Relationship between fibrinogen levels and cardiovascular events in patients receiving percutaneous coronary intervention: a large single-center study

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Abstract

Background: It is currently unclear if fibrinogen is a risk factor for adverse events in patients receiving percutaneous coronary intervention (PCI) or merely serves as a marker of pre-existing comorbidities and other causal factors. We therefore investigated the association between fibrinogen levels and 2-year all-cause mortality, and compared the additional predictive value of adding fibrinogen to a basic model including traditional risk factors in patients receiving contemporary PCI.

Methods: A total of 6293 patients undergoing PCI with measured baseline fibrinogen levels were enrolled from January to December 2013 in Fuwai Hospital. Patients were divided into three groups according to tertiles of baseline fibrinogen levels: low fibrinogen, <2.98 g/L; medium fibrinogen, 2.98 to 3.58 g/L; and high fibrinogen, ≥3.58 g/L. Independent predictors of 2-year clinical outcomes were determined by multivariate Cox proportional hazards regression modeling. The increased discriminative value of fibrinogen for predicting all-cause mortality was assessed using the C-statistic and integrated discrimination improvement (IDI).

Results: The 2-year all-cause mortality rate was 1.2%. It was significantly higher in the high fibrinogen compared with the low and medium fibrinogen groups according to Kaplan-Meier analyses (1.7% *vs.* 0.9% and 1.7% *vs.* 1.0%, respectively; log-rank, $P=0.022$). Fibrinogen was significantly associated with all-cause mortality according to multivariate Cox regression (hazard ratio 1.339, 95% confidence interval: 1.109–1.763, $P=0.005$), together with traditional risk factors including age, sex, diabetes mellitus, left ventricular ejection fraction, creatinine clearance, and low-density lipoprotein cholesterol. The area under the curve for all-cause mortality in the basic model including traditional risk factors was 0.776, and this value increased to 0.787 when fibrinogen was added to the model (IDI=0.003, $Z=0.140$, $P=0.889$).

Conclusions: Fibrinogen is associated with 2-year all-cause mortality in patients receiving PCI, but provides no additional information over a model including traditional risk factors.

Keywords: Fibrinogen; Percutaneous coronary intervention; Risk factor; Prognosis

Introduction

Many studies have correlated fibrinogen with coronary artery disease (CAD); however, whether this is a causal relationship or a reflection of residual confounding by other risk factors remains unclear.[1-8] Some studies showed significant associations between fibrinogen and adverse events after adjusting for confounding factors, while others found that fibrinogen added no additional prognostic information compared with a basic model including traditional risk factors.[5,9,10] The fibrates clofibrate and bezafibrate demonstrated fibrinogen-lowering effects in previous randomized controlled studies, but the effect of this reduction on the long-term prognosis of patients with coronary heart disease is still unclear.[11,12] We therefore carried out a large cohort study to investigate the association between fibrinogen and 2-year all-cause mortality in patients undergoing contemporary percutaneous coronary intervention (PCI). We also assessed the additive predictive value of fibrinogen compared with a basic model including traditional risk factors.

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Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of Fuwai Hospital (No. IRB2012-BG-006 2017-860). Written informed consent was obtained from all patients prior to their enrollment in this study.

Study population

A total of 6293 consecutive patients from a single center (Fu Wai Hospital, National Center for Cardiovascular Diseases, Beijing, China) who underwent PCI from January to December in 2013 were enrolled and data were collected prospectively. All patients were diagnosed with acute coronary syndrome (ACS) or stable CAD and underwent primary or elective PCI.

Laboratory examination and procedural details

Blood samples were taken in the morning after fasting for at least 12 h and collected into vacuum tubes with sodium citrate for measurement of fibrinogen before angiography. Fibrinogen was measured using a BCS analyzer (Multifibren U; Siemens Healthcare, Erlangen, Germany), according to a modification of the Clauss method.

The PCI strategy and stent type were chosen according to the treating physician's discretion. Before the procedure, patients who underwent elective PCI and who were not taking long-term aspirin or $P2Y_{12}$ inhibitors received 300 mg aspirin and clopidogrel (loading dose, 300 mg) orally. Patients with ACS who were scheduled for PCI received the same dose of aspirin and clopidogrel (loading dose of 300 or 600 mg) as soon as possible. All patients received unfractionated heparin (100 U/kg) during the procedure. Aspirin was prescribed at a dose of 100 mg/d indefinitely after the procedure, and clopidogrel 75 mg/d was advised for at least 1 year after PCI.

Definitions and endpoints

Patients were divided into three groups according to the tertiles of baseline fibrinogen levels: low fibrinogen, <2.98 g/L, medium fibrinogen, 2.98 to <3.58 g/L, and high fibrinogen, ≥3.58 g/L. Clinical outcomes included all-cause mortality, cardiac mortality, myocardial infarction (MI), stroke, revascularization, stent thrombosis (ST), major adverse cardiovascular and cerebrovascular events (MACCE), and bleeding. Death that could not be attributed to any non-cardiac etiology was considered cardiac mortality. Patient deaths were confirmed from medical records or follow-up information. MI was defined according to the third universal definition of MI.[13] Bleeding was quantified according to the Bleeding Academic Research Consortium Definition criteria,[14] including types 1 to 5 in the analysis. MACCE was defined as the occurrence of all-cause mortality, MI, stroke, ST, and repeat revascularization during follow-up. All endpoints were adjudicated centrally by two independent cardiologists, and disagreement was resolved by consensus.

Patient follow-up

All the patients were evaluated by clinic visits or by phone at 1, 3, 6, and 12 months, and annually thereafter. Patients were advised to return for coronary angiography if clinically indicated by symptoms or documentation of myocardial ischemia. A total of 6258 patients (99.4%) completed the 2-year follow-up in this study.

Statistical analysis

Baseline descriptive statistics are reported as mean ± standard deviation (SD) or median (interquartile range) for continuous variables. Categorical variables are expressed as numbers and percentages. For differences among groups, continuous variables were tested by analysis of variance or Kruskal-Wallis test, and categorical variables were tested by Chi-squared or Fisher exact test, as appropriate. The Shapiro-Wilk test was used to determine whether random samples came from a normal distribution. Survival curves were constructed with Kaplan-Meier estimates and compared with log-rank tests for time to clinical endpoints.

Multivariate Cox proportional hazards regression modeling was performed to determine the independent predictors of 2-year clinical outcomes. Variables that were significantly different at baseline ($P < 0.05$) and those judged to be of clinical importance based on previously published reports were eligible for inclusion in the multivariate model-building process. Results are reported as hazard ratios (HRs) with associated 95% confidence interval (CI) and P values. The increased discriminative value of fibrinogen for prediction all-cause mortality was assessed using the C-statistic and integrated discrimination improvement (IDI). A $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 23 (IBM Corporation, Armonk, NY, USA) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics according to fibrinogen groups

The baseline characteristics of the overall study population are shown in Table 1. As expected, patients in the high fibrinogen group were older and had a higher prevalence of traditional risk factors, such as hypertension, diabetes mellitus, previous MI, previous PCI, previous cardiovascular disease, worse left ventricular ejection fraction (LVEF), and worse creatinine clearance (CCr) compared with the other two groups (all $P < 0.05$). Laboratory data showed higher total cholesterol, low-density lipoprotein cholesterol, triglyceride, high-sensitivity C-reactive protein levels, and *N*-terminal pro-brain natriuretic peptide levels, and lower high-density lipoprotein cholesterol levels in the high fibrinogen group compared with the other two groups. With regard to clinical presentation, there were more patients with ACS in the high fibrinogen group compared with the other two groups, but fewer patients with stable angina pectoris and silent ischemia. Regarding angiographic and procedural characteristics, patients in

Table 1: Clinical characteristics of the patients receiving percutaneous coronary intervention.

Items	<2.98 g/L (*n*=2111)	2.98–3.58 g/L (*n*=2071)	≥3.58 g/L (*n*=2111)	Statistics	*P*
Demographic characteristics					
Age (years)	57.3±10.2	58.1±10.2	59.6±10.7	27.8*	<0.001
Female gender, *n* (%)	346 (16.4)	477 (23.0)	584 (27.7)	78.1†	<0.001
BMI (kg/m^2)	25.7±3.1	26.1±3.2	26.0±3.3	8.3*	<0.001
Co-existing conditions, *n* (%)					
Hypertension	1271 (60.2)	1353 (65.3)	1402 (66.4)	20.1†	<0.001
Diabetes mellitus	435 (25.3)	663 (32.0)	706 (33.4)	37.3†	<0.001
Dyslipidemia	1435 (68.0)	1642 (70.6)	1456 (69.0)	3.4†	0.181
Current smoking	1222 (57.9)	1193 (57.6)	1166 (55.2)	7.0†	0.133
Previous MI	472 (22.4)	403 (19.5)	377 (17.9)	13.8†	0.001
Previous PCI	601 (28.5)	485 (23.4)	435 (20.6)	36.6†	<0.001
Previous CABG	104 (4.9)	77 (3.7)	88 (4.2)	3.8†	0.148
CVD	209 (9.9)	213 (10.3)	256 (12.1)	6.2†	0.045
PAD	66 (3.1)	57 (2.8)	58 (2.7)	0.7†	0.700
LVEF ≤ 40%	18 (0.9)	25 (1.2)	59 (2.8)	28.4†	<0.001
CCr ≤ 60 mL/min/1.73 m^2	62 (2.5)	69 (3.3)	153 (7.2)	65.8†	<0.001
Laboratory data					
Total cholesterol (mmol/L)	4.0±1.1	4.2±1.1	4.3±1.1	40.9*	<0.001
LDL-C (mmol/L)	2.3±0.9	2.5±0.9	2.6±0.9	38.0*	<0.001
HDL-C (mmol/L)	1.02±0.27	1.03±0.28	1.01±0.28	2.9*	0.057
Triglyceride (mmol/L)	1.5 (1.1–2.1)	1.6 (1.2–2.2)	1.6 (1.2–2.1)	25.1†	<0.001
Hs-CRP (mmol/L)	0.9 (0.5–1.5)	1.5 (0.9–2.7)	3.9 (1.9–10.0)	1863.5†	<0.001
NT-proBNP (pg/mL)	498 (400–663)	561 (438–744)	663 (491–964)	253.6†	<0.001
Clinical presentation, *n* (%)					
ACS	1099 (52.1)	1186 (57.3)	1373 (65.0)	53.0†	<0.001
Stable angina pectoris	805 (38.1)	694 (33.5)	583 (27.6)	74.0†	<0.001
Silent ischemia	207 (9.8)	191 (9.2)	155 (7.3)	8.7†	0.013
Angiographic and procedural characteristics					
SYNTAX score	11.7±7.6	12.3±8.0	13.2±8.2	19.0*	<0.001
LM and/or three-vessel disease, *n* (%)	884 (41.9)	921 (44.5)	1030 (48.8)	20.8†	<0.001
No. of target lesion	1.37±0.63	1.42±0.68	1.45±0.72	6.5*	0.002
Number of stents	1.80±1.13	1.82±1.17	1.86±1.18	1.8*	0.172
DES, *n* (%)	1886 (89.3)	1854 (89.5)	1869 (88.5)	1.2†	0.550
Procedure success, *n* (%)	2064 (97.8)	2042 (98.6)	2065 (97.8)	8.1†	0.089
Medication at discharge, *n* (%)					
DAPT	2042 (96.7)	2012 (97.2)	2054 (97.3)	1.3†	0.526
Beta blocker	1917 (90.8)	1095 (92.0)	1930 (91.4)	1.8†	0.399
Statin	2043 (96.8)	1997 (96.4)	2030 (96.2)	1.2†	0.555

Data are expressed as mean ± standard deviation or number (percentage). * *F* values. † Chi-squared values. ACS: Acute coronary syndrome; BMI: Body mass index; CABG: Coronary artery bypass grafting; CCr: Creatinine clearance rate; CVD: Cerebrovascular disease; DAPT: Dual anti-platelet therapy; DES: Drug-eluting stent; HDL-C: High-density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; LM: Left main; MI: Myocardial infarction; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAD: Peripheral vascular disease; PCI: Percutaneous coronary intervention; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

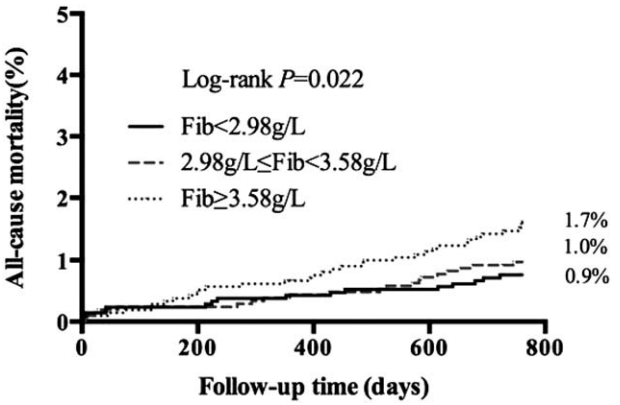

Figure 1: Kaplan-Meier curves for 2-year adverse events. Cumulative Kaplan-Meier event curves for 2-year all-cause mortality were significantly higher in the upper tertile according to fibrinogen (Fib) levels.

the high fibrinogen group had a higher SYNTAX score and more left main and/or three-vessel disease compared with the other two groups.

Predictive value of fibrinogen for all-cause mortality

The 2-year all-cause mortality rate was 1.2%. The effect of fibrinogen levels on 2-year all-cause mortality according to Kaplan-Meier analyses is shown in Figure 1. The 2-year all-cause mortality rate was significantly higher in the upper tertile of patients according to fibrinogen levels (log-rank, $P=0.022$).

Univariate Cox regression showed that fibrinogen was associated with all-cause mortality (HR 1.496, 95% CI: 1.221–1.833, $P<0.001$) and cardiac mortality (HR 1.439, 95% CI: 1.112–1.864, $P=0.006$) [Figure 2A]. Fibrinogen remained independently associated with

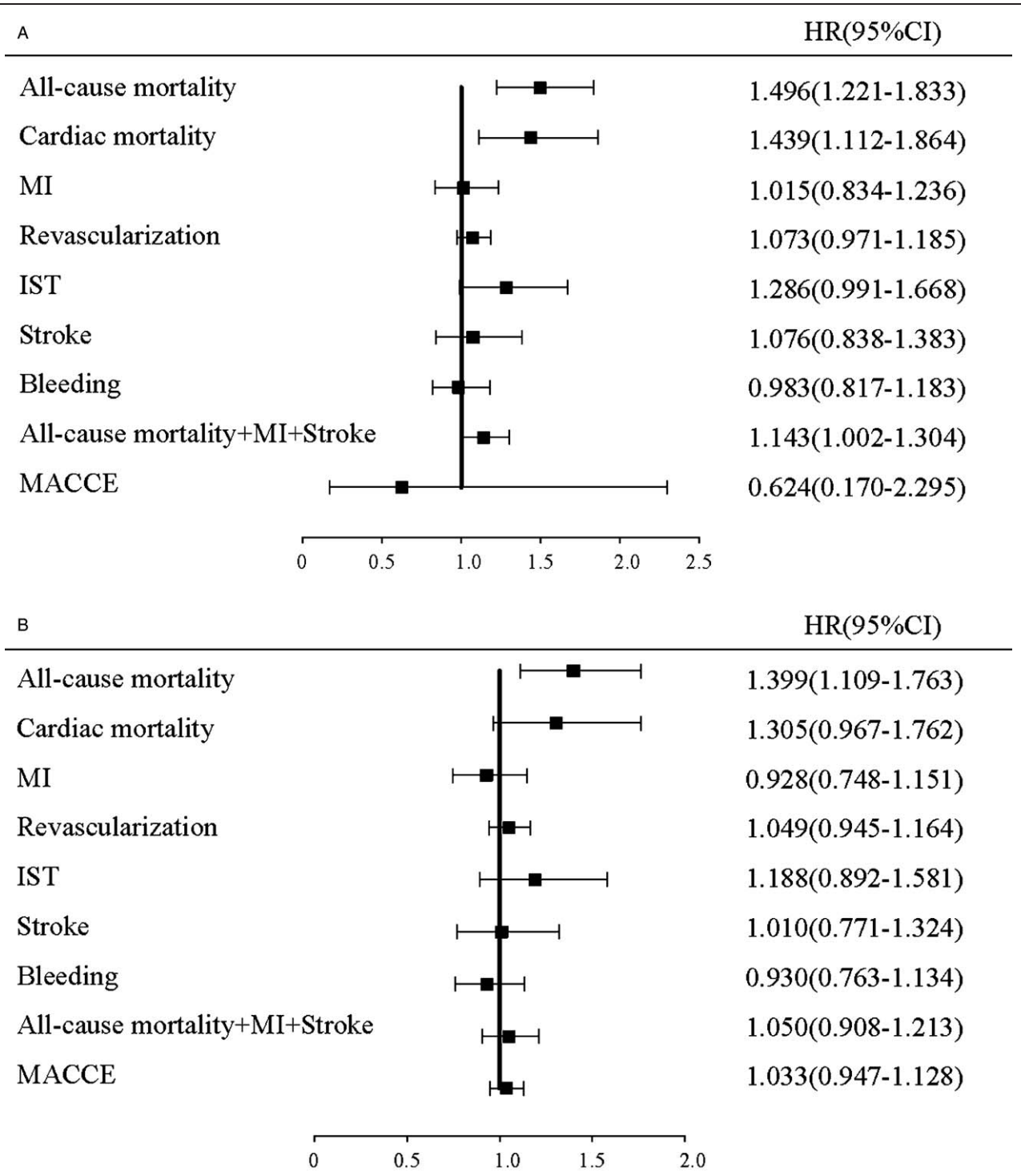

Figure 2: Cox regression analysis of fibrinogen for 2-year clinical outcomes. (A) Univariate Cox regression of fibrinogen for 2-year clinical outcomes. (B) Multivariate Cox regression of fibrinogen for 2-year clinical outcomes. IST: Intra stent thrombosis; MACCE: Major adverse cardiovascular and cerebrovascular events; MI: Myocardial infarction.

all-cause mortality after adjusting for potential confounders (HR 1.339, 95% CI: 1.109–1.763, $P=0.005$) [Figure 2B].

Traditional risk factors associated with all-cause mortality

To place the predictive value of fibrinogen in the context of traditional risk factors, we evaluated all variables in multivariate models. We directly compared the predictive powers by presenting the HRs associated with continuous variables per increment SD. As expected, traditional risk factors including age (HR 1.062, 95% CI: 1.024–1.101, $P<0.001$), sex (HR 0.320, 95% CI: 0.121–0.845, $P=0.021$), diabetes mellitus (HR 2.108, 95% CI: 1.107–4.016, $P=0.023$), LVEF (HR 4.701, 95% CI: 1.408–15.702, $P=0.012$), baseline CCr (HR 0.373, 95% CI: 0.158–0.878, $P=0.024$), and low-density lipoprotein cholesterol (LDL-C) (HR 0.516, 95% CI: 0.320–0.832,

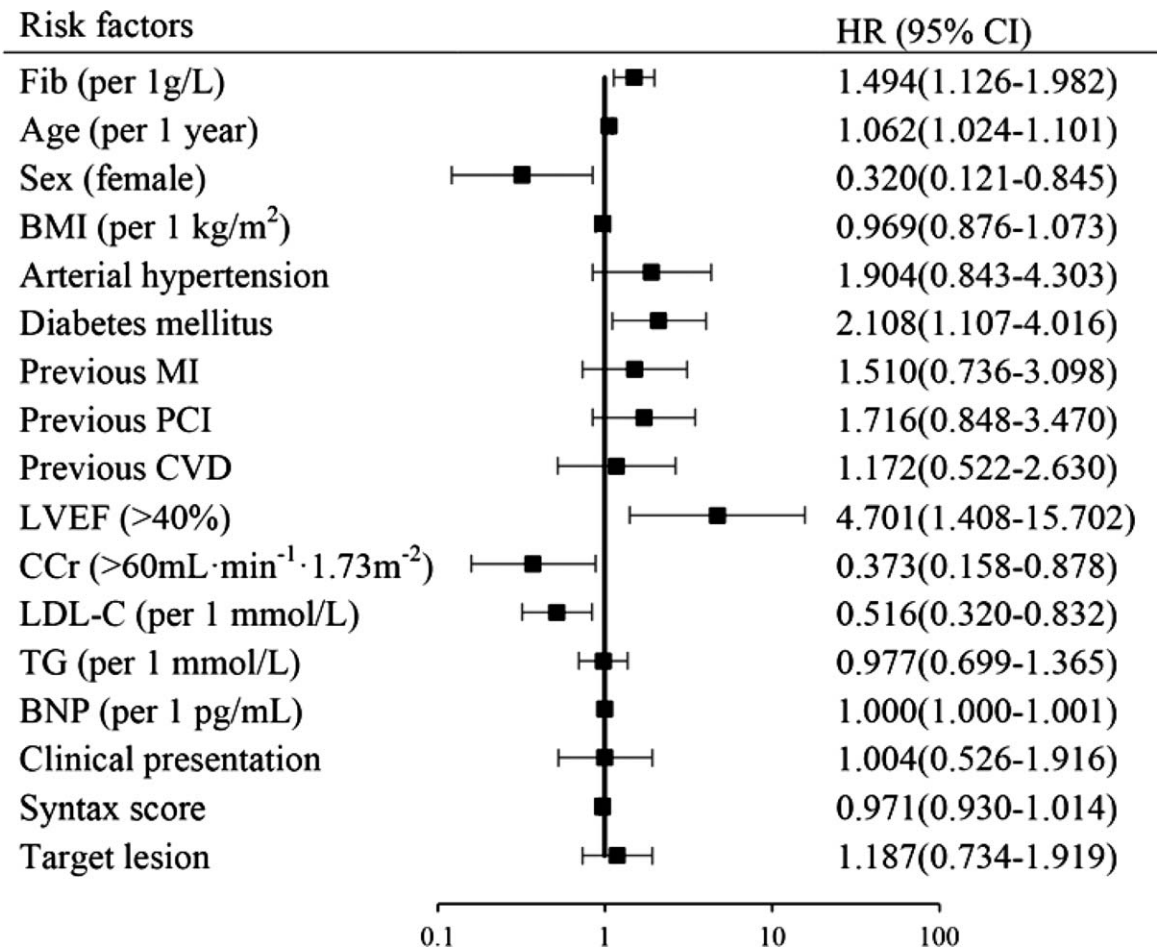

Figure 3: Results of multivariate Cox regression regarding 2-year all-cause mortality. BMI: Body mass index; BNP: Brain natriuretic peptide; CCr: Creatinine clearance rate; CVD: Cerebrovascular disease; Fib: Fibrinogen; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; TG: Triglyceride.

$P = 0.007$) were the strongest predictors of 2-year all-cause mortality [Figure 3].

Subgroup analysis of all-cause mortality

Subgroup analysis showed that fibrinogen was associated with all-cause mortality in patients who were aged >65 years, male, had a body mass index ≤30 kg/m^2, with or without previous MI or PCI, patients with hypertension, patients with or without diabetes mellitus, ACS or stable CAD, CCr >60 mL/min, LVEF >40%, and a SYNTAX score <22 (all $P < 0.05$) [Figure 4]. All P values for interaction in subgroups were >0.05.

Incremental effect of fibrinogen on all-cause mortality in addition to traditional risk factors

To determine if fibrinogen provided additional value compared with traditional risk factor screening, we computed the area under the receiver operating characteristic curve (AUC) associated with the prediction of different logistic regression models. We additionally included fibrinogen considering all-cause mortality at 2 years as a binary variable. The basic model including the traditional risk factors age, sex, diabetes mellitus, LVEF, baseline CCr, and LDL-C showed an AUC of 0.776 (95% CI: 0.725–0.827). The inclusion of fibrinogen only modestly improved the predictive value of the basic model, with an increase in the AUC to 0.787 (95% CI: 0.736–0.838; IDI = 0.003, $z = 0.140$, $P = 0.889$).

Discussion

This study assessed the effect of serum fibrinogen levels on 2-year all-cause mortality after PCI in a large cohort of real-world patients in a large Chinese cardiovascular center. The major findings revealed that fibrinogen levels were related to 2-year all-cause mortality in unselected Chinese patients who received PCI, independent of traditional cardiovascular risk factors, the extent of angiographic CAD, LVEF, and renal function. However, simple and readily available traditional risk factors remained the strongest risk predictors for 2-year all-cause mortality, and fibrinogen added little additional prognostic information compared with traditional risk factors of CAD.

Fibrinogen levels were first reported to be related to MI in 1954, since when numerous studies have identified relationships between fibrinogen levels and cardiovascular risk factors, and the incidence and adverse clinical

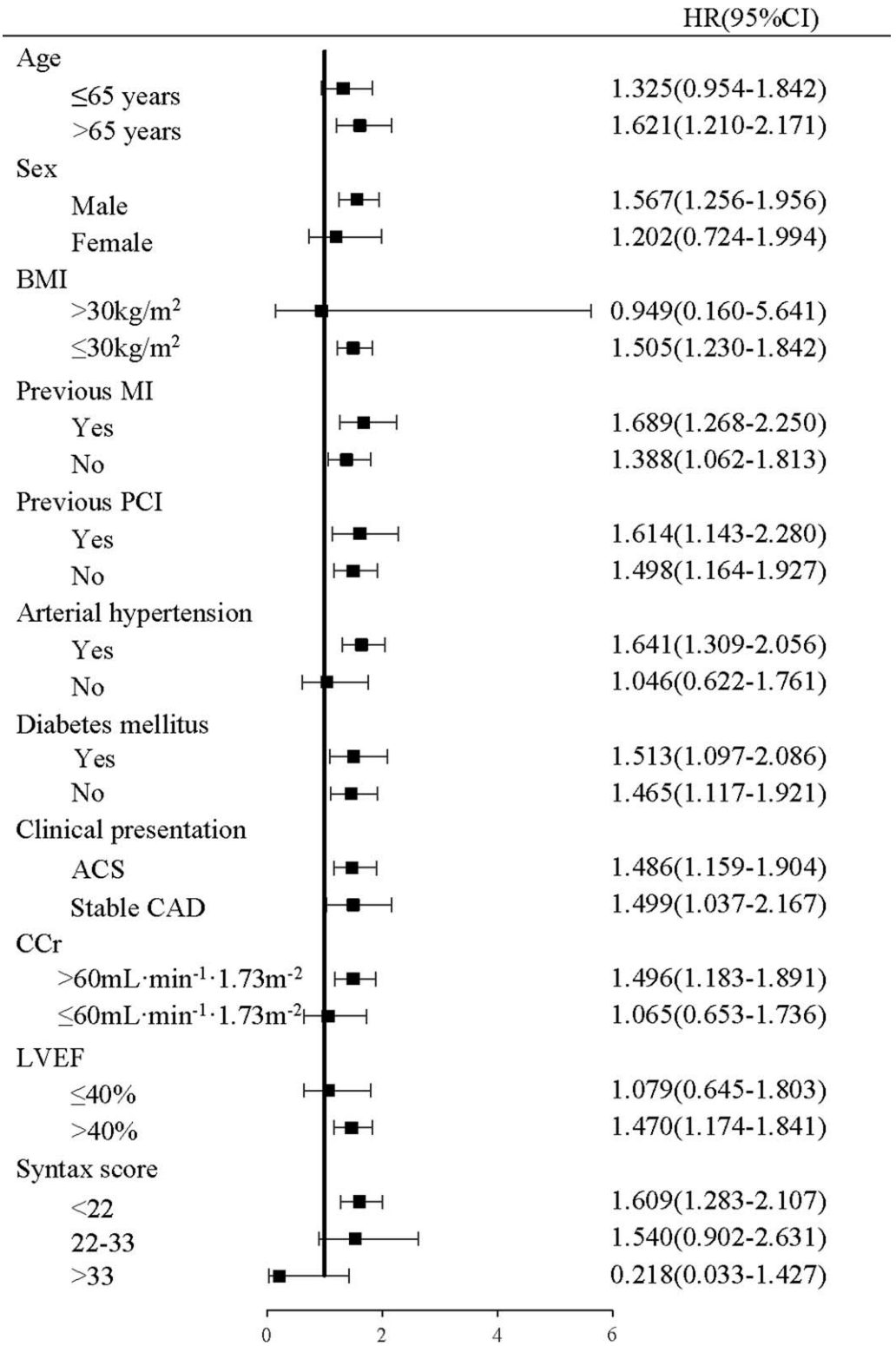

Figure 4: All-cause mortality in subgroups of patients. ACS: Acute coronary syndrome; BMI: Body mass index; CAD: Coronary artery disease; CCr: Creatinine clearance rate; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

outcomes of CAD. However, whether or not fibrinogen plays a causal role in atherothrombosis or only acts as a biomarker has remained controversial. In the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study, which included middle-aged men without CAD at entry, fibrinogen levels were associated with the incidence of acute coronary events, independently of traditional risk factors for CAD.[15] A meta-analysis also showed an association between plasma fibrinogen levels and the risk of CAD, even after adjustment.[3] The AtheroGene study,[9] which included patients with confirmed stable CAD, showed that fibrinogen levels predicted future

cardiovascular risk independent of traditional risk factors. The present large cohort study carried out in Chinese patients who underwent contemporary PCI found that fibrinogen levels were significantly related to 2-year all-cause mortality, independently of traditional risk factors. These results were thus in accordance with those of the AtheroGene and PRIME studies.[9,15]

Regarding the relationship between fibrinogen and traditional risk factors, Sinning *et al*[9] in the AtheroGene study found that fibrinogen could predict future cardiovascular risk in patients with stable angina pectoris, but did not provide any further information in addition to that obtained from traditional risk factors. Ndrepepa found similar results in a study of patients with CAD.[16] The current study also indicated that fibrinogen only added a small amount of additional information above that obtained from traditional risk factors. This may suggest that fibrinogen serves as a biomarker of poor long-term prognosis in patients with coronary heart disease undergoing PCI.

Fibrinogen plays important roles in platelet aggregation, plasma viscosity, and fibrin formation. It is an acute-phase reactant that is increased in inflammatory states. In accordance with the hypothesis that inflammation plays an important role in plaque rupture and thrombosis, elevated fibrinogen levels have been identified in patients with unstable angina.[17,18] Previous studies also showed that fibrinogen levels were associated with traditional cardiovascular risk factors such as age,[19] smoking,[20] obesity,[21] and diabetes mellitus.[22] These risk factors accounted for most of the risk of MI in previous studies.[20,23,24] A meta-analysis[12] showed that a third of the variation in fibrinogen levels could be explained by cohort, age, and sex, 7% by established risk factors like smoking, body mass index, and high-density lipoprotein cholesterol, and 10% by inflammatory markers. Fibrates have been shown to lower fibrinogen levels independent of changes in cholesterol and triglyceride concentrations,[11] but few randomized controlled trials have explored the relationship between lowering fibrinogen and the prognosis of CAD. The continuing controversy over whether fibrinogen is a causal factor or just a biomarker of CAD indicates the need for more studies aimed at exploring the relationship between fibrinogen and CAD. Randomized controlled trials also need to be conducted to determine if lowering fibrinogen levels can improve the long-term prognosis in patients with CAD.

This study had several limitations. First, we only performed baseline measurements and were thus unable to determine any variability in fibrinogen levels during the course of the study. However, this limitation would be likely to affect both traditional risk factors and fibrinogen. Therefore, after correction for regression or other biases introduced because of measurement errors, traditional markers may predict an even greater proportion of adverse clinical outcomes. Second, this study was carried out in patients who received PCI, and the results may not be applicable to the general population. Finally, this study was carried out in a single center, and further multicenter studies are required to confirm our findings.

In conclusion, the present study suggests that fibrinogen is associated with 2-year all-cause mortality in patients receiving PCI, but provides no additional information over a model including traditional risk factors.

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Conflicts of interest

None.

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