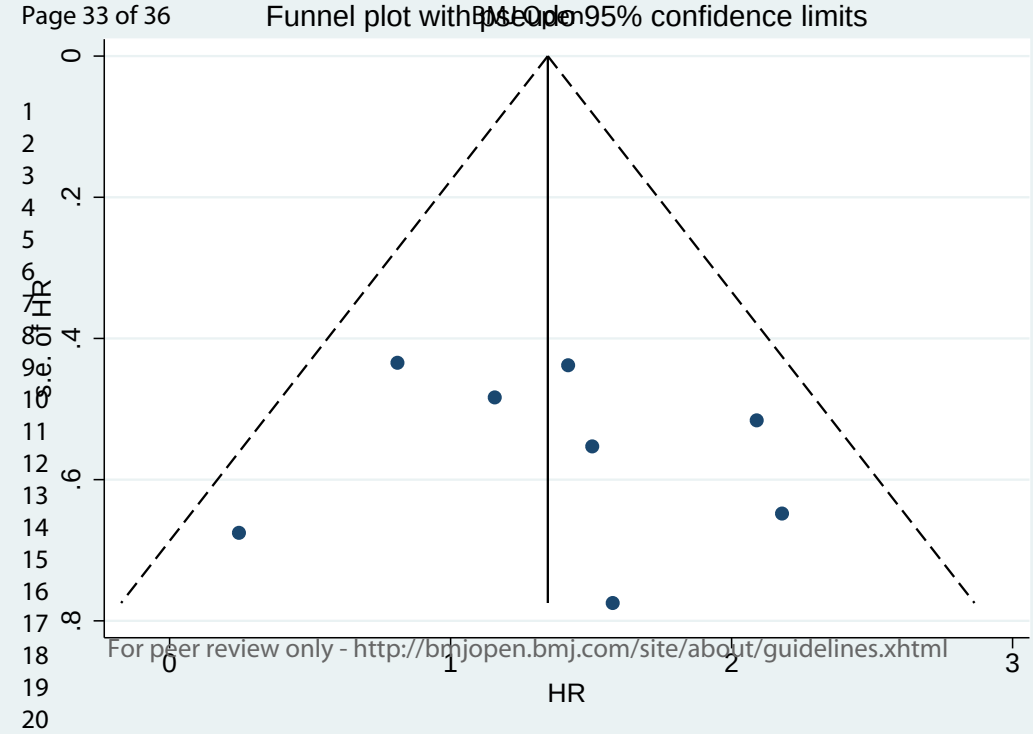
19 death[MeSH Terms]

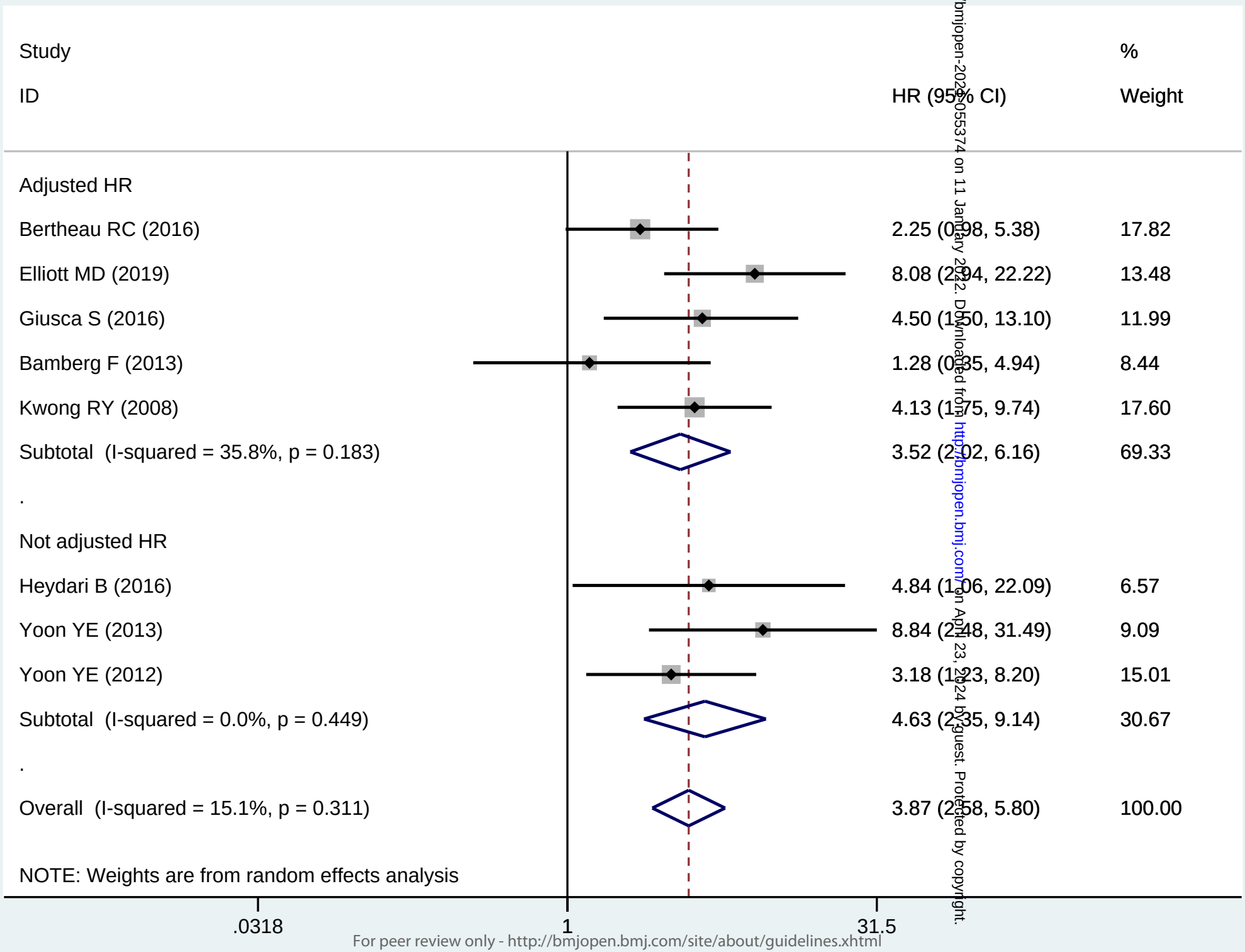
20 models, statistical[MeSH Terms]

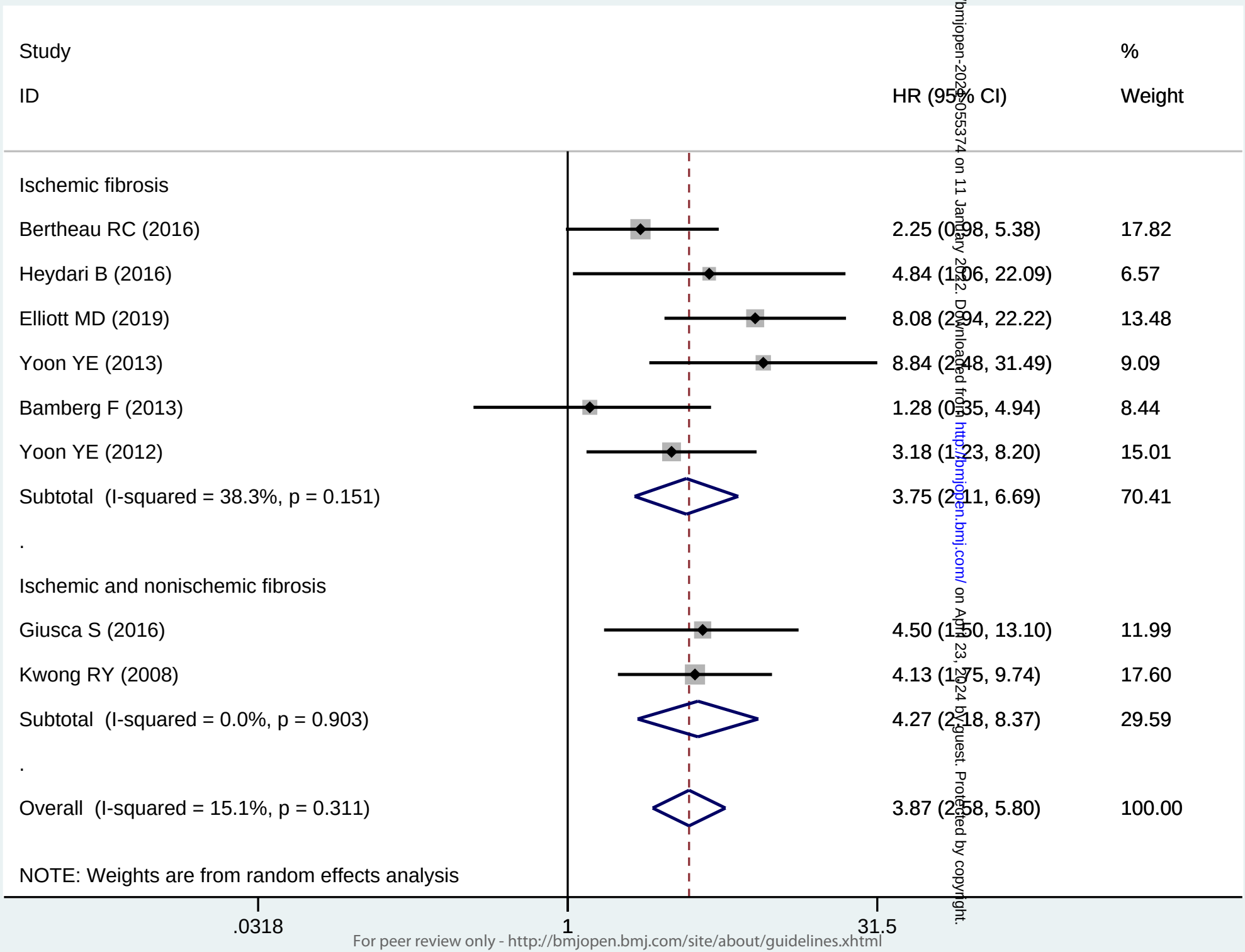
21 15 or 16 or 17 or 18 or 19 or 20

22 4 and 14 and 21

1 to 26 were performed in Cochrane Library.







MOOSE Checklist

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Corresponding Author :

Yingkun Guo, MD, PHD

Department of Radiology, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education; West China Second University Hospital, Sichuan University,

Address: 20# South Renmin Road, Chengdu, Sichuan 610041, China.

Phone No: +86-18980006572

Fax No: +86 28-85502946(H)

Email Address: gykpanda@163.com

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.
√	Hypothesis statement	LGE is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes.
√	Description of study outcomes	MACCE/MACE
√	Type of exposure or intervention used	LGE-MRI
√	Type of study designs used	We included case-control studies, prospective cohort studies, retrospective studies, and randomized controlled studies.
√	Study population	Patients with diabetes.

Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators ZY and RX are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	See the section of "Data Sources and Searches" in the article.
√	Databases and registries searched	PubMed and EMBASE, Cochrane Library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	Articles published in the English language were included.
√	Method of handling abstracts and unpublished studies	Only studies published in peer-reviewed journals were included.
√	Description of any contact with authors	Not.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and HR (95% CI).
√	Assessment of confounding	We extracted the adjustment HR if the study reported the HR with adjustment models.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
√	Assessment of heterogeneity	To analyze the heterogeneity of the included studies, we used forest plots and the I^2 statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 summary table detailing the search strategy used for database search, 1 flow chart,1 summary

		table, 4 forest plots, 1 funnel plots.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 1
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses.
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.
√	Assessment of quality of included studies	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	In this article, we discussed the potential reasons that patients with diabetes have more myocardial fibrosis than who without diabetes. In addition, we discussed the myocardial fibrosis detected by LGE-MRI may increase the risk of MACCE/MACE, and the limitations of our study.
√	Generalization of the conclusions	The presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted.
√	Guidelines for future research	Myocardial fibrosis detected by LGE-MRI may be a risk marker for improving risk stratification in patients with diabetes.
√	Disclosure of funding source	This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586，81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).

BMJ Open

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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Complete List of Authors:	Yang, Zhi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education; Chengdu Fifth People's Hospital, Department of Radiology Xu, Rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Wang, Jia-rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Xu, Hua-yan; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Fu, Hang; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Xie, Ling-jun; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Yang, Meng-xi ; Sichuan University West China Hospital, Department of Radiology Zhang, Lu; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Wen, Ling-yi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Liu, Hui; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education Li, Hong; Sichuan University West China Second University Hospital, Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education Yang, Zhi-gang; Sichuan University West China Hospital, Department of Radiology Guo, Ying-kun ; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education

Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diabetes and endocrinology, Cardiovascular medicine
Keywords:	RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, DIABETES & ENDOCRINOLOGY

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

Zhi Yang[1,2*], MS; Rong Xu[1*], MS; Jia-rong Wang[1], MD; Hua-yan Xu[1], MD; Hang Fu[1], MS; Ling-jun Xie[1], MS; Meng-xi Yang[4], MS; Lu Zhang[1], MS; Ling-yi Wen[1], MD; Hui Liu[1], MS; Hong Li[3], MD; Zhi-gang Yang[4†], MD; Ying-kun Guo[1†], MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

*** These authors contributed equally to this work and should be considered the co-first authors.**

† Guarantor and correspondent:
These two authors contributed equally to this work and should be considered corresponding authors.

Zhigang Yang, PhD, MD
Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University，No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)
E-mail: yangzg666@163.com

Yingkun Guo, MD
Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China
Tel: +86-28-85503275(O)
E-mail: gykpanda@163.com

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 (MOOSE) statement.

Data sources We searched the MEDLINE, Embase and Cochrane by Ovid databases for studies

published up to Aug 27, 2021.

Eligibility criteria Prospective or respective cohort studies were included if they reported the hazard ratio (HR) and 95% confidence intervals (CI) 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 hazard ratios (HR) and 95% confidence intervals (CIs) were analysed using a random effects model. Heterogeneity was assessed using forest plots and I^2 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 1.42-4.71; P=0.002) and MACEs (HR: 5.28; 95% CI 3.20-8.70; 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 2.38-6.07; 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.

Keywords: Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

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 (MOOSE) statement.

*All included studies were not community-based epidemiology research and came from developed countries.

*Reduced LVEF and nonischaemic subgroup analyses were not performed due to the limited number of related studies.

INTRODUCTION

Diabetes is becoming a global health care 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 ischemic myocardial fibrosis and non-ischemic myocardial fibrosis than their nondiabetic counterparts, and the mechanism has been confirmed extensively.[2-5] The phenotype of unrecognized ischemic 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-ischemic myocardial fibrosis in patients with diabetes.[6-8] In addition, diffuse interstitial myocardial fibrosis can increase the risk of non-ischemic myocardial fibrosis, and was associated with increased risk of left ventricular (LV) dysfunction in patients with diabetes.[9 10] However, Non-ischemic myocardial fibrosis, may be a biomarker for risk stratification, has not been systematically characterized.[3 9]

Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) is the most reliable tool for identifying and quantifying focal myocardial fibrosis in vivo and allows discrimination between ischaemic and nonischaemic fibrosis without ionizing radiation.[11-13] LGE-MRI, a promising technique, can provide more histological information than unenhanced cardiac MRI to illuminate the complex pathophysiologic 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 MRI may be considered an imaging technique for stratifying cardiovascular risk in patients with diabetes.[14 15] This may highlight the role of LGE-MRI in the risk stratification of patients with diabetes.

Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.[2] Although several studies have demonstrated that focal myocardial fibrosis detected by LGE-MRI may predict MACEs in patients with diabetes, the prognostic value of focal myocardial fibrosis for major cardiac and cerebrovascular events (MACCEs) is unclear. [3 16-21] In addition, most previous studies were single-centre studies and have been limited by small numbers of events. Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected by LGE-MRI with future MACCEs and MACEs in patients with diabetes.

METHODS

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) 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 Aug 27, 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 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 revascularization, and hospitalization for unstable angina; the study reported the hazard ratio (HR) and 95% confidence intervals (CI) 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 9 points involving 3 factors: patient selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).[26] We categorized the quality of studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 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 revascularization, 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 nonischaemic fibrosis as described previously.[3]

We pooled the adjusted HRs with 95% CIs using a random effects model. In addition, we calculated the annualized 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 I^2 statistic.[27] We assigned I^2 values of 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively. Considering the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 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 version 12 (StataCorp). *P* values were two sided, with a level of 0.05 considered significant.

Patient and Public Involvement

No patient involved.

RESULTS

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[29-34] 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, 8 studies[2 3 16-21] fulfilled our inclusion criteria and were included in this meta-analysis (Fig. 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[2 17-21] reported the duration of diabetes, and the mean duration of diabetes was 15 years. A total of 6 studies[2 3 16 19-21] 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 6 studies.[2 3 18-21] All of the included studies reported multiple clinical

outcomes. The main characteristics of the included articles are shown in Table 1.

Among the 8 selected studies, 6 studies[16-21] (75%) were conducted in a single centre (Germany, n=2; USA, n=2; Japan, n=2), and 2 studies[2 3] were performed in multiple centres (USA, n=1; Europe, n=1). Five articles[2 3 17 20 21] (62.5%) reported adjusted HR. Seven studies[2 16-21] reported patients with ischaemic fibrosis, and the remaining 1 studies[3] reported patients with ischaemic and nonischaemic 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 (Supplemental Fig. S1).

Prevalence of LGE-MRI-detected myocardial fibrosis and annualized 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 annualized event rates for MACCEs of 4.3%.

Additionally, 3 studies[2 19 21] 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 annualized event rate of patients with diabetes and LGE-MRI-detected myocardial fibrosis was 11.94%.

MACCEs and MACEs

A total of 8 studies reported the outcome of MACCEs or MACEs, and the presence of myocardial fibrosis detected by LGE-MRI was a strong predictor of MACCEs and MACEs in patients with diabetes (random effects HR 3.87, 95% CI 2.58-5.80; P<0.0001) (Fig. 2). There was low heterogeneity (I^2=15.1%, P=0.311) in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study at a time did not reveal any significant changes in the HR values.

In the analysis of the outcome of MACCEs, 3 articles[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 1.42-4.71; P=0.002), with no evidence of heterogeneity (I^2=14.1%; P=0.312) (Fig. 2).

To explore the association between myocardial fibrosis and the outcome of MACEs in patients with diabetes, we included 5 articles[2 3 16 18 19] that provided a subgroup outcome analysis of MACEs. The results showed that the presence of LGE-MRI-detected myocardial fibrosis in diabetes was associated with a significantly higher risk of MACEs. As in the discovery analyses, the pooled HR obtained via the random effects model was 5.28 (95% CI 3.20-8.70; P<0.001), with no significant heterogeneity (I^2=0%; P=0.643) (Fig. 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 2.02-6.16; I^2=35.8%) and 4.63 (95% CI 2.35-9.14; I^2=0%), respectively. There was no significant heterogeneity among the studies (Supplemental Fig. 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 by LGE-MRI was significantly associated with increased MACCEs and MACEs (random effects HR 3.80, 95% CI 2.38-6.07; I^2=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. (Supplemental Fig. S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup analysis with 6 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 2.22-7.25; P<0.001), and there was a medium amount of heterogeneity among the studies (I^2=37.9%; P=0.153) (Fig. 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 nonischaemic 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.[2 3 17] 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.[2 17] All studies included in our meta-analysis involved patients who had suffered a unrecognized myocardial infarction, which implied they might represented a higher-risk population. Current guidelines recommend that MRI may serve as a risk tool in asymptomatic diabetic patients with moderate or high risk of cardiovascular disease.[14] 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 annualized 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 8-fold higher risk for death/MI even in asymptomatic patients with diabetes.[2] Notably, other techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than LGE-MRI.[35 36] 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.[37-39] Moreover, hyperglycaemic metabolism, microvascular disease, and cardiac autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.[4 40 41] 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.[6 42 43] 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.[3 44-46] 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.[16 47] 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.[48 49] Furthermore, subjects with diabetes had higher LV and left atrial remodelling due to myocardial fibrosis.[7 45 50] 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.[11] Although two studies[20 21] 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 8-fold higher risk for all-cause mortality and MI.[2] The prevalence of ischaemic myocardial fibrosis detected by LGE-MRI among patients with diabetes is higher than that among nondiabetic patients.[3 30] Although there were several studies have reported the prognostic value of ischemic myocardial fibrosis detected by LGE-MRI in patients with diabetes, the prognostic value of non-ischemic 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-ischemic myocardial fibrosis in patients

with diabetes, more relevant studies are needed.

However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies[20 21] were from the same group of patients but reported different outcomes. However, when we excluded either of the above articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of myocardial fibrosis in patients with diabetes was not obtained via community-based epidemiology research. Therefore, the prevalence of myocardial fibrosis may be higher in this study, which pooled studies including high-risk or average-risk populations with diabetes. Third, a previous study found that nonischaemic LGE-MRI-detected myocardial fibrosis is associated with increased myocardial mass, increased myocardial extracellular volume and impaired diastolic parameters.[7] However, subgroup analysis was not conducted to evaluate the effect of nonischaemic myocardial fibrosis on MACCEs/MACEs in patients with diabetes due to a lack of information. Further studies are needed to establish nonischaemic LGE-MRI lesions and their prognosis. Fourth, most studies selected in this meta-analysis reported adjusted HR, and various adjustments for adverse outcomes among the selected studies may affect the pooled results. However, the heterogeneity among the selected studies was low, and publication bias did not exist. This might strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration to the prevalence and incidence of LGE-MRI-detected myocardial fibrosis was not revealed. However, diabetes duration plays a central role in the assessment of cardiovascular risk.[14 51] Hence, prospective studies that evaluate the association between diabetes duration and myocardial fibrosis and determine the best time to screen myocardial fibrosis by LGE-MRI for risk stratification in patients with diabetes 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 diabetic patients, 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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Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. 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; HR, hazard ratios; CI, confidence interval.

Figure 3. Forest plots of 6 studies for pooled HR for MACCEs and MACEs in patients with diabetes with normal LV ejection fraction and myocardial fibrosis detected by LGE. HR, hazard ratio; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.

Table legend

Table 1. Description of the Studies Included in the Meta-Analysis

Supplement legend

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

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forest plots of pooled HRs for MACCEs and MACEs in adjusted or not adjusted HR studies. HR, hazard ratios; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.

Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCEs and MACEs in patients with diabetes and different patterns of myocardial fibrosis detected by LGE. HR, hazard ratios; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.

Notes

Author affiliations

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.

2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.

3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.

4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

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Competing interests

The authors report no conflicts of interest.

Contributors

Zhi Yang and Rong Xu conceived of this study, participated in its design and coordination and drafted the manuscript. Contribution to the conceptualization and design: Jia-rong Wang, Hua-yan Xu, Hang Fu, Ling-jun Xie and Meng-xi Yang. Data analysis and interpretation: Lu Zhang, Ling-yi Wen, Hui Liu and Hong Li. Obtaining funding: Zhi-gang Yang and Ying-kun Guo. Zhi-gang Yang and Ying-kun Guo interpreted the results, critically revised the manuscript, and helped to and approved the final version. All authors read and approved this manuscript.

Patient consent for publication

Not required.

Ethics approval

Ethics approval was not required for this meta-analysis.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

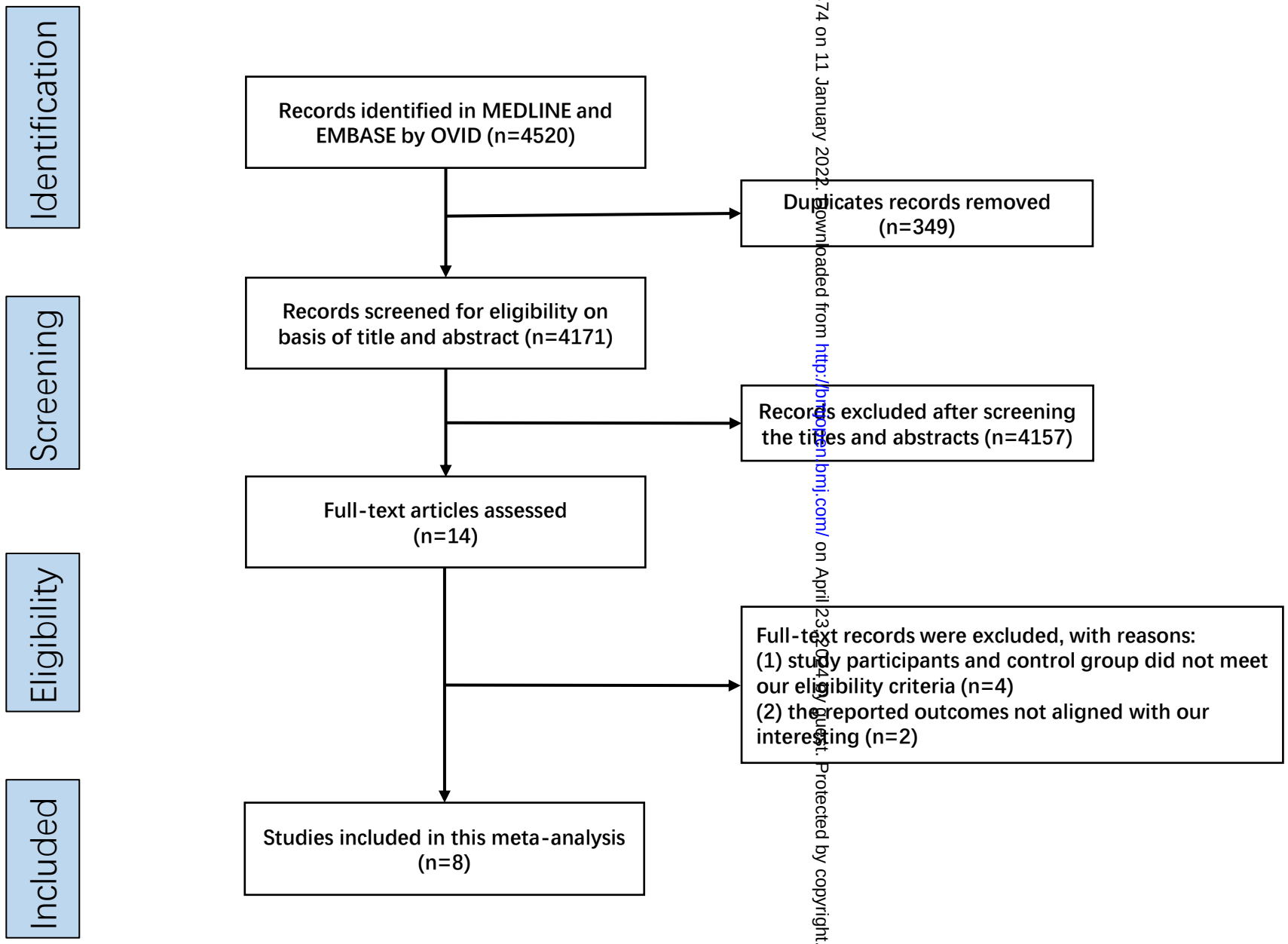
No additional data are available.

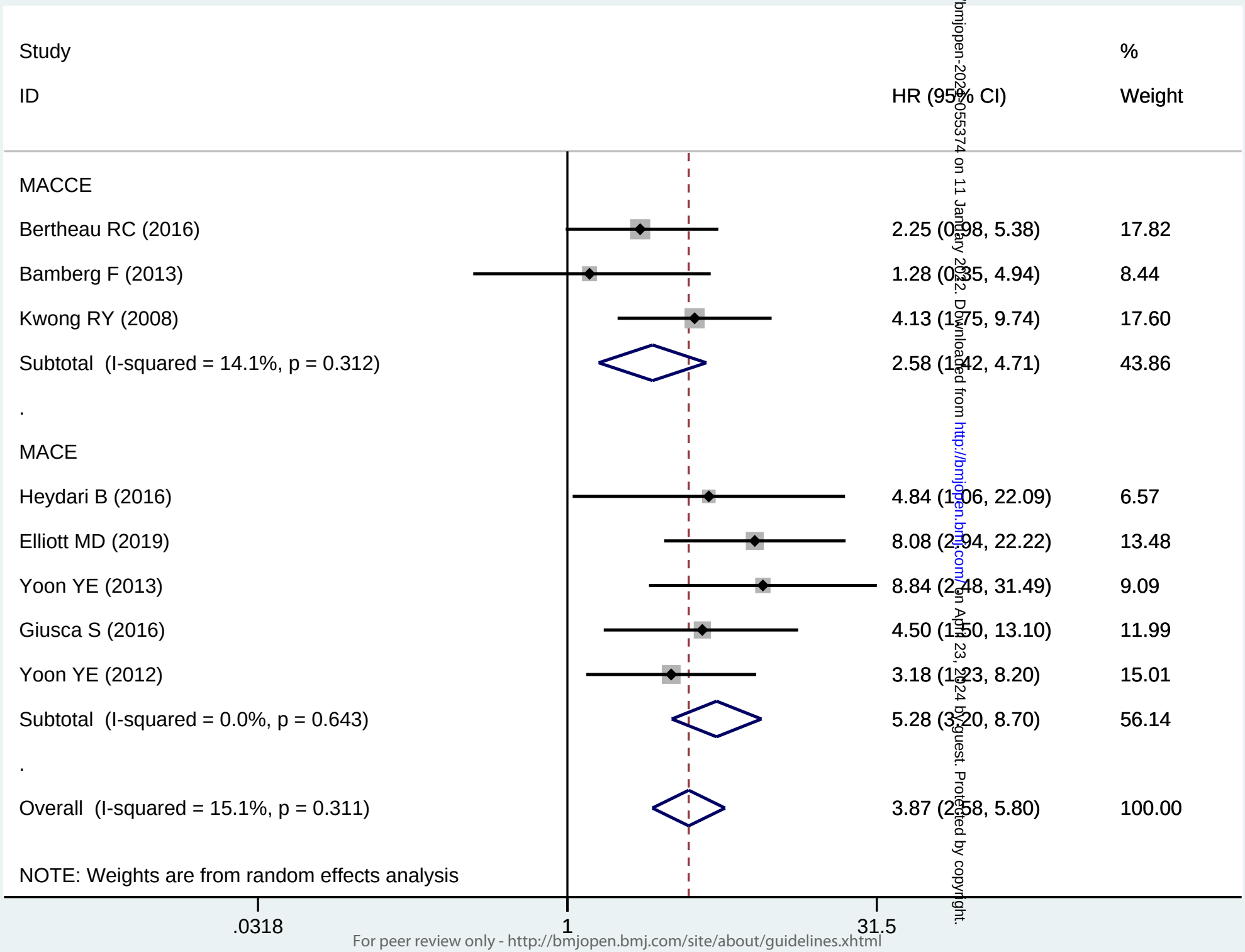
Table 1 Description of the Studies Included in the Meta-Analysis

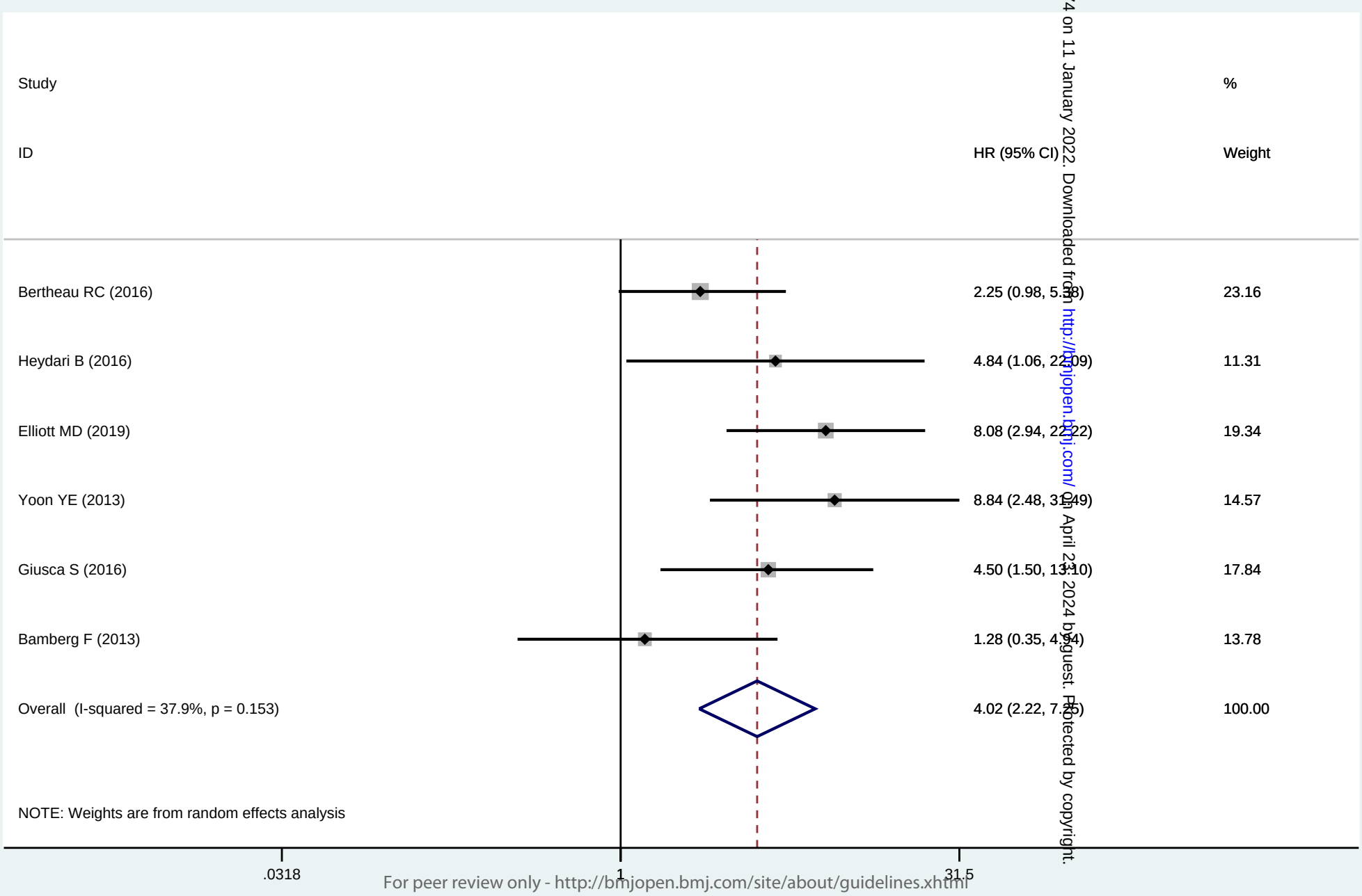
First Author, Year	Journal	patients	HbAlc, %	LGE Definition	DM (type)	Mean age (years)	Duration of Diabetes (years)	LVEF (%)	Follow-up duration (months)	male	LGE(+)	Total events	Adjusted HR	Fibrosis type	Type design	Outcome	NOS
Berthe au RC,2016	Eur Radiol	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischaemic	Prospective, single-centre	MACCES	7
Heyda ri B,2016	Circ Cardiovasc Imaging	173	7.9±1.8	2 SD	NA	61.7±11.9	NA	51.8±7.6	34.8±30	109	88	21	NO	Ischaemic	Prospective, single-centre	MACES	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischaemic	Prospective, two-centre	MACES	9
Yoon YE,2013	Eur Radiol	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischaemic	Retrospective, single-centre	MACES	7
Giusca S,2016	Eur Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±11.6	35 (23-51.6)	250	176	26	YES	Ischaemic and	Prospective,	MACES	8

	sc Imaging												nonischaemic	multicentre		
Bamberg F,2013	Radiology	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischaemic	Prospective, single-centre	MACCES	7
Kwong RY,2008	Circulation	107	7.3±1.6	2 SD	NA	59±12	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischaemic	Prospective, single-centre	MACCES	9
Yoon YE,2012	Radiology	151	7.4±1.6	visual	NA	67±9	14±11	NA	30(6-103)	113	58	24	NO	Ischaemic	Retrospective, single-centre	MACES	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle–Ottawa Scale; HR, hazard ratio; NR, not reported; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events.







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 Tabe 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 Tabe S1-2

Search methodology

Search strategies

1 diabetes[Title/Abstract]
2 "diabetes mellitus"[Title/Abstract]
3 "diabetic*"[Title/Abstract]
4 1 or 2 or 3
5 mri[Title/Abstract]
6 MR[Title/Abstract]
7 "magnetic resonance imag*"[Title/Abstract]
8 "Magnetic Resonance Imaging"[MeSH Terms]
9 "cardiac magnetic resonance"[Title/Abstract]

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 Tabe S1-3

Search methodolog

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

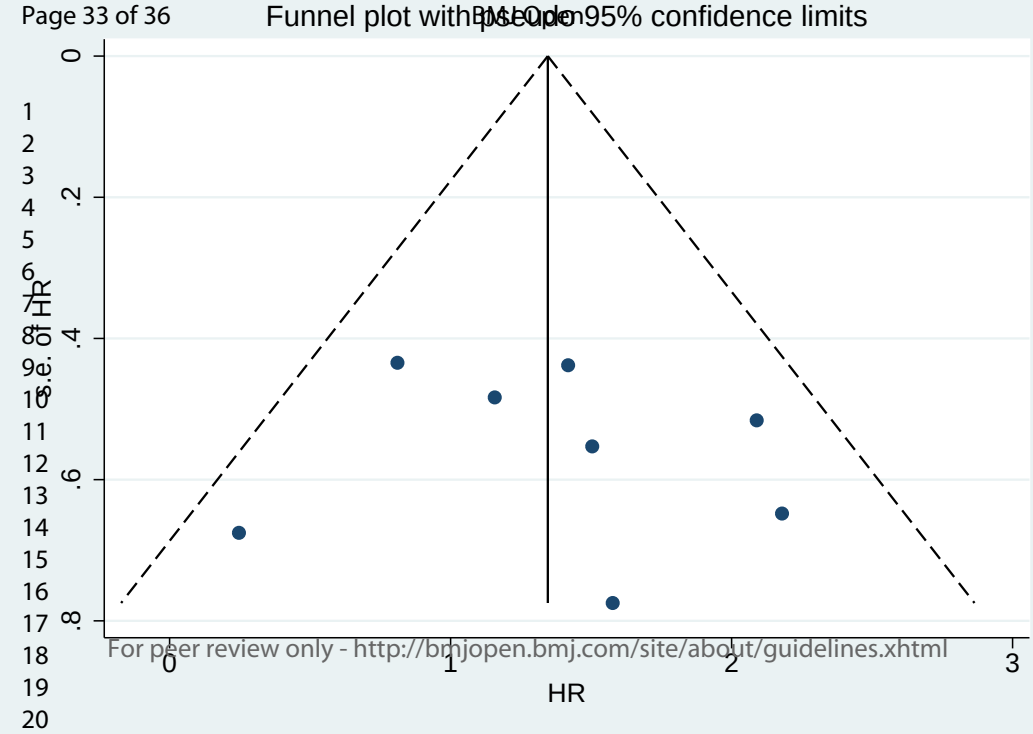
19 death[MeSH Terms]

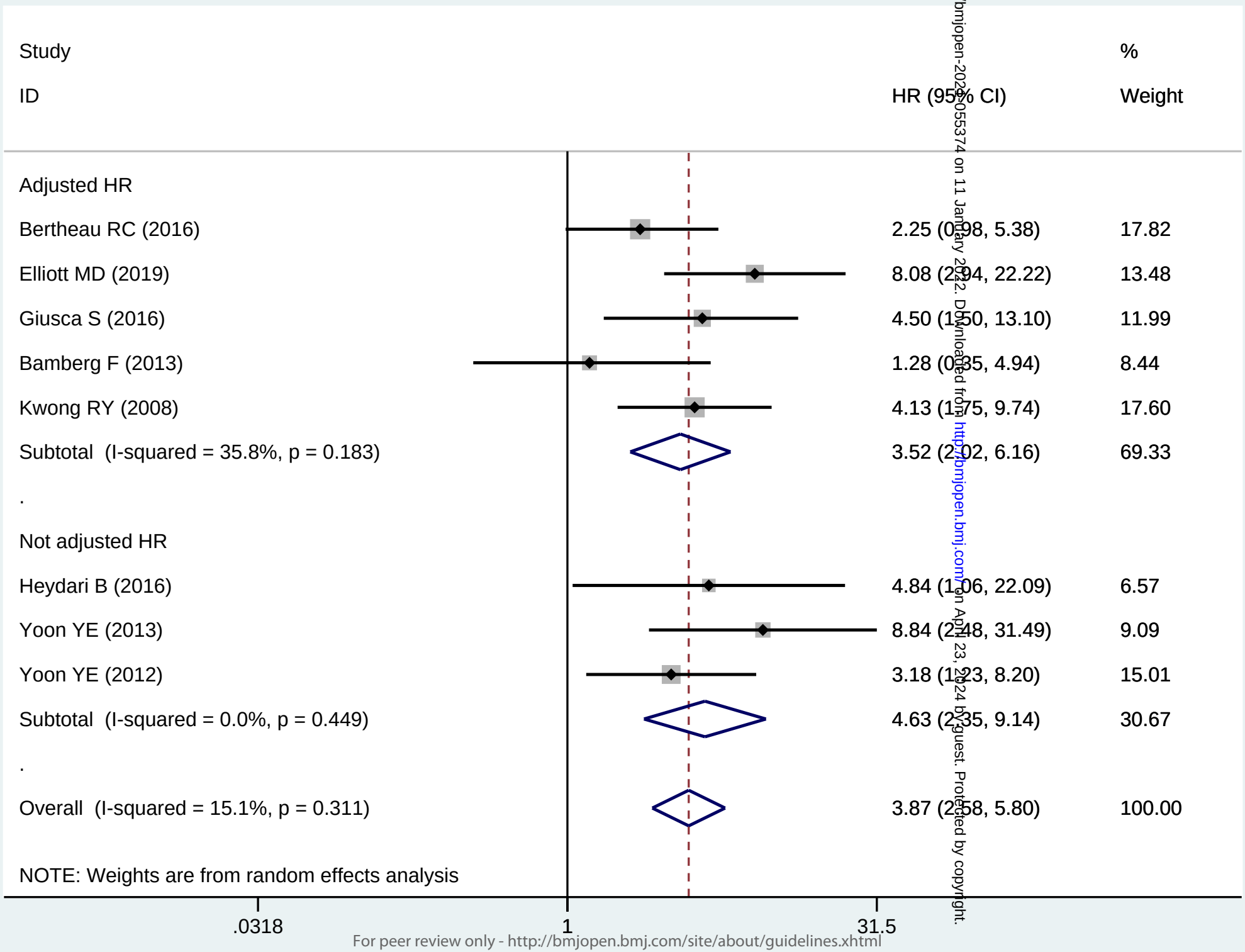
20 models, statistical[MeSH Terms]

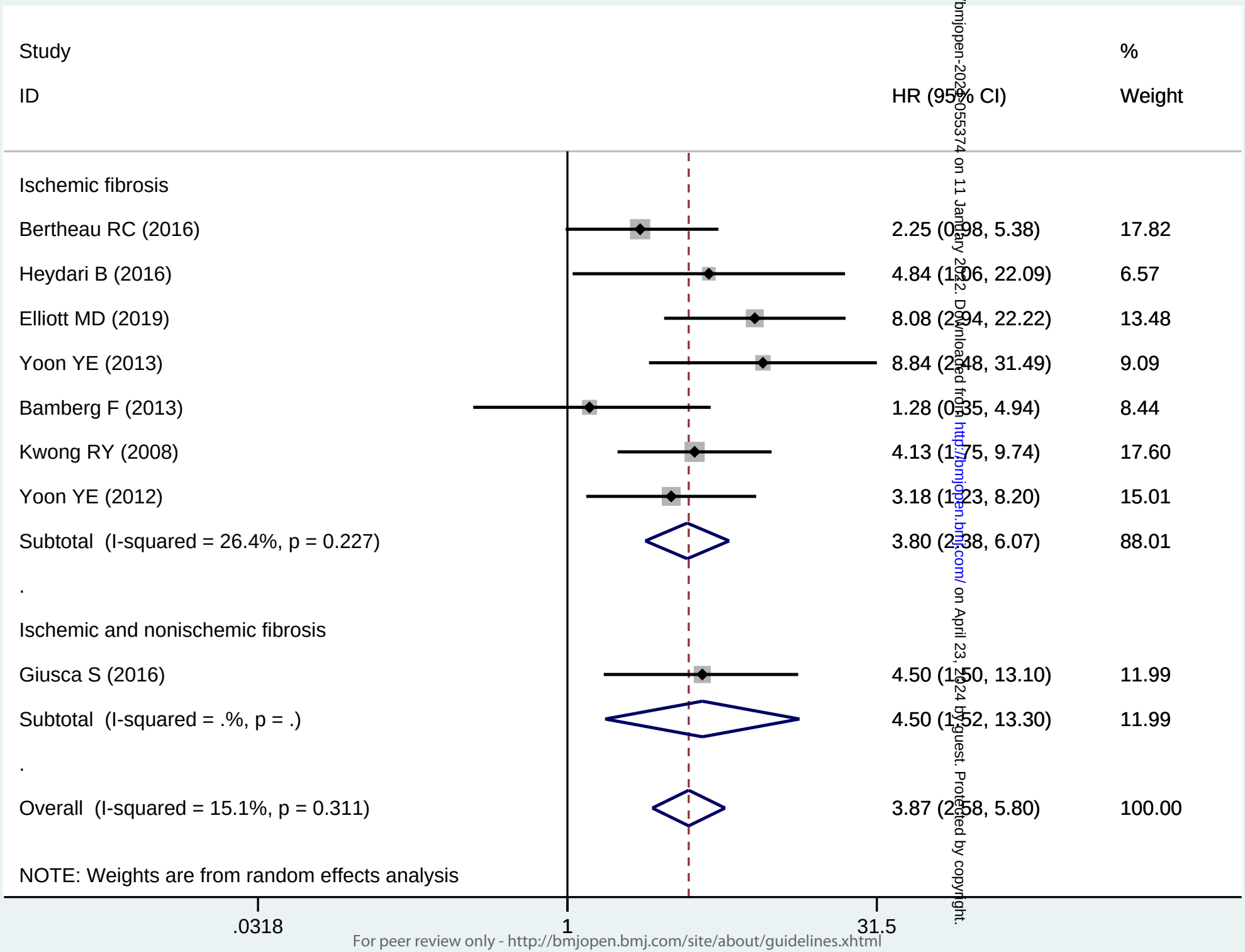
21 15 or 16 or 17 or 18 or 19 or 20

22 4 and 14 and 21

1 to 26 were performed in Cochrane Library.







MOOSE Checklist

Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Corresponding Author :

Yingkun Guo, MD, PHD

Department of Radiology, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education; West China Second University Hospital, Sichuan University,

Address: 20# South Renmin Road, Chengdu, Sichuan 610041, China.

Phone No: +86-18980006572

Fax No: +86 28-85502946(H)

Email Address: gykpanda@163.com

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.
√	Hypothesis statement	LGE is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes.
√	Description of study outcomes	MACCE/MACE
√	Type of exposure or intervention used	LGE-MRI
√	Type of study designs used	We included case-control studies, prospective cohort studies, retrospective studies, and randomized controlled studies.
√	Study population	Patients with diabetes.

Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators ZY and RX are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	See the section of "Data Sources and Searches" in the article.
√	Databases and registries searched	PubMed and EMBASE, Cochrane Library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	Articles published in the English language were included.
√	Method of handling abstracts and unpublished studies	Only studies published in peer-reviewed journals were included.
√	Description of any contact with authors	Not.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and HR (95% CI).
√	Assessment of confounding	We extracted the adjustment HR if the study reported the HR with adjustment models.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
√	Assessment of heterogeneity	To analyze the heterogeneity of the included studies, we used forest plots and the I^2 statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 summary table detailing the search strategy used for database search, 1 flow chart,1 summary

		table, 4 forest plots, 1 funnel plots.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 1
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses.
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.
√	Assessment of quality of included studies	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	In this article, we discussed the potential reasons that patients with diabetes have more myocardial fibrosis than who without diabetes. In addition, we discussed the myocardial fibrosis detected by LGE-MRI may increase the risk of MACCE/MACE, and the limitations of our study.
√	Generalization of the conclusions	The presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted.
√	Guidelines for future research	Myocardial fibrosis detected by LGE-MRI may be a risk marker for improving risk stratification in patients with diabetes.
√	Disclosure of funding source	This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586，81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).