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Review article

C-reactive protein for predicting cardiovascular and all-cause mortality in type 2 diabetic patients: A meta-analysis

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ABSTRACT

Aims: There is interest in using blood C-reactive protein (CRP) to predict adverse prognosis outcomes patients with type 2 diabetes. This meta-analysis aimed to investigate the association between elevated baseline CRP level and unfavorable outcomes in type 2 diabetes patients.

Materials/methods: PubMed and Embase databases were systematically searched for studies on the association of elevated baseline CRP level with cardiovascular mortality and all-cause mortality from their inception to July 2018. Pooled risk ratio (RR) with 95% confidence intervals (CI) was calculated for the highest versus the lowest CRP level.

Results: Six prospective cohort studies and two post hoc analyses of randomized controlled trials involving 22,322 type 2 diabetes patients were included. Meta-analysis indicated that type 2 diabetes patients with the highest CRP level had a greater risk of all-cause mortality (RR 2.03; 95% CI 1.49–2.75) and cardiovascular mortality (RR 1.76; 95% CI 1.46–2.13). Subgroups analysis indicated that the increased cardiovascular and all-cause mortality risk was consistently found in different study design, follow-up duration or patients with or without cardiovascular risk/established cardiovascular disease subgroups.

Conclusions: This meta-analysis indicates that elevated baseline serum CRP level is independently associated with future cardiovascular and all-cause mortality in type 2 diabetes patients.

1. Introduction

Type 2 diabetes is one of the most common chronic diseases worldwide. The incidence of type 2 diabetes continues to increase particular in low-and middle-income countries [1].Type 2 diabetes and its complications have become serious public health challenges [2]. Patients with type 2 diabetes frequently have coexistent cardiovascular risk factors such as obesity, hypertension and dyslipidemia. Globally, overall cardiovascular disease (CVD) affects approximately 32.2% of type 2 diabetes patients [3]. Cardiovascular complications are the leading cause of morbidity and mortality in diabetic patients [4].Therefore, early risk prediction of death and cardiovascular events is a major clinical issue.

Low-grade inflammation is a common feature of type 2 diabetes [5]. Inflammation plays an important role in the development of type 2 diabetes [6,7]. Inflammatory cytokines have been involved in the development of type 2 diabetes [8]. C-reactive protein (CRP) is a well established inflammatory biomarker. CRP is widely used in clinical practice, particularly in CVD risk stratification [9]. Elevated CRP level has been recognized as an independent predictor of all-cause and cardiovascular mortality in the general population [10]. However, this meta-analysis did report the risk estimate by diabetic and non-diabetic individuals. Therefore, only few studies have addressed the association between higher CRP level and mortality or cardiovascular events in patients with type 2 diabetes. Nevertheless, the prognostic significance of CRP level in type 2 diabetic patients is less consistent [11–14]. One reason for explaining these disparate findings may be the different baseline cardiovascular risk factors or preexisting cardiovascular disease in these diabetic patients.

To date, no previous systematic review or meta-analysis has

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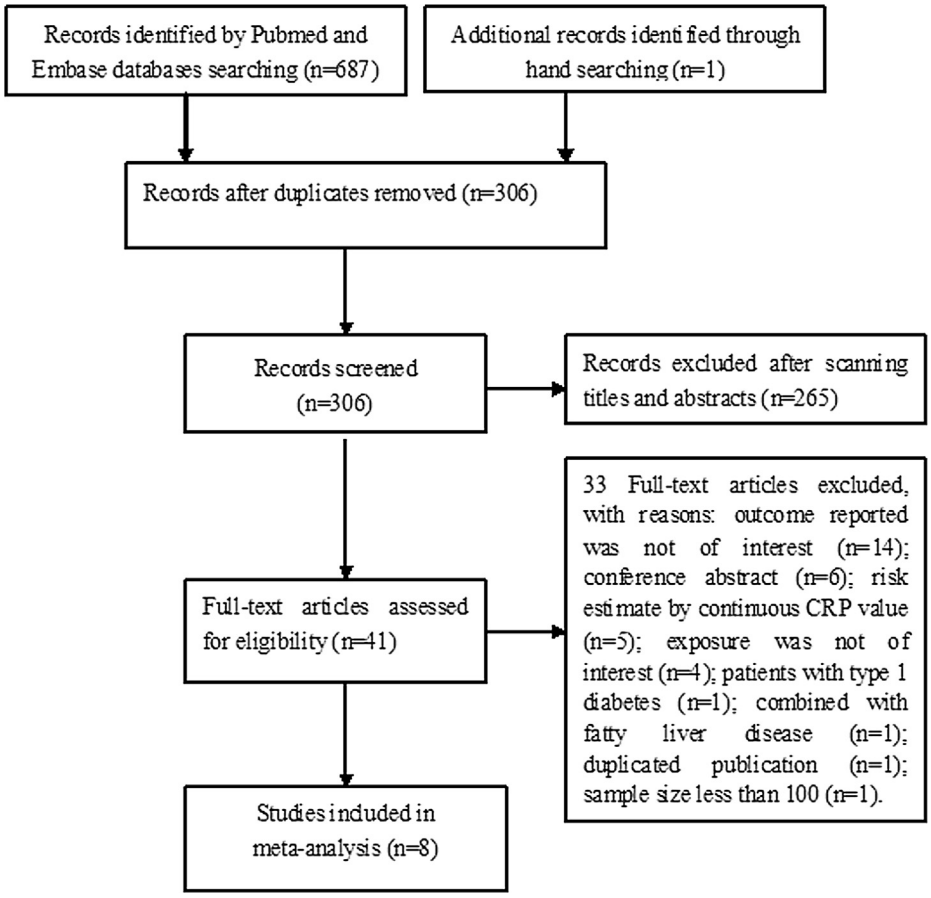

Fig. 1. Flow diagram of the study selection process.

summarized the association of CRP level with subsequent risk of mortality and major cardiovascular events (MACE) in type 2 diabetes patients. We therefore conducted this meta-analysis to investigate the prognostic value of baseline CRP level in type 2 diabetes patients in terms of cardiovascular and all-cause mortality.

2. Materials and methods

2.1. Search strategy

The present meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [15]. PubMed and Embase databases were systematically searched from their inception to July 2018, without language restriction. Search terms were as follows: “C-reactive protein” OR “CRP” AND “type 2 diabetes” OR “diabetic’ OR “non-insulin-dependent diabetes mellitus” AND “mortality” OR “death” OR “cardiovascular events” AND “follow-up” OR “longitudinal”. Additionally, reference lists from the included studies, reviews or editorials were also manually scanned for additional articles.

2.2. Study selection

Two authors independently identified articles satisfying the following inclusion criteria: (1) prospective or retrospective observational studies and post hoc analyses of randomized controlled trials (RCTs); (2) study population consisted of all type 2 diabetic patients; (3) CRP level was measured at baseline; (4) outcome measures were cardiovascular or all-cause mortality; and (5) provided multivariable adjusted risk ratios (RR), hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals (CI) for the highest versus the lowest CRP categories in each study. Studies were excluded if (1) study population was not restricted in type 2 diabetes patients; (2) sample size less than 100; and (3) risk estimate reported by unit of CRP or logarithmically transformed CRP rise.

2.3. Data extraction and quality assessment

Extracted data for this meta-analysis included the first author’s last name, year of publication, country of origin, study design, sample size, percentage of male, age, percentage of patients with preexisting CVD, cutoff value of CRP comparison, duration of follow-up, number of events, outcome measures, risk estimates from most fully adjusted multivariate models, and adjustment for confounders. For assessment of methodological quality, we applied the Newcastle–Ottawa Scale (NOS) based on patient selection, comparability of groups and ascertainment of outcome [16]. A nine-star system is applied to determine the study quality. Studies receiving 7 stars or over were considered to be high quality. Data extraction and quality assessment were performed by two independent authors using a standard extraction form. Discrepancies between the two authors were solved by a third author.

2.4. Data synthesis

To assess the prognostic value of CRP, we pooled the most fully adjusted risk estimates for the highest versus the lowest CRP categories in each of studies. Heterogeneity between studies was examined by the I^2 test and Cochran’s Q statistic. A value > 50% for the I^2 test or P-value < 0.10 for the Q statistic was considered as meaningful level of heterogeneity. We selected a random effect model in the presence of statistical heterogeneity; otherwise, a fixed-effect model was applied. Publication bias was explored using the Begg’s rank correlation and Egger’s linear regression test. Subgroup analysis was conducted

Table 1
Main characteristics of the included studies.

First author/ publication year	Location	Study design	Sample size (% male)	Age/range Mean (SD)	Patients characteristics	CRP comparison	Reported OR or HR (95% CI)	Follow-up duration	Adjusted covariates	Overall NOS
Jager 1999 [11]	Netherlands	Prospective	169 (NP)	50–75	15% IHD,11% PAD, 5% stroke	> 2.84 mg/L vs. < 2.84 mg/L	CV death: NP; 1.34 (0.41–4.43)	5.0 years	Age, sex, HDL,TG, impaired glucose tolerance, hypertension, current smoking, and PAD	7
Stehouwer 2002 [12]	Netherlands	Prospective	328 (61.6)	53.8 ± 8.6	9.7% previous CVD	> 5.5 mg/L vs. < 1.9 mg/L	Total death; 113; 1.66 (0.95 –2.92);	9.0 years	Age, sex, diabetes duration, prior CVD, TC, urinary albumin excretion, BMI, SBP, HbA1c, and soluble vascular cell adhesion molecule 1	7
Linnemann 2006 [16]	Germany	Prospective	292 (50.3)	64.8 ± 5.9	Suspected cerebrovascular disease or PAD	≥9.2 mg/L vs. ≤2.7 mg/L	Total death:55; 3.3 (1.27–8.70); CV death:31; 5.4 (1.44–20.0)	5.3 years	Age, sex, BMI, IHD, internal carotid stenosis, PAD, postprandial blood glucose, and ESR	7
Bruno 2009 [17]	Italy	Prospective	2381(49.7)	67.6 ± 10.4	21.4% previous CVD	> 4.4 mg/L vs. < 1.6 mg/L	Total death:496; 1.65 (1.20–2.28); CV death:233; 1.76 (1.09–2.82)	5.4 years	Age, sex, diabetes duration, hypertension, LDL, HDL, HbA1c, smoking, CVD, diabetes treatment, waist circumference, statins, and albumin excretion rate	8
Cox 2012 [18]	USA	Prospective	846 (52.4)	62.4 ± 8.9	40.7% previous CVD	> 10 mg/dL vs. < 1.0 mg/dL	Total death:160; 5.09 (2.70 – 9.57)	7.3 years	Age, sex, BMI, and diabetes duration	6
Cardoso 2016 [13]	Brazil	Prospective	616 (36.9)	60.1 ± 9.4	Vascular complication, or > 2 CV risk factors	≥4.8 mg/L vs. < 1.6 mg/L	Total death:129; 1.54 (1.00–2.38); CV death:53; 1.24 (0.62–2.48)	8.4 years	Age, sex, DM duration, BMI, smoking, PA, hypertension, antihypertensive drugs, SBP, vascular complications, HbA1c, HDL, LDL use of aspirin, statins, and insulin in the first year of follow-up	7
Scirica 2016 [19]	Multi-nations	Post hoc analysis of RCT	12,310 (66.6);	65.1 ± 8.5	Established CVD or multiple risk factors	> 3.0 mg/L vs. < 3.0 mg/L	CV death: NP; 2.09 (1.57–2.77)	2.1 years	Age, sex, SBP, history of heart failure, diabetes duration, prior MI, history of hypertension or hyperlipidemia, smoking, eGFR, and treatment arms,	7
Hwang 2018 [14]	USA	Post hoc analysis of RCT	5380 (67.9);	60.9 ± 9.9	With ACS	> 3.0 mg/L vs. < 1.0 mg/L	Total death; NP; 1.77 (1.29 –2.42); CV death: NP; 1.40 (0.98–2.00)	1.5 years	Age, sex, BMI, current smoking, TC, eGFR, SBP, DBP, HbA1c, and diabetes duration	7

Abbreviations: NP, not provided; BMI, body mass index; OR, odds ratio; HR, hazard ratio; CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; PA, physical activity; HbA1c, glycosylated hemoglobin; ESR, erythrocyte sedimentation rate; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CRP, c-reactive protein; ACS, acute coronary syndrome; IHD, ischemic heart disease; PAD, peripheral arterial disease; MI, myocardial infarction; NOS, Newcastle-Ottawa Scale.

according to study design (cohort versus post hoc analyses of RCT), sample size (> 1000 or < 1000), patients 'characteristics (high CVD risk [> 30% previous CVD cases] or low CVD risk), and follow-up duration. Sensitivity analysis was performed by excluding one study at a time to evaluate the single study on the overall estimate. All statistical analyses were done using STATA 12.0 (College Station, Texas, USA. StataCorp LP).

3. Results

3.1. Literature search and study characteristics

Our initial literature searches yielded 687 records after removal of duplications. Two hundred and sixty-five articles were removed after screening the titles and abstracts. Forty-one articles were assessed for eligibility by evaluation of full text manuscript. Of these potentially eligible articles, 30 were further excluded. Ultimately, 8 studies [11–14,17–20] met the inclusion criteria (Fig. 1).

The main characteristics of the included studies are shown in Table 1. These studies were published from 1999 to 2018 and sample size ranged from 169 to 12,310. A total of 22,322 type 2 diabetic patients were identified in the included studies. Mean/median duration of follow-up ranged from 1.5 to 9.0 years. The percentage of patients with preexisting CVD or risk factors in the studies ranged from 9.7% to 100%. Three studies [13,14,20] measured the CRP level using high sensitivity assays. Based on NOS system, the methodological quality scores ranged from 6 to 8 stars, indicative of overall medium to good quality.

3.2. All-cause mortality

Of the 8 included studies, six [12–14,17–19] assessed all-cause mortality risk. As shown in Fig. 2, the pooled RR was 2.03 (95% CI 1.49–2.75) in the highest CRP level compared with the lowest in a random effect model. However, between-study heterogeneity was statistically significant (I^2 = 60.3%; p = 0.027). Statistically significant publication bias was not observed across studies (Begg's test, p = 0.452; Egger's test, p = 0.167). Sensitivity analysis indicated that removal of any single study had no significant effect on the pooled risk estimates (data not shown).

3.3. Cardiovascular mortality

Cardiovascular mortality events were reported in 6 studies [11,13,14,17,18,20]. As shown in Fig. 3, the pooled RR was 1.76 (95% CI 1.46–2.13) in the highest CRP level compared with the lowest in a fixed-effect model, with no evidence of significant heterogeneity (I^2 = 28.2%; p = 0.224). There was no evidence of significant publication bias across studies (Begg's test, p = 0.707; Egger's test, p = 0.944). Sensitivity analyses showed that the pooled RR (95% CI) ranged between 1.54 (1.20–1.99) and 1.93 (1.54–2.41) when removal of any single study.

3.4. Subgroup analysis

Irrespective of study design, patients with or without higher cardiovascular risk/established CVD or follow-up duration, increased risk of all-cause mortality and cardiovascular mortality was consistently found in each named subgroup. However, *lack of* statistical significance for cardiovascular mortality was observed in the sample size < 1000 subgroup. The detailed results of subgroup analysis are shown in Table 2.

4. Discussion

To our knowledge, this is the first meta-analysis to evaluate the association of CRP with cardiovascular and all-cause mortality events in type 2 diabetes patients. The findings of the current meta-analysis indicate that elevated CRP level in type 2 diabetes patients independently predicts cardiovascular and all-cause mortality events. Individuals with the highest CRP level had a 76% and 2-fold higher risk of cardiovascular and all-cause mortality. Our finding that elevated CRP level was associated with an increased risk of cardiovascular and all-cause mortality is consistent with a previous meta-analysis [10] assessing the association in the general population [10].

A variety of studies not meeting the inclusion criteria also confirmed the prognostic value of elevated CRP level. In four U.K. prospective cohort studies [21], the hazard ratio for a logarithmically transformed SD CRP rise was 1.46 (95% CI 1.18–1.81) and 1.21 (95% CI 1.05–1.38) for all-cause mortality. In addition to contributing to risk for mortality, elevated CRP level independently predicted major cardiovascular events by CRP categorical analysis [22–24]. Similarly, in a cohort of 1059 type 2 diabetic patients, CRP was also an independent risk factor

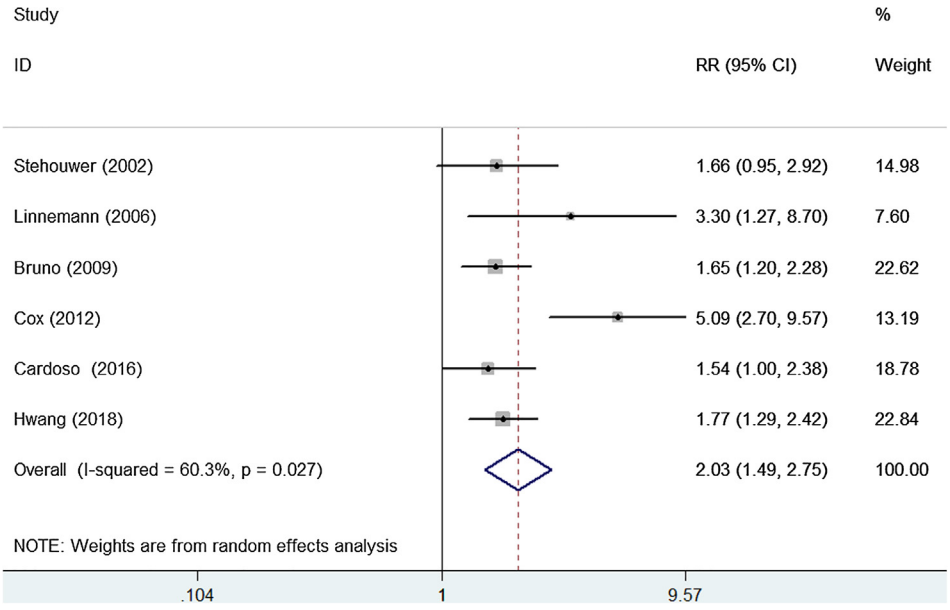

Fig. 2. Forest plots showing pooled RR with 95% CI of all-cause mortality for the highest versus the lowest C-reactive protein level.

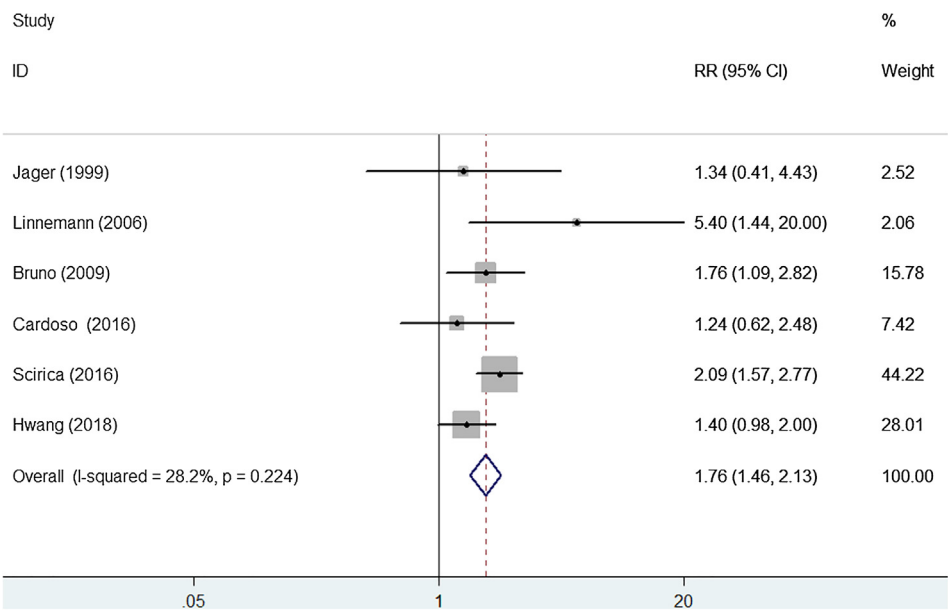

Fig. 3. Forest plots showing pooled RR with 95% CI of cardiovascular mortality for the highest versus the lowest C-reactive protein level.

Table 2
Results of subgroup analysis.

Subgroup	No. of studies	Pooled RR	95% CI	Heterogeneity between studies
1. All-cause mortality				
Study design				
Cohort	5	2.17	1.43–3.28	p = 0.014; I^2 = 67.9%;
Hoc analyses of RCT	1	1.77	1.29–2.42	—
Follow-up duration				
> 6 years	3	2.29	1.41–4.61	p = 0.006; I^2 = 80.3%
< 6 years	3	1.77	1.42–2.20	p = 0.408; I^2 = 0.0%
Sample size				
> 1000	2	1.71	1.37–2.14	p = 0.759; I^2 = 0.0%
< 1000	4	2.44	1.36–4.38	p = 0.620; I^2 = 0.0%
Patients 'characteristics				
High CVD risk/established CVD	4	2.40	1.44–4.00	P = 0.010; I^2 = 73.6%
Low CVD risk	2	1.65	1.25–2.18	p = 0.985; I^2 = 0.0%
2. Cardiovascular mortality				
Study design				
Cohort	4	1.70	1.19–2.43	p = 0.269; I^2 = 23.8%;
Hoc analyses of RCT	2	1.79	1.43–2.23	p = 0.085; I^2 = 66.3%
Follow-up duration				
> 5 years	3	1.74	1.20–2.53	p = 0.152; I^2 = 46.9%
≤5 years	3	1.77	1.42–2.20	p = 0.203; I^2 = 37.2%
Sample size				
> 1000	3	1.78	1.46–2.18	p = 0.226; I^2 = 32.7%
< 1000	3	1.62	0.94–2.80	p = 0.143; I^2 = 48.5%
Patients 'characteristics				
High CVD risk/established CVD	4	1.78	1.44–2.19	P = 0.080; I^2 = 55.5%
Low CVD risk	2	1.70	1.09–2.64	p = 0.677; I^2 = 0.0%

RR, risk ratio; CI, confidence intervals; RCT, randomized controlled trials; CVD, cardiovascular disease.

for coronary heart disease mortality [25]. Apart from type 2 diabetes, higher baseline plasma CRP level independently predicted CVD events in African Americans with type 1 diabetes during 6-year follow-up [26]. Taken together, CRP may serve as a valuable prognostic biomarker in diabetic patients.

There are several possible explanations for the prognostic significance of CRP in patients with type 2 diabetes. Diabetic patients had a high prevalence of dyslipidaemia, hypertension, obesity, and insulin resistance, which favor systemic and coronary inflammation. Hyperglycemia can trigger inflammation. Type 2 diabetes-associated CRP elevation at least partly contributed to the subsequent death event by promoting inflammation. In addition, CRP level may directly reflect the progression of atherosclerosis [27].

There were several potential limitations in our meta-analysis. First, CRP level was only determined at baseline rather than several times, which may have led to selection bias. In addition, the presence of co-morbidities such as infections (which could cause a rise of CRP at baseline) was not reported in the included studies. Second, various thresholds of CRP were used in the included studies and we were unable to identify optimal cutoff points of CRP for risk stratification. Third, most studies did not consider the use of drugs such as aspirin and statins that could interfere with the CRP level. Fourth, due to insufficient data,

the dose-response associations between CRP and mortality risk could not be summarized in the current analysis. Fifth, there were huge differences in CVD risk factors between the study populations, which may have confounded the current findings. Finally, our findings could not be generalized to younger type 2 diabetes because of the analyzed studies enrolled relatively older patients.

5. Conclusions

Elevated CRP level in patients with type 2 diabetes is independently associated with an increased risk of cardiovascular and all-cause mortality. CRP level should be routinely measured in the assessment of type 2 diabetes patients, particularly in those with high prevalence of conventional risk factors or pre-existing CVD. Moreover, studies comparing the prognostic significance of other inflammatory biomarker or concurrently multiple biomarkers should likewise be performed.

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Conflict of interest

There are no conflicts of interest for any of the authors.

Authors' contributions

R Tian and M Tian searched the literature, and performed statistical analysis. L Wang and H Qian extracted the data and selected the study. SY Zhang and HY Pang assessed the study quality. ZY Liu drafted the manuscript. LG Fang and R Tian revised the manuscript. ZJ Shen designed the study, interpreted the results, and approved the final manuscript.

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