Systematic Review and Meta-Analysis

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Blood fibrinogen level as a biomarker of adverse outcomes in patients with coronary artery disease

A systematic review and meta-analysis

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Abstract

Background: The association between elevated fibrinogen level and adverse outcomes in patients with coronary artery disease (CAD) remains conflicting. This systematic review and meta-analysis aims to evaluate the association between fibrinogen level and adverse outcomes in CAD patients.

Methods: Relevant studies were identified by searching PubMed, Web of Science, and Embase databases from their inception to September 30, 2021. Observational studies that investigated the association of blood fibrinogen level with cardiovascular death, all-cause mortality, and major adverse cardiovascular events were eligible.

Results: A total of 20,395 CAD patients from 15 articles (13 studies) were included. Comparison with the highest and the lowest fibrinogen level indicated that elevated fibrinogen level was associated with higher risk of cardiovascular death (risk ratio [RR] 2.24; 95% confidence interval [CI] 1.69–2.98), all-cause mortality (RR 1.88; 95% CI 1.50–2.36), and major adverse cardiovascular events (RR 1.46; 95% CI 1.18–1.81).

Conclusion: Elevated fibrinogen level is significantly associated with an increased risk of cardiovascular and all-cause mortality in patients with CAD. Baseline fibrinogen level can serve as a promising biomarker for risk stratification of CAD.

Abbreviations: ACS = acute coronary syndrome,CAD = coronary artery disease, CI = confidence interval, MACE = major adverse cardiovascular event,NOS = Newcastle-Ottawa Scale, OR = odds ratio, RR = risk ratio.

Keywords: all-cause mortality, cardiovascular events, cardiovascular mortality, coronary artery disease, fibrinogen, meta-analysis

1. Introduction

Despite advances in aggressive treatment strategies, coronary artery disease (CAD) remains the main cause of death worldwide.[1] CAD patients still suffer substantial risk for death and cardiovascular events. Risk stratification for death and cardiovascular events among CAD patients is essential in facilitating more effective secondary prevention. However, use of current traditional risk factors does not fully predict the adverse outcomes of CAD.[2] In order to improve risk stratification, identification of additional predictors is an urgent need.

Inflammation and thrombogenesis has been implicated in the pathogenesis of CAD. Fibrinogen, mainly synthesized by hepatocytes, is a biomarker of both thrombogenesis and inflammation.[3,4] Higher fibrinogen level has been identified as a risk factor of cardiovascular events in the general population.[5] Blood fibrinogen level was higher in patients with CAD compared with the normal individuals.[6] In patients with established CAD, the associations between elevated fibrinogen level and survival or cardiovascular events remain uncertain.[7–12] Considering blood fibrinogen level as a prognostic marker remains elusive in patients with CAD, we conducted this meta-analysis to address the prognostic significance of elevated fibrinogen level in CAD patients, in terms of cardiovascular events, cardiovascular, and all-cause mortality.

2. Methods

2.1. Literature search

The current meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Ethical approval was not necessary because this study only analyzed the study-level data. Two authors comprehensively searched online medical databases (PubMed, Web of Science, and Embase) from their inception to September 30, 2021. The following keywords with their combinations were applied for literature search: "fibrinogen" AND "coronary artery disease" OR "coronary heart disease" OR "ischemic heart disease" OR "ischaemic heart disease" OR "acute coronary syndromes" OR "myocardial infarction" OR "angina" AND "death" OR "mortality" AND "follow-up" OR "follow up." We also manually scanned the reference lists of included studies and pertinent reviews to identify potentially eligible studies.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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2.2. Inclusion and exclusion criteria

The eligible studies should satisfy all the following inclusion criteria:

1. Original prospective or retrospective observational studies that focused on CAD patients;
2. Evaluation of the prognostic utility of fibrinogen level at baseline for predicting cardiovascular death, all-cause mortality, and major adverse cardiovascular events ([MACEs] including death, stroke, nonfatal myocardial infarction, revascularization, etc) during at least 1 year of follow-up; and
3. Reported multivariable adjusted hazard ratio, risk ratio (RR), or odds ratio (OR) with their corresponding 95% confidence interval (CI) or data to calculate them.

For multiple publications overlapping with the same patient population, only the study with the longer follow-up or specific subgroup was included. Exclusion criteria were:

1. Without reporting adjusted risk estimate;
2. Providing risk estimate by per unit increment in fibrinogen level;
3. Patients concurrent with other specific diseases; and
4. Reviews or conference abstracts.

2.3. Data extraction and quality assessment

The following information was extracted from the eligible studies by 2 independent authors: surname of the first author, publication year, region of origin, study design, type of CAD, sample size, proportion of male gender, baseline age of patients, fibrinogen level cutoff, definition of MACEs, outcome measures, number of events, fully adjusted risk estimate, covariates adjusted in the analysis, and duration of follow-up. Two authors independently evaluated the methodological quality of eligible studies using the Newcastle-Ottawa Scale (NOS) for cohort studies.[13] Studies with NOS score ≥7 was graded as high quality. Any discrepancies were settled by discussing with a third author to reach consensus.

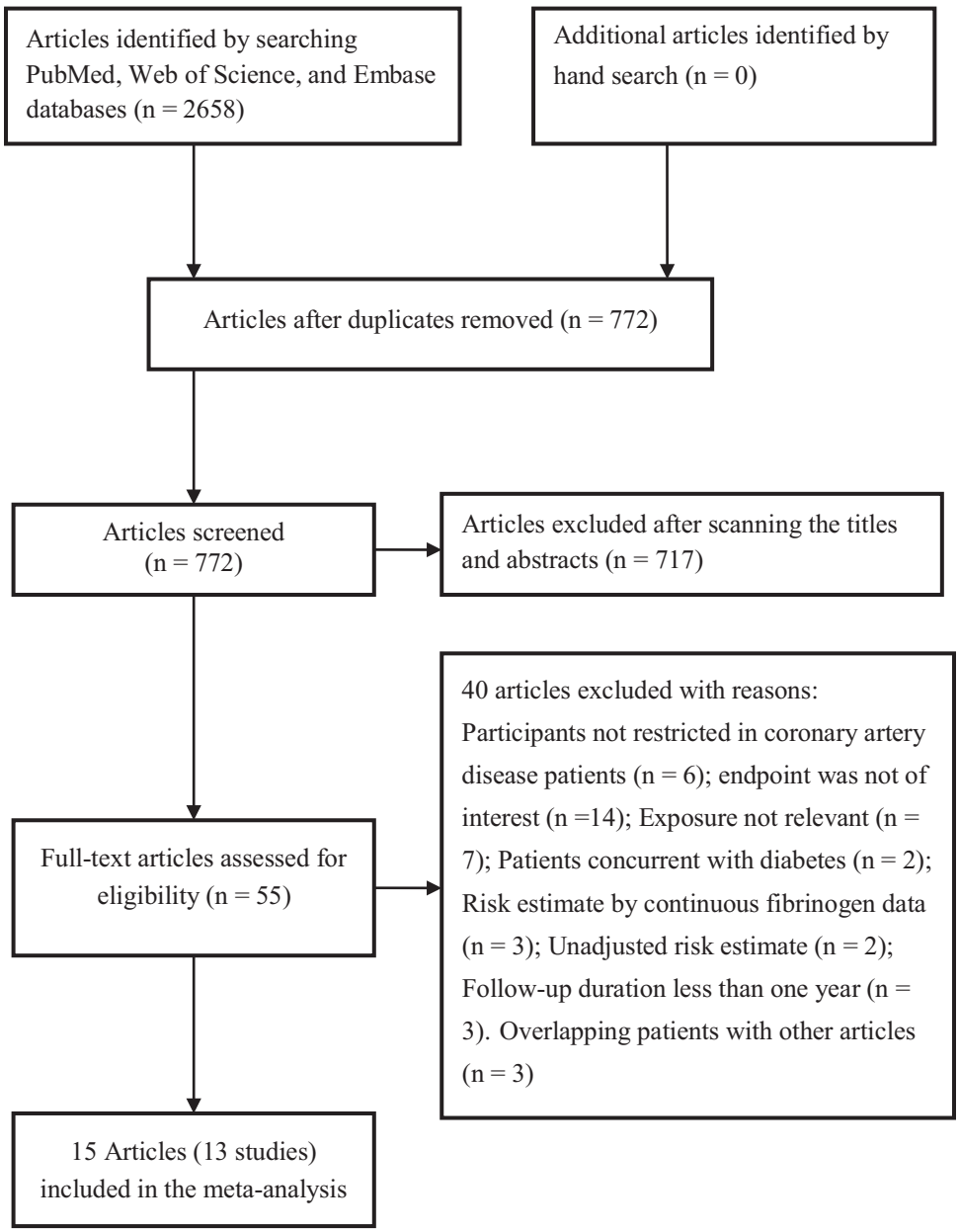

Figure 1. Flow chart of the study selection process.

Table 1

Basic characteristic of the included studies.

Author/year	Region	Study design	Patients (% male)	Mean age (yr)	Definition of MACEs	Cutoff value (mg/mL)	Follow-up (yrs)	HR or OR (95% CI)	Adjustment for variables	NOS score
Lindahl 2000[7]	Sweden	P	Unstable CAD 917 (64.4)	Median 69	—	≥400 vs. <340	3.1	CV death: 92 2.3 (1.3–4.1)	Age, sex, BMI, smoking status	7
Koukkunen 2001[8]	Finland	P	UA 363 (60)	Median 68 (34–96)	Coronary death, nonfatal MI, UA hospitalization or revascularization	≥375 vs. <375	1.4	MACEs: 86 1.07 (0.85–1.35)	Age, sex duration of pain, creatine kinase-MB	7
Retterstol 2003[9]	Norway	P	Post-MI 247 (78.1)	Median 49 (31–63)	Cardiac death, MI, or cardiac arrest	>400 vs. <280	10	Total death: 43 1.8 (1.0–3.6) CV death: 35 2.2 (1.1–4.4) MACEs: 68 1.1 (0.6–1.9)	Age, LVEF, TC, smoking, hypertension	8
Huang 2006[14]	China	R	Stable CAD 185 (53)	69.4 ± 16.3	CV death, nonfatal MI, stroke, TIA	>400 vs. <400	3.0	CV death: 10 2.98 (1.22–3.78) MACEs: 31 1.97 (1.68–2.40)	Hypertension, lipids, BMI, smoking	6
Sinning 2006[15]	Germany	P	Stable angina 1806 (78.7)	61.7 ± 9.4	CV death and nonfatal MI	>390 vs. <270	3.5	CV death: NP 2.22 (1.23–4.03); MACEs: 183 1.66 (1.05–2.69)	Ae, sex, BMI, hypertension, DM, smoking status, HDL. number of diseased vessels, statin, beta-blocker therapy	7
Shlipak 2008[10]	USA	P	CAD 979 (82)	66.8 ± 11.0	Stroke, MI, and cardiac death	>443 vs. ≤443	3.5	MACEs: 142 1.15 (0.78–1.69)	Age, sex, race, DM, BMI, current smoking, prior MI, cerebrovascular accident, CHF, LVEF, hypertension, creatinine acetylsalicylic acid use	7
Shi 2010[16]	China	R	ACS 136 (59)	56 ± 12	CV death. reocclusion	>350 vs. ≤350	2.0	MACEs: 33 5.21 (2.32–39.2)	CRP, white blood cell count	6
van Loon 2012[11]	Netherlands	R	CAD 353 (56)	43.8 ± 5.9	MI, stroke, death, revascularization	>340 vs. <340	4.2	Total death: 11 10.4 (1.18–91.8); MACEs: 55 1.15 (0.74–1.77)	Age, sex, family history of cardiovascular disease, hypertension, DM, TC, HDL, hypercholesterolemia, BMI, smoking	7
Chen 2013[12]	Taiwan	P	CAD 170 (81.8)	65.3 ± 10.2	Death, MI. UA	≥257.9 vs. <257.9	9.86	MACEs: 61 1.09 (0.78–2.81)	Age, sex, hypertension, smoking, LVEF, soluble p-selectin, CRP, troponin-I	8
Peng 2016[17]	China	R	Stable CAD 866 (80.9)	63.9±11.1	–	≥500 vs. <200	2.2	Total death: 258 1.86 (1.24–2.79)*	Age, sex, hypertension, DM, SBP, DBP, heart rate, LVEF, blood glucose, TC, creatinine, severity of CAD	8
Peng 2017[18]	China	R	ACS 2253 (78.7)	64.7 ± 10.6	–	>357 vs. <279	2.3	Total death: 223 1.83 (1.09–3.08) CV death: 130 1.28 (0.67–2.45)	Age, sex, hypertension, DM,SBP, DBP, heart rate, Killip class, glucose, TC, creatinine, left main artery/three vessel diseases, use of aspirin, clopidogrel, statin, ACEI or ARB, beta-blockers	8
Ang 2017[19]	USA	R	CAD 332 (69.9)	66.6 ±19.5	Death, MI, ACS rehospitalization, TIA, stroke, stent thrombosis, revascularization	≥280 vs. <280	2.0	MACEs: 123 3.0 (1.6–5.4)	White blood cell count, prior CABG, ACS indication, bypass graft PCI, total stent length, stent diameter, post-PCI prasugrel use	7
Zhang 2019[20]	China	P	ACS 411 (77.1)	60.6 ± 10.4	Death, nonfatal MI cerebrovascular event, UA, TVR	>363 vs. <291	2.3	MACEs: 137 1.66 (1.00–2.76)	Multivariable adjusted	7

(Continued)

Table1
(Continued)

Author/year	Region	Study design	Patients (% male)	Mean age (yr)	Definition of MACEs	Cutoff value (mg/mL)	Follow-up (yrs)	HR or OR (95% CI)	Adjustment for variables	NOS score
Liu 2020[21]	China	P	Stable CAD 5237 (71.2)	57.8 ± 10.1	CV death, nonfatal MI, stroke, revascularization	>339 vs. <282	3.3	MACEs: 462 1.34 (1.02–1.75)	Age, sex, BMI, smoking, hypertension, family history CAD, LVEF, LDL, HDL, TG, hs-CRP, creatinine	8
Yuan 2021[22]	China	P	CAD 6140(77.7)	58.4 ± 10.4	–	>359 vs. <298	5.1	Total death: 214 1.86 (1.28–2.69)	Age, sex, BMI, hypertension, DM, family history of CAD, prior PCI/CABG, LVEF, LDL, creatine, DES implantation, clopidogrel, ACEI/ARB	8

ACEI = angiotensin-converting enzyme inhibitors, ACS = acute coronary syndromes, ARB = angiotensin II receptor blockers, BMI = body mass index, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CHF = chronic heart failure, CI = confidence intervals, CRP = C-reactive protein, CV = cardiovascular, DBP = diastolic blood pressure, DES = drug-eluting stents, DM = diabetes mellitus, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, hs-CRP = high sensitivity C-reactive protein, LDL = low density lipoprotein, LVEF = left ventricular ejection fraction, MACEs = major adverse cardiovascular events, MI = myocardial infarction, NOS = Newcastle-Ottawa Scale, NP = not provided, OR = odds ratio, P = prospective, PCI = percutaneous coronary intervention, R = retrospective, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, TIA = transient ischemic attack, TVR = target vessel revascularization, UA = unstable angina.
*Data from subgroup.

2.4. Statistical analysis

We performed the meta-analysis using STATA 12.0 (STATA Corp LP, College Station, TX). The most fully adjusted risk estimates were applied to summarize the prognostic value of fibrinogen level for the highest versus the lowest category. Statistical heterogeneity of between studies was evaluated using the Cochrane Q test ($P < .10$ suggesting significance) and I^2 statistic ($I^2 \geq 50\%$ suggesting significance). When there was significant heterogeneity, we selected a random effect model for meta-analysis; otherwise, a fixed-effect model was used. A sensitivity analysis was conducted by omitting 1 study at each time to recalculate the overall risk estimate. Subgroup analyses were conducted according to the study design, CAD type, sample sizes, mean/median age, follow-up duration, whether adjusted smoking in originally statistical model, and NOS score. Moreover, Begg rank correlation test and Egger regression test were applied to check the likelihood of publication bias.

3. Results

3.1. Search results and study characteristics

Our electronic database search yielded a total of 2658 potentially relevant articles. After removing duplicates, 772 articles were retained. After scanning the titles and abstracts, 717 articles were removed due to being obviously irrelevant. Thus, 55 full-text articles were retrieved for detailed evaluation. According to our inclusion and exclusion criteria, 40 articles were further excluded for various reasons (Fig. 1). Finally, 15 articles (13 studies)[7–12,14–22] were included in the meta-analysis.

The main characteristics of the included studies are summarized in Table 1. These included studies enrolled a total of 20,395 CAD patients, with sample sizes ranging from 136 to 6140. The included articles were published from 2000 to 2021. Six articles[11,14,16–19] were the retrospective studies and others adopted prospective designs. The follow-up duration ranged from 1.4 to 10 years. The methodological quality of the included studies was moderate to high, with the NOS score ranging from 6 to 8.

3.2. Major adverse cardiovascular events

Eleven studies[8–12,14–16,19–21] provided data on association of elevated fibrinogen level with MACEs (Fig. 2). A random effect model meta-analysis showed that the pooled RR of MACEs was 1.46 (95% CI 1.18–1.81) for the highest versus the lowest level of fibrinogen. There was significant heterogeneity between studies (I^2 = 68.2%; P = .001). Sensitivity analysis confirmed that the pooled risk estimate was stable (data not shown). Begg test (P = .350) and Egger test (P = .997) revealed no evidence of publication bias. Results of subgroup analysis are shown in Table 2.

3.3. Cardiovascular and all-cause mortality

Five studies[7,9,14,15,18] provided data on association of elevated fibrinogen level with cardiovascular mortality (Fig. 3A). A fixed-effect model meta-analysis showed that the pooled RR of cardiovascular mortality was 2.24 (95% CI 1.69–2.98) for the highest versus the lowest level of fibrinogen. There was no significant heterogeneity across the studies (I^2 = 5.2%; P = .377). Five studies[9,11,17,18,22] provided data on association of elevated fibrinogen level with all-cause mortality (Fig. 3B). The pooled RR of all-cause mortality was 1.88 (95% CI 1.50–2.36) for the highest versus the lowest level of fibrinogen in a fixed-effect model, without significant heterogeneity across the studies (I^2 = 0%; P = .662). Sensitivity analyses showed only slight changes in the original pooling risk estimate of cardiovascular and all-cause mortality (data not shown).

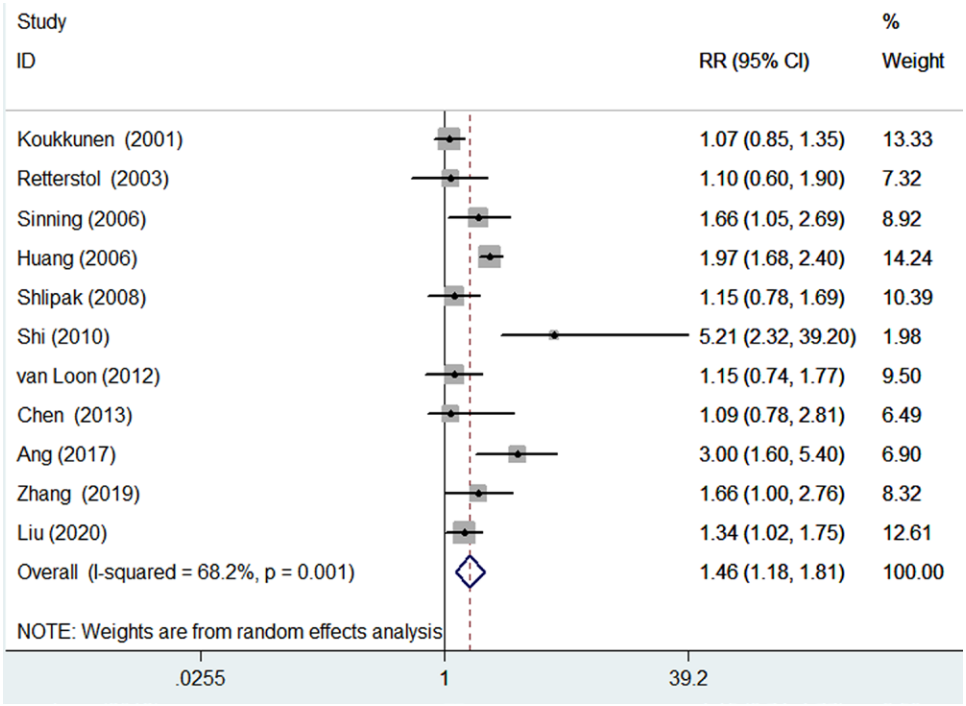

Figure 2. Forest plots showing pooled RR with 95% CI of major adverse cardiovascular events for the highest versus the lowest category of fibrinogen level. CI = confidence intervals, RR = risk ratio.

Table 2

Subgroup analyses on cardiovascular events.

Subgroup	Number of studies	Pooled risk ratios	95% confidence intervals	Heterogeneity between studies
Study design				
Prospective	7	1.23	1.07–1.41	$P = .534$; $I^2 = 0.0\%$
Retrospective	4	2.00	1.29–3.08	$P = .025$; $I^2 = 68.0\%$
Sample sizes				
<300	4	1.60	1.00–2.55	$P = .041$; $I^2 = 63.7\%$
≥300	7	1.59	1.23–2.06	$P = .049$; $I^2 = 52.5\%$
Follow-up duration				
≥4 yr	3	1.12	0.83–1.52	$P = .988$; $I^2 = 0.0\%$
<4 yr	8	1.59	1.23–2.06	$P < .001$; $I^2 = 74.7\%$
CAD type				
Stable	3	1.66	1.26–2.18	$P = .064$; $I^2 = 63.6\%$
ACS	4	1.35	0.91–2.00	$P = .081$; $I^2 = 55.4\%$
NOS score				
≥7	9	1.32	1.11–1.58	$P = .107$; $I^2 = 39.2\%$
<7	2	2.46	1.10–5.49	$P = .181$; $I^2 = 44.1\%$

ACS = acute coronary syndromes, CAD = coronary artery disease, NOS = Newcastle-Ottawa Scale.

4. Discussion

The current meta-analysis suggests that elevated fibrinogen level at baseline is significantly associated with an increased risk of cardiovascular and all-cause mortality in patients with CAD. Comparing with the highest and the lowest fibrinogen level, CAD patients with the highest fibrinogen level conferred approximately 1.24-fold and 88% higher risk of cardiovascular and all-cause mortality, respectively. Regarding the MACEs, CAD patients with the highest fibrinogen level exhibited approximately a 46% higher risk of MACEs. However, elevated fibrinogen level appeared to be not associated with an increased risk of MACEs in patients with mean/median age <60 years, follow-up duration ≥4 years, and acute coronary syndromes (ACS) subtype subgroups.

A previous well-designed individual patient-level meta-analysis[5] demonstrated that elevated fibrinogen level was associated with the age-specific incidence rates of CAD and all-cause mortality among individuals without cardiovascular disease at baseline. By contrast, our meta-analysis focused on the prognostic utility of fibrinogen level in CAD patients. Our study further confirmed the prognostic significance of fibrinogen level in predicting cardiovascular and all-cause mortality in patients with CAD. Moreover, the prognostic value of elevated fibrinogen level in predicting cardiovascular and all-cause mortality was also supported in the studies that analyzed fibrinogen level by continuous analysis. In 13,195 patients with angiography-proved CAD, each 50 mg/dL increase in fibrinogen level, the adjusted risk for all-cause and cardiac mortality was 7% and 5%, respectively.[23]

Patients with CAD constitute a very heterogeneous population. Subtypes of CAD may affect the association of fibrinogen level with clinical prognosis.[17] Our subgroup analysis showed

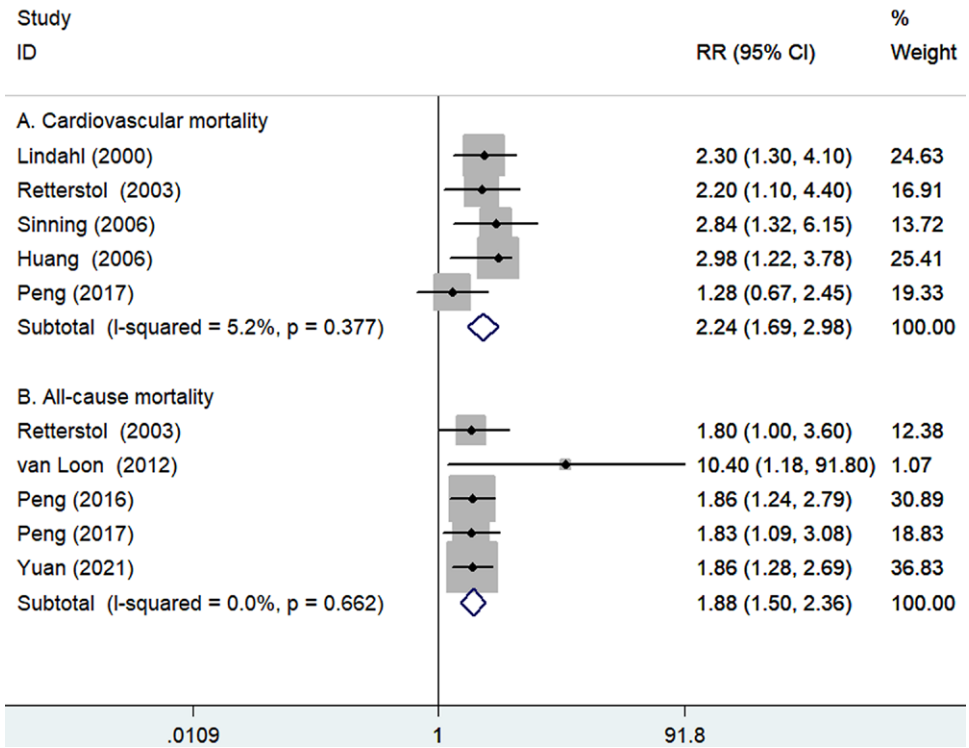

Figure 3. Forest plots showing pooled RR with 95% CI of cardiovascular (A) and all-cause mortality (B) for the highest versus the lowest category of fibrinogen level. CI = confidence intervals, RR = risk ratio.

that the prognostic value of fibrinogen level in predicting MACEs was statistically significant in stable CAD patients but not in those with ACS. However, whether fibrinogen has a distinct effect on the prognosis of the subtypes of ACS should be further investigated in future studies. Moreover, there was a close relationship between an elevated fibrinogen level and increased risk of MACEs in the subgroup with follow-up duration <4 years, indicating that the prognostic role of fibrinogen weakened with the lengthening of the follow-up. In terms of short-term effect, Mahmud et al's study[24] showed that serum fibrinogen ≥280 mg/dL was independently associated with 6-month MACEs (OR 2.60; 95% CI 1.33–5.11) after percutaneous coronary intervention. Another study[25] also demonstrated that fibrinogen was an important and independent determinant of short-term outcome (OR 2.83; 95% CI 1.13–7.10) in patients with unstable angina.

The exact mechanisms underlying the prognostic role of fibrinogen in CAD remain uncertain. One possible explanation may be that the fibrinogen level is produced and released in response to systemic inflammation. Inflammation is an important determinant of prognosis of CAD patients. On the other hand, hyperfibrinogenemia can induce blood viscosity, erythrocyte aggregation, platelet aggregation, and endothelial cell injury, which causes impaired microcirculatory flow.[26]

Our meta-analysis holds important implications for clinical practice. Elevated fibrinogen level was associated with adverse prognosis in patients with CAD. Measurement of blood level of fibrinogen has potential to identify those with high-risk CAD patients. CAD patients with hyperfibrinogenemia should be monitored and receive intensive preventive therapies. However, whether CAD patients can benefit from reduction of blood fibrinogen level should be further investigated in future well-designed randomized controlled trials.

The current meta-analysis should be interpreted in the context of some potential limitations. First, this is not an individual-level meta-analysis and patients' characteristics may have potential to affect the pooling results. Second, cutoff values of elevated fibrinogen level were different across studies and we failed to establish the optimal threshold of elevated fibrinogen level because this is a study-level meta-analysis. Third, significant heterogeneity existed in pooling MACEs. Various definitions of MACEs may contribute to the significant heterogeneity. Nevertheless, there were differences in cutoff value of elevated fibrinogen level, length of follow-up, and subtypes of CAD. Fourth, there is still a possibility of residual confounding in the statistical model and lack of adjustment for some potential confounding may have led to overestimate the risk estimate. Finally, we failed to evaluate the prognostic value of fibrinogen level in the subset of ACS due to lack of sufficient data.

5. Conclusion

Elevated fibrinogen level is significantly associated with an increased risk of cardiovascular and all-cause mortality in patients with CAD. Baseline fibrinogen level can serve as a promising biomarker for risk stratification of CAD. However, more prospective studies are necessary to evaluate whether the prognostic role of fibrinogen level is different in subtypes of CAD.

Author contributions

XL contributed to study conception/design and interpretation of data; ZC and GZ contributed to literature search, data extraction, quality assessment, and statistical analysis. ZC drafted the manuscript. All the authors approved the final version of the manuscript.

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