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High Fibrinogen Levels with Diabetes Mellitus are Associated with All-Cause and Cardiovascular Mortality in Patients with End-Stage Renal Disease and Acute Coronary Syndrome

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Objective: As a biomarker of inflammation and a core component in the coagulation pathway, fibrinogen contributes to atherosclerosis and subsequent adverse cardiovascular events and is modified by the occurrence of diabetes mellitus. However, the association between fibrinogen, diabetes status, and mortality in patients with end-stage renal disease (ESRD) and acute coronary syndrome (ACS) remains scarce.

Methods: A multi-center cohort study enrolled 1079 patients with ESRD and ACS between January 2015 and June 2021. Patients were classified into three groups based on fibrinogen tertiles and were further categorized by diabetes status. The primary outcome was all-cause mortality, while the secondary outcome was cardiovascular mortality.

Results: During a median 21.5 months of follow-up, 386 cases of all-cause mortality were recorded, including 262 cases of cardiovascular mortality. Multivariable Cox regression model revealed that patients with the third tertile of fibrinogen and those with diabetes experienced a significantly increased risk of all-cause mortality (fibrinogen: hazard ratio [HR], 1.70; 95% confidence interval [CI], 1.32–2.19; diabetes: HR, 1.36; 95% CI, 1.10–1.68). When patients were stratified by both fibrinogen levels and diabetes status, patients in the third fibrinogen tertile with diabetes had the highest risk of all-cause mortality (HR 2.43, 95% CI 1.69–3.48) compared to those in the first fibrinogen tertile without diabetes. Similar associations were observed for cardiovascular mortality. Notably, incorporating the combined fibrinogen and diabetes status into the Global Registry of Acute Coronary Events (GRACE) score or baseline risk model led to significant improvements in the C-statistics for predicting mortality, surpassing the advancements achieved with any single biomarker.

Conclusion: In patients with ESRD and ACS, elevated fibrinogen and diabetes were associated with an increased risk of all-cause and cardiovascular mortality. Categorizing patients based on fibrinogen levels and diabetes status could provide valuable information for risk stratification of these patients.

Keywords: Acute coronary syndrome, Diabetes mellitus, End-stage renal disease, Fibrinogen, Prognosis

Background

Patients with acute coronary syndrome (ACS) exhibit diverse clinical characteristics and varying levels of cardiovascular risk.[1,2] Particularly, those with end-stage renal disease (ESRD) face an ACS-related mortality risk over ten times higher than the general population, making them highly vulnerable within the ACS spectrum.[3–5] Notably, the risk elevation observed in individuals with ESRD and ACS cannot be solely linked to conventional cardiovascular risk factors.[3–5] Furthermore, the widely used Global Registry of Acute Coronary Events (GRACE) risk score frequently fails to accurately predict risk of adverse events in these patients.[6] Consequently, further exploration of additional prognostic

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variables is clinically significant for enhancing the precision of prognosis assessment and identifying potential treatment targets in this vulnerable patient population.

Inflammation and coagulation play a crucial role in the progression of atherosclerosis.[7,8] As a core component of coagulation and a well-established marker of inflammation, fibrinogen is associated with both coronary severity and poor outcomes in ACS patients.[9–11] Notably, patients with ESRD, especially among those requiring dialysis, frequently experience elevated levels of fibrinogen, which have been linked to increased cardiovascular morbidity and mortality.[12–14] The prevalence of diabetes mellitus (DM) is rising rapidly, with diabetic nephropathy as the primary cause of ESRD worldwide.[4,15] Furthermore, patients with DM exhibit higher fibrinogen levels, which have been linked to glycemic abnormalities and insulin resistance.[16,17] In addition, the prognostic value of fibrinogen appears to be modified by the occurrence of DM in patients with ACS.[18,19] Elevated fibrinogen predicts major cardiovascular events in individuals with DM but lacks significance in those without DM. Recent studies suggest that the combination of fibrinogen and DM status provides incremental value in cardiovascular risk stratification for stable coronary artery disease (CAD) patients.[20] However, whether these associations could be extrapolated to ACS patients, especially those with ESRD, remains unknown. Collectively, these findings suggest the potential for a synergistic impact of fibrinogen and DM status on unfavorable prognosis among patients with ESRD and ACS.

In this multi-center study, our objective was to evaluate the association between fibrinogen, DM status, and mortality in patients with ESRD and ACS. Additionally, we seek to determine the additional predictive value of integrating the combination of fibrinogen and DM status into the baseline risk model or GRACE risk score.

Methods

Study Design and Population

This study is based on data from the Coronary Revascularization in Patients On Dialysis in China-Retrospective (CRUISE-R) cohort study (ClinicalTrials.gov NCT05841082), a multi-center, observational registry in China.[21,22] The study involved an analysis of 455,617 cardiac catheterizations carried out between January 2015 and June 2021. To ensure data quality, specific exclusion criteria were applied. This involved excluding patients without dialysis therapy or who had a dialysis duration of less than 3 months (n=453,421), individuals without coronary stenosis >50% (n=328), those with indications for coronary angiography other than coronary stenosis (n=87), and readmitted individuals (n=532). Consequently, the CRUISE-R study enrolled 1,249 ESRD patients on dialysis with obstructive CAD. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the China-Japan Friendship Hospital Ethics Committee (No. 2020–112-K71), and informed consent was waived due to the retrospective nature of the study and the anonymized processing of patient data.

In this study, 90 patients with missing fibrinogen data and 80 individuals diagnosed with stable angina were further excluded. The remaining 1079 patients with ESRD and ACS were included in the analysis. This study adhered to the reporting guidelines proposed by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Data Collection

Qualified study coordinators extracted comprehensive demographic and clinical data from electronic medical records. This encompassed details like age, gender, comorbidities (including hypertension, DM, smoking status, cardiovascular history), dialysis modality, and dialysis vintage. Laboratory assessments included fibrinogen levels, total cholesterol levels, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, triglyceride levels, serum creatinine concentrations, and hemoglobin levels. Medication usage, like calcium-channel blocker, β-blocker, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor, dual antiplatelet therapy, and statins, was documented. Survival evaluation data were gathered by trained nurses during visits to outpatient clinics and through telephone interviews, continuing until June 30th, 2022. In cases where individuals could not be reached for phone interviews, their survival status was determined using the most recent approved time point, which included the date of their latest outpatient clinic visit or hospital discharge.

Outcomes and Definitions

In this study, the primary outcome assessed was all-cause mortality. Secondary outcome examined was cardiovascular mortality, specified as death due to sudden cardiac death, heart failure, acute myocardial infarction, cardiovascular procedures, cardiovascular hemorrhage, or stroke. The confirmation of a DM diagnosis was based on documented prior diagnoses, current or past use of oral hypoglycemic drugs or insulin, or the presence of HbA1c levels ≥ 6.5% upon admission. Information essential for determining the GRACE risk scores, which span from 1 to 372, was collected from hospital admission records.[23] In this study, we used standard evaluation methods described by Mintz et al to determine the presence and severity of calcification lesion.[24] Briefly, moderate calcification was identified by radiopaque regions visible before contrast administration, partially extending into the target lesion during the cardiac cycle. Severe calcification was defined as radiopaque regions observed prior to contrast injection, with no detectable cardiac motion. Lesions that did not meet these criteria were classified as non-calcified or mildly calcified. Dual antiplatelet therapy refers to a treatment strategy that involves using two different medications to inhibit platelet aggregation, including aspirin and a P2Y12 receptor inhibitor.

Statistical Analysis

For continuous variables, baseline characteristics were presented as mean (standard deviation) or median (interquartile range). Categorical variables were displayed as frequencies with percentages and were evaluated using the chi-square test or Fisher's exact test, when applicable. To determine the event-free survival rates among the different groups, we employed the Kaplan-Meier method and compared them using the Log rank test. The association between fibrinogen categories and DM status with clinical outcomes was assessed using univariable and multivariable Cox proportional hazard models. The candidate variables considered for the multivariable model included age, sex, hypertension, current smoking status, peripheral arterial disease, valvular disease, cerebrovascular disease, atrial fibrillation, previous coronary intervention, insulin therapy, dialysis vintage, dialysis modality, index presentation, hemoglobin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, radial access, extent of disease, moderate or severe calcification, PCI treatment, calcium-channel blockers, β-blockers, dual antiplatelet therapy, angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, and statins. Variables that showed statistical significance in the univariate model or held clinical relevance were incorporated into the multivariable analysis. Hazard ratios (HRs) were reported along with their corresponding 95% confidence intervals (CIs). We validated the proportional hazards assumption using Schoenfeld residuals. Missing values were estimated using multiple imputation. To explore potential non-linear associations between fibrinogen and clinical outcomes, we employed restricted cubic spline (RCS) analyses. In these RCS models, we made adjustments by including the confounding variables integrated into the multivariable Cox model. To examine the joint association of fibrinogen and DM status, a new variable combining fibrinogen tertiles and DM status was created. This variable included six categories representing six combinations of fibrinogen tertiles (≤3.68 g/L, 3.68–4.57 g/L, and >4.57 g/L) and DM status (DM and non-DM). Kaplan-Meier curves and Cox proportional hazard models were also applied to explore the association between the combined variable and endpoints. The incremental predictive performance after introducing fibrinogen categories, DM status, and combined categories to the GRACE score or the fully adjusted baseline risk model was assessed using the C-statistic and ΔC-statistic. To validate the main findings, we conducted a sensitivity analysis by excluding patients who died during hospitalization. All statistical analyses were conducted with a two-sided approach, and a significance level below 0.05 was considered to indicate statistical significance. The software packages SPSS 23.0 (IBM SPSS 23 Inc) and R 3.6.1 (R Development Core Team, Vienna, Austria) were used for data analysis.

Results

Baseline Characteristics

In the present study, a total of 1079 patients were included. The study population had a mean age of 62.1 ± 10.4 years, with 73.1% being male. A majority of participants had a medical history of hypertension (93.3%) or DM (54.3%). The median (IQR) levels of fibrinogen in the whole cohort were 4.1 (3.4–4.9) g/L. Based on fibrinogen tertiles, patients were classified into three groups: low fibrinogen (≤ 3.68 g/L), medium fibrinogen (3.68–4.57 g/L), and high fibrinogen (> 4.57 g/L). The baseline characteristics among the three groups stratified by fibrinogen tertiles were presented in Table 1.

Table 1 Baseline Demographic and Clinical Data of the Study Patients According to Tertiles of Fibrinogen

Characteristic	Overall *N* = 1079	Low fibrinogen *N* = 360	Medium Fib *N* = 360	High Fib *N* = 359	*P* value
Age, mean (SD), yrs	62.1 (10.4)	62.7 (10.4)	61.7 (10.7)	62.0 (10.1)	0.404
Male, No. (%)	789 (73.1)	276 (76.7)	256 (71.1)	257 (71.6)	0.176
Medical history and risk factors, No. (%)					
Hypertension	1007 (93.3)	331 (91.9)	339 (94.2)	337 (93.9)	0.431
DM	586 (54.3)	187 (51.9)	184 (51.1)	215 (59.9)	0.033
Current smoker	189 (17.5)	73 (20.3)	63 (17.5)	53 (14.8)	0.151
Atrial fibrillation	97 (9.0)	38 (10.6)	26 (7.2)	33 (9.2)	0.291
Cerebrovascular disease	210 (19.5)	75 (20.8)	64 (17.8)	71 (19.8)	0.575
Valvular disease	34 (3.2)	12 (3.3)	11 (3.1)	11 (3.1)	0.971
Peripheral arterial disease	105 (9.7)	36 (10.0)	27 (7.5)	42 (11.7)	0.161
Previous intervention, No. (%)					
PCI	209 (19.4)	81 (22.5)	69 (19.2)	59 (16.4)	0.120
CABG	15 (1.4)	4 (1.1)	7 (1.9)	4 (1.1)	0.546
Dialysis modality, No. (%)					<0.001
Hemodialysis	982 (91.0)	346 (96.1)	333 (92.5)	303 (84.4)	
Peritoneal dialysis	97 (9.0)	14 (3.9)	27 (7.5)	56 (15.6)	
Vintage of dialysis, yrs					0.444
<1	220 (20.4)	74 (20.6)	67 (18.6)	79 (22.0)	
1–5	503 (46.6)	158 (43.9)	169 (46.9)	176 (49.0)	
5–10	286 (26.5)	100 (27.8)	103 (28.6)	83 (23.1)	
≥10	70 (6.5)	28 (7.8)	21 (5.8)	21 (5.8)	
Insulin therapy, No. (%)	372 (34.5)	117 (32.5)	118 (32.8)	137 (38.2)	0.198
Index presentation, No. (%)					<0.001
STEMI	143 (13.3)	42 (11.7)	38 (10.6)	63 (17.5)	
NSTEMI	540 (50.0)	170 (47.2)	173 (48.1)	197 (54.9)	
Unstable angina	396 (36.7)	148 (41.1)	149 (41.4)	99 (27.6)	
GRACE score	158.0 [133.0, 183.0]	154.5 [132.0, 180.0]	153.0 [131.8, 178.0]	164.0 [141.5, 189.0]	<0.001
Hemoglobin, g/L	104.8 (20.1)	106.0 (19.0)	104.8 (20.6)	103.6 (20.8)	0.280
Serum creatinine, mg/dl	8.6 [6.7, 11.0]	8.1 [6.6, 10.4]	8.8 [6.7, 11.1]	8.9 [6.8, 11.5]	0.026
Fibrinogen, g/L	4.1 [3.4, 4.9]	3.2 [2.8, 3.4]	4.1 [3.9, 4.3]	5.3 [4.9, 6.1]	<0.001
TG, mmol/L	1.5 [1.1, 2.3]	1.4 [1.0, 2.2]	1.7 [1.1, 2.4]	1.6 [1.2, 2.3]	<0.001
TC, mmol/L	3.7 [3.1, 4.5]	3.5 [3.0, 4.3]	3.8 [3.2, 4.6]	3.9 [3.2, 4.6]	<0.001
HDL-C, mmol/L	0.9 [0.7, 1.1]	0.9 [0.7, 1.1]	0.9 [0.8, 1.2]	0.9 [0.7, 1.1]	0.047
LDL-C, mmol/L	2.1 [1.6, 2.7]	2.0 [1.5, 2.5]	2.2 [1.6, 2.8]	2.2 [1.8, 2.9]	<0.001
Procedure characteristic, No. (%)					
Radial access	827 (76.6)	276 (76.7)	279 (77.5)	272 (75.8)	0.860
Extent of disease					
Any left main disease	128 (11.9)	43 (11.9)	34 (9.4)	51 (14.2)	0.142
2-vessel disease	296 (27.4)	95 (26.4)	99 (27.5)	102 (28.4)	0.831
≥3-vessel disease	627 (58.1)	210 (58.3)	204 (56.7)	213 (59.3)	0.765
Moderate or severe calcification	473 (43.8)	151 (41.9)	163 (45.3)	159 (44.3)	0.651
PCI treatment	774 (71.7)	251 (69.7)	260 (72.2)	263 (73.3)	0.556
Discharge medications, No. (%)					
Dual antiplatelet therapy	951 (88.1)	318 (88.3)	314 (87.2)	319 (88.9)	0.787
ACE inhibitor or ARB	502 (46.5)	160 (44.4)	167 (46.4)	175 (48.7)	0.511
β-blocker	878 (81.4)	287 (79.7)	287 (79.7)	304 (84.7)	0.143
Calcium-channel blocker	697 (64.6)	233 (64.7)	241 (66.9)	223 (62.1)	0.399
Statin	1017 (94.3)	333 (92.5)	339 (94.2)	345 (96.1)	0.116

Note: Data are presented as mean (SD) or n (%).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; DM, diabetes mellitus; GRACE, Global Registry of Acute Coronary Events; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglycerides.

Compared with the low fibrinogen group, patients with elevated fibrinogen levels had a higher prevalence of DM, underwent peritoneal dialysis more frequently, and a higher portion exhibited acute myocardial infarction as their primary symptom. Additionally, patients with higher fibrinogen levels demonstrated higher GRACE risk scores as well as higher levels of serum creatinine, total cholesterol, triglycerides, and low-density lipoprotein cholesterol. The baseline and clinical characteristics of patients with and without DM were compared in Table 2. Patients with DM exhibited advanced age, a higher proportion of peripheral arterial disease, and a greater likelihood of presenting with non-ST-segment elevation myocardial infarction as their primary symptom. In addition, patients with DM demonstrated higher GRACE risk scores, higher levels of fibrinogen, triglyceride and high-density lipoprotein cholesterol, and shorter vintage of dialysis. Furthermore, a detailed comparison between the final study population and those excluded due to missing fibrinogen measurements is presented in Table S1.

Independent Association of Fibrinogen and Diabetes Status with Outcomes

Throughout a median follow-up period of 21.5 (interquartile range:11.5–34.1) months, there were 386 occurrences of all-cause mortality, out of which 262 were specifically attributed to cardiovascular death. The risk of all-cause mortality

Table 2 Baseline Demographic and Clinical Data of the Study Patients According to Diabetes Status

Characteristic	Non-DM (*N* = 493)	DM (*N* = 586)	*P* value
Age, mean (SD), yrs	61.3 (11.5)	62.8 (9.3)	0.016
Male, No. (%)	349 (70.8)	440 (75.1)	0.129
Medical history and risk factors, No. (%)			
Hypertension	454 (92.1)	553 (94.4)	0.170
Current smoker	88 (17.8)	101 (17.2)	0.854
Atrial fibrillation	39 (7.9)	58 (9.9)	0.303
Cerebrovascular disease	83 (16.8)	127 (21.7)	0.055
Valvular disease	22 (4.5)	12 (2.0)	0.037
Peripheral arterial disease	32 (6.5)	73 (12.5)	0.001
Previous intervention, No. (%)			
PCI	85 (17.2)	124 (21.2)	0.122
CABG	7 (1.4)	8 (1.4)	1.0
Dialysis modality, No. (%)			0.697
Hemodialysis	451 (91.5)	531 (90.6)	
Peritoneal dialysis	42 (8.5)	55 (9.4)	
Vintage of dialysis, yrs			<0.001
<1	78 (15.8)	142 (24.2)	
1–5	199 (40.4)	304 (51.9)	
5–10	167 (33.9)	119 (20.3)	
≥10	49 (9.9)	21 (3.6)	
Index presentation, No. (%)			0.021
STEMI	71 (14.4)	72 (12.3)	
NSTEMI	224 (45.4)	316 (53.9)	
Unstable angina	198 (40.2)	198 (33.8)	
GRACE score	154.0 [132.0, 178.0]	161.0 [136.0, 186.0]	0.010
Hemoglobin, g/L	105.2 (20.7)	104.5 (19.6)	0.553
Serum creatinine, mg/dl	9.0 [7.0, 11.2]	8.2 [6.4, 10.6]	0.001
Fibrinogen, g/L	4.0 [3.4, 4.7]	4.2 [3.5, 5.0]	0.037
TG, mmol/L	1.5 [1.1, 2.2]	1.6 [1.2, 2.4]	0.011
TC, mmol/L	3.7 [3.2, 4.5]	3.7 [3.1, 4.5]	0.482
HDL-C, mmol/L	0.9 [0.8, 1.2]	0.9 [0.7, 1.1]	<0.001
LDL-C, mmol/L	2.1 [1.7, 2.8]	2.1 [1.6, 2.7]	0.441

(*Continued*)

Table 2 (Continued).

Characteristic	Non-DM (*N* = 493)	DM (*N* = 586)	*P* value
Procedure characteristic, No. (%)			
Radial access	375 (76.1)	452 (77.1)	0.733
Extent of disease			
Any left main disease	54 (11.0)	74 (12.6)	0.451
2-vessel disease	130 (26.4)	166 (28.3)	0.516
≥3-vessel disease	285 (57.8)	342 (58.4)	0.903
Moderate or severe calcification	231 (46.9)	242 (41.3)	0.076
PCI treatment	346 (70.2)	428 (73.0)	0.332
Discharge medications, No. (%)			
Dual antiplatelet therapy	441 (89.5)	510 (87.0)	0.258
ACE inhibitor or ARB	222 (45.0)	280 (47.8)	0.400
β-blocker	396 (80.3)	482 (82.3)	0.464
Calcium-channel blocker	288 (58.4)	409 (69.8)	<0.001
Statin	462 (93.7)	555 (94.7)	0.568

Notes: Data are presented as mean (SD) or n (%).
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; DM, diabetes mellitus; GRACE, Global Registry of Acute Coronary Events; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglycerides.

among individuals categorized as having low fibrinogen, medium fibrinogen, and high fibrinogen were 30.3%, 34.4%, and 42.6%, respectively. Similarly, the incidence of cardiovascular mortality demonstrated an increasing trend corresponding to higher fibrinogen levels (19.4% for the low fibrinogen group, 23.6% for the medium fibrinogen group, and 29.8% for the high fibrinogen group). Kaplan-Meier analysis observed a significantly higher risk of all-cause mortality and cardiovascular mortality in patients with high fibrinogen compared to the other two groups (both Log rank test $P < 0.05$; Figure 1 A and B). As depicted in Table 3, univariate Cox regression models indicated that individuals in the high fibrinogen group faced a 1.60-fold and 1.73-fold increased risk of all-cause mortality and cardiovascular mortality, respectively, when compared to those in the low fibrinogen group. After adjusting for potential confounders, patients with high fibrinogen were found to be significantly associated with an elevated risk of all-cause death (adjusted HR 1.70, 95% CI 1.32–2.19, $P<0.001$) and cardiovascular death (adjusted HR 1.81, 95% CI 1.33–2.48, $P<0.001$) (Table 3). Additionally, subsequent RCS analyses failed to detect a significant non-linear relationship between fibrinogen on a continuous scale and the primary and secondary outcomes, after adjustment for potential confounders (both P values for nonlinearity >0.05; Figure 2).

Moreover, individuals with DM demonstrated a heightened occurrence of both all-cause and cardiovascular mortality in comparison to those without DM (39.1% vs 31.8%, 26.8% vs 21.3%, respectively) (Table 3). The Kaplan-Meier analysis further identified a significantly higher risk of mortality in DM patients in comparison to those without the condition. (both Log rank tests $P < 0.05$; Figure 1 C and D). Upon accounting for potential confounding factors, an independent association between DM and all-cause mortality was noted. (adjusted HR 1.36, 95% CI 1.10–1.68, $P=0.004$). Correspondingly, individuals with DM exhibited an independent association with a heightened risk of cardiovascular mortality compared to those in the non-DM group (adjusted HR 1.36, 95% CI 1.05–1.77, $P=0.022$) (Table 3).

Joint Association of Fibrinogen and Diabetes Status with Adverse Outcomes

To evaluate the joint association of fibrinogen and DM status on adverse outcomes, patients were categorized into 6 groups based on fibrinogen tertiles and DM status. Kaplan-Meier analysis indicated that the group with high fibrinogen levels and DM exhibited the highest risk of all-cause mortality and cardiovascular mortality compared to the other groups (both Log rank tests $P < 0.05$; Figure 3). Upon accounting for potential confounding factors, patients with high fibrinogen

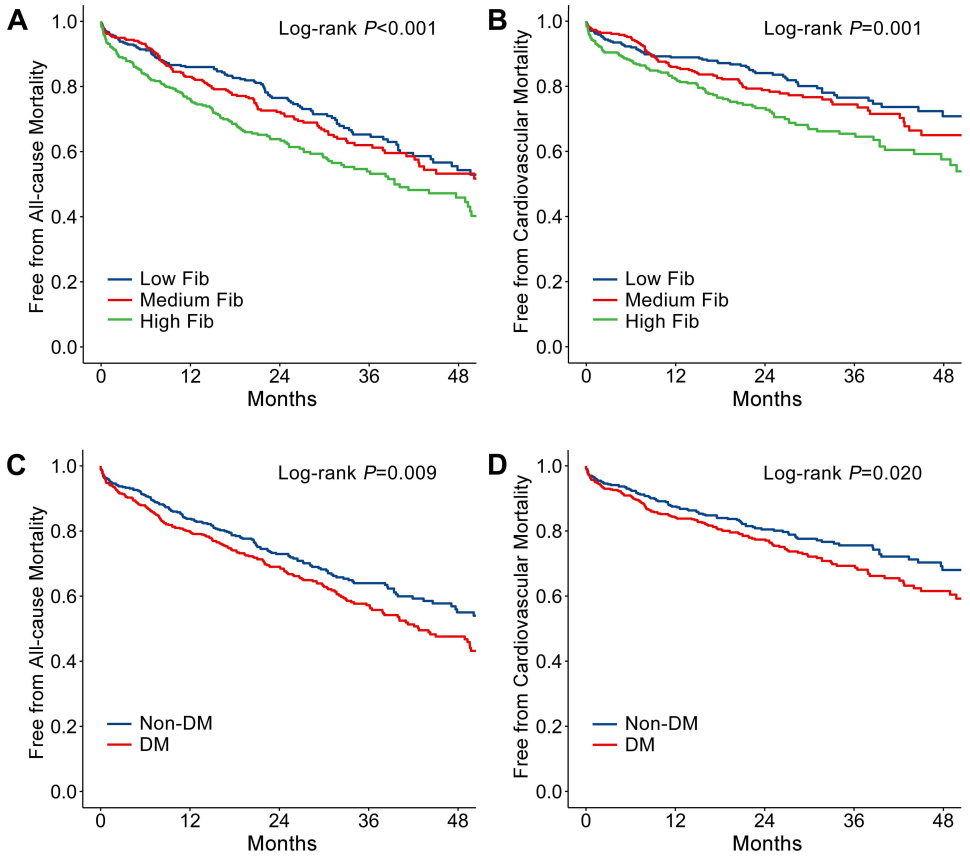

Figure 1 Kaplan–Meier curves for clinical outcomes according to tertiles of fibrinogen **(A** and **B)** and diabetes status **(C** and **D). (A)** All-cause mortality according to fibrinogen tertiles. **(B)** Cardiovascular mortality according to fibrinogen tertiles. **(C)** All-cause mortality according to diabetes status.
Abbreviations: Cardiovascular mortality according to diabetes status. DM, diabetes mellitus; Fib, fibrinogen.

and DM showed the highest risk of all-cause mortality (adjusted HR 2.43, 95% CI 1.69–3.48, *P*<0.001) and cardiovascular mortality (adjusted HR 2.77, 95% CI 1.74–4.38, *P*<0.001). In addition, an independent association between medium or high fibrinogen levels and both all-cause death and cardiovascular death was observed regardless of DM status (Figure 4). Furthermore, the HRs for medium or high fibrinogen levels on mortality were higher in patients with DM. Notably, the HR for patients with medium fibrinogen and DM on all-cause mortality was even higher than that for patients with high fibrinogen but without DM.

Table 3 Associations Between Fibrinogen and Diabetes Status and Clinical Outcomes

	Event (%)	Univariate analysis			Multivariable analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
All-cause Mortality							
Fibrinogen							
Low	109 (30.3)	Reference			Reference		
Medium	124 (34.4)	1.19	0.92–1.54	0.181	1.38	1.06–1.79	0.017
High	153 (42.6)	1.60	1.25–2.04	<0.001	1.70	1.32–2.19	<0.001
DM status							
Non-DM	157 (31.8)	Reference			Reference		
DM	229 (39.1)	1.31	1.07–1.61	0.009	1.36	1.10–1.68	0.004

(*Continued*)

Table 3 (Continued).

	Event (%)	Univariate analysis			Multivariable analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Cardiovascular Mortality							
Fibrinogen							
Low	70 (19.4)	Reference			Reference		
Medium	85 (23.6)	1.27	0.93–1.74	0.138	1.46	1.06–2.02	0.022
High	107 (29.8)	1.73	1.28–2.33	<0.001	1.81	1.33–2.48	<0.001
DM status							
Non-DM	105 (21.3)	Reference			Reference		
DM	157 (26.8)	1.33	1.04–1.71	0.023	1.36	1.05–1.77	0.022

Notes: Multivariable Cox regression analysis for all-cause mortality: adjusted for age, sex, atrial fibrillation, cerebrovascular disease, valvular disease, current smoker, index presentation, triglycerides, radial access, left main disease, 3-vessel disease, moderate or severe calcification, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and calcium-channel blocker. Multivariable Cox regression analysis for cardiovascular mortality: adjusted for age, sex, atrial fibrillation, current smoker, dialysis vintage, index presentation, triglycerides, left main disease, 3-vessel disease, moderate or severe calcification, percutaneous coronary intervention treatment, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and calcium-channel blocker.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.

The incremental predictive value of incorporating fibrinogen categories, DM status, and combined categories into the GRACE score was presented (Table 4). Incorporating fibrinogen into the GRACE risk score led to a marginal increase in the C-statistic for all-cause mortality (ΔC-statistic 0.009 [−0.001, 0.019], *P*=0.065) and cardiovascular mortality (ΔC-statistic 0.009 [−0.004, 0.021], *P*=0.162), although this increase was not statistically significant. Similar results were observed when adding DM status to the GRACE risk score (both *P* values >0.05) (Table 4). Importantly, the integration of combined categories (comprising fibrinogen categories and DM status) into the GRACE score significantly improved its ability to predict all-cause mortality (ΔC-statistic 0.016 [0.005, 0.027], *P*=0.005) and cardiovascular mortality (ΔC-statistic 0.019 [0.005, 0.033], *P*=0.007). In addition, fully adjusted baseline risk models were constructed to forecast both all-cause and cardiovascular mortality (without fibrinogen, DM status, or combined categories) (Table S2 and S3). Similarly, when the combined variables of fibrinogen and DM status were included in the baseline risk model, notable enhancements in the C-statistics for forecasting both all-cause mortality and cardiovascular mortality were observed (Table 4).

Sensitivity Analysis

To assess the robustness of our main findings, we conducted a sensitivity analysis by excluding 39 patients who died during their hospitalization. Kaplan-Meier survival curves depicted a substantial increase in the risk of all-cause and

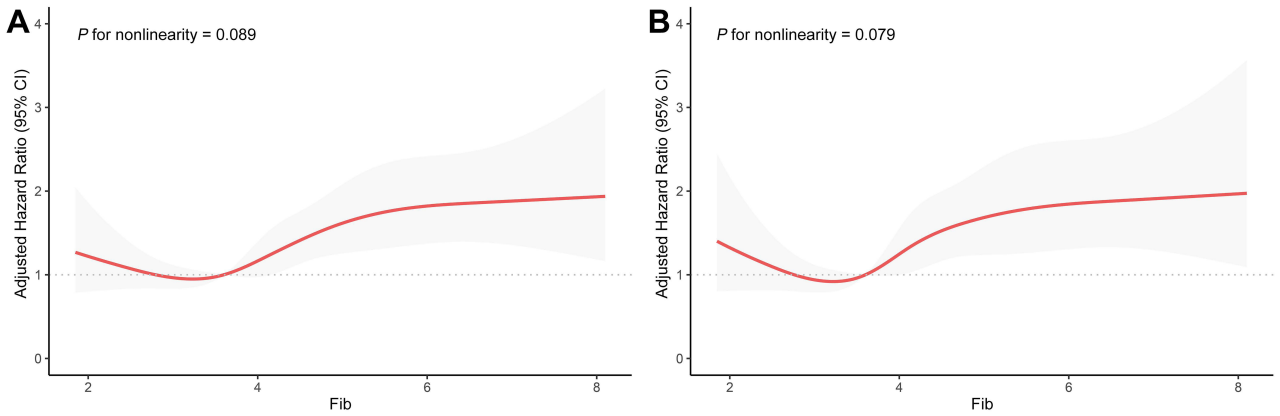

Figure 2 Multivariable restricted cubic spline analysis for the association of fibrinogen with all-cause mortality **(A)** and cardiovascular mortality **(B)**.

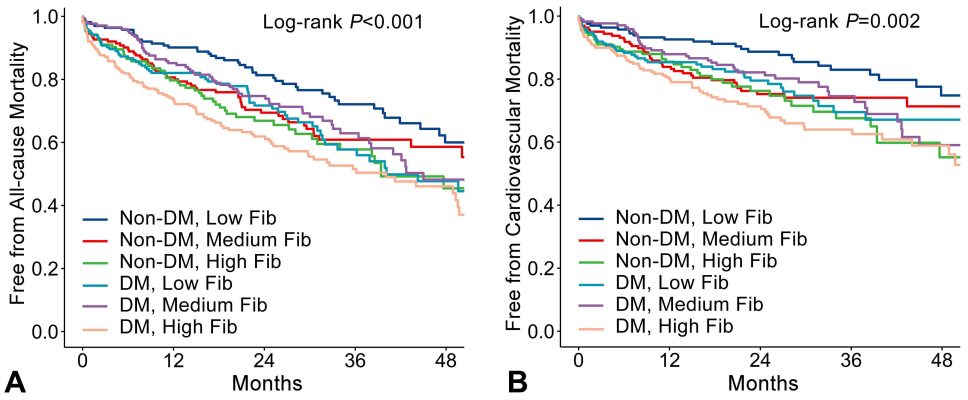

Figure 3 Kaplan–Meier curves for all-cause mortality **(A)** and cardiovascular mortality **(B)** according to the status of fibrinogen tertiles and diabetes mellitus.
Abbreviations: DM, diabetes mellitus; Fib, fibrinogen.

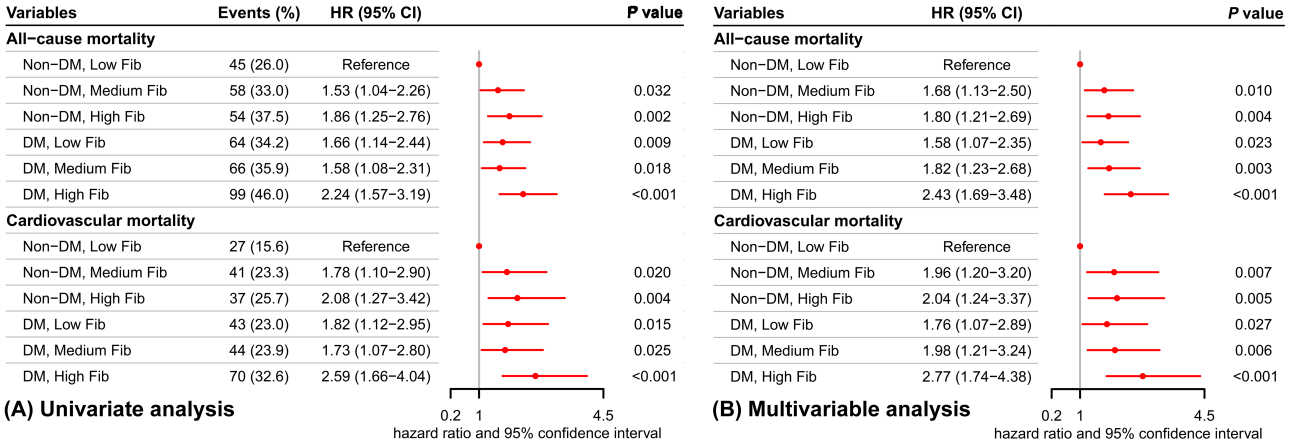

Figure 4 Univariate **(A)** and multivariable **(B)** Cox regression analysis of the fibrinogen tertiles and the status of diabetes mellitus for clinical outcomes.
Abbreviations: CI, confidence interval; DM, diabetes mellitus; Fib, fibrinogen; HR, hazard ratio.

cardiovascular mortality among patients with elevated fibrinogen levels and DM, in contrast to the other groups (both Log rank test $P < 0.05$) (Figure S1). In multivariable Cox regression model, individuals with high fibrinogen and DM exhibited the highest risk of all-cause mortality and cardiovascular mortality. (Table S4). Notably, the HR for patients

Table 4 Incremental Predictive Value of Adding the Fibrinogen, Diabetes Status, and Combined Categories to the GRACE Risk Score or Baseline Risk Model for Clinical Outcomes

	C-statistic (95% CI)	ΔC-statistic (95% CI)	*P* value
All-cause mortality			
GRACE score	0.647 (0.616, 0.678)	Reference	
GRACE score + fibrinogen	0.657 (0.626, 0.688)	0.009 (−0.001, 0.019)	0.065
GRACE score + DM status	0.650 (0.621, 0.679)	0.003 (−0.003, 0.009)	0.388
GRACE score + combined categories	0.663 (0.634, 0.692)	0.016 (0.005, 0.027)	0.005
Baseline risk model[a]	0.681 (0.654, 0.708)	Reference	
Baseline risk model + fibrinogen	0.692 (0.665, 0.719)	0.011 (0.001, 0.021)	0.030
Baseline risk model + DM status	0.684 (0.657, 0.711)	0.003 (−0.004, 0.011)	0.356
Baseline risk model + combined categories	0.697 (0.670, 0.724)	0.016 (0.005, 0.028)	0.006

(*Continued*)

Table 4 (Continued).

	C-statistic (95% CI)	ΔC-statistic (95% CI)	*P* value
Cardiovascular mortality			
GRACE score	0.658 (0.623, 0.693)	Reference	
GRACE score + fibrinogen	0.667 (0.630, 0.704)	0.009 (−0.004, 0.021)	0.162
GRACE score + DM status	0.662 (0.627, 0.697)	0.003 (−0.004, 0.010)	0.379
GRACE score + combined categories	0.678 (0.643, 0.713)	0.019 (0.005, 0.033)	0.007
Baseline risk model[b]	0.719 (0.688, 0.750)	Reference	
Baseline risk model + fibrinogen	0.725 (0.694, 0.756)	0.007 (−0.003, 0.016)	0.176
Baseline risk model + DM status	0.721 (0.690, 0.752)	0.002 (−0.005, 0.010)	0.520
Baseline risk model + combined categories	0.733 (0.702, 0.764)	0.014 (0.000, 0.028)	0.045

Notes: [a]Variables included in the baseline risk model for all-cause mortality are shown in Table S2. [b]Variables included in the baseline risk model for cardiovascular mortality are shown in Table S3.
Abbreviations: CI, confidence interval; DM, diabetes mellitus; GRACE, Global Registry of Acute Coronary Events.

with medium fibrinogen and DM on all-cause mortality and cardiovascular mortality was even higher than that for patients with high fibrinogen but without DM (Table S4).

Discussion

This study, to our knowledge, is the first to evaluate the association between fibrinogen levels, DM status, and mortality in patients with ESRD and ACS. Our findings revealed that both fibrinogen and DM were independent predictors of all-cause and cardiovascular mortality after adjusting for clinical risk factors. Furthermore, patients with high fibrinogen levels and DM had the highest risk of all-cause and cardiovascular mortality risk. Incorporating the combination of fibrinogen categories and DM status into the baseline risk model or GRACE risk score significantly improved the predictive abilities for mortality, surpassing the advancements achieved with any single biomarker.

Elevated fibrinogen levels are established risk factors for atherosclerosis.[25] Plasma fibrinogen participates in chronic low-grade inflammation by upregulating pro-inflammatory cytokines, activating platelets, and enhancing the expression of adhesion molecules. These actions induce vascular inflammation, endothelial dysfunction, and macrophage infiltration, thereby exacerbating atherosclerotic plaque development[26,27] Fibrinogen also facilitates the onset and progression of coronary atherosclerosis through interactions with inflammatory cells, vascular endothelium, and pro-thrombotic molecules.[28] As an acute-phase protein, fibrinogen levels might rise during acute coronary when acute coronary syndrome occurs.[29]

Considerable evidence has demonstrated a significant association between higher fibrinogen levels and adverse outcomes in patients with ACS. A study conducted by Mahmud et al involving ACS patients undergoing PCI observed a noteworthy correlation between higher fibrinogen levels and 12-month major adverse cardiovascular events (MACE).[10] Similarly, a retrospective study conducted across multiple centers validated a positive correlation between fibrinogen levels and a heightened risk of major adverse cardiovascular and cerebrovascular events in ACS patients.[30] Furthermore, a recent prospective study further validated these findings by highlighting a more pronounced independent association between fibrinogen and poor outcomes in individuals with DM.[18] However, the representation of ESRD patients in these studies was either limited or completely excluded. In this context, our study had a specific focus on ESRD patients with ACS and observed a significant association between higher fibrinogen levels and an increased risk of all-cause mortality and cardiovascular mortality. In our study, 386 cases of all-cause mortality were recorded, including 262 cases of cardiovascular mortality. As shown in Table 3, we included 15 clinically important factors in the multivariable model for all-cause mortality and 14 clinically important factors in the multivariable model for cardiovascular mortality. The sample size in our analysis meets the statistical requirement that there should be 10 or more events per variable. The correlation appeared to follow a J-shaped curve, as indicated by subsequent RCS analysis, although the non-linear test did not reach statistical significance. This indicates that it might be reasonable to use fibrinogen categories to identify high-risk patients with poor outcomes in this population.

After considering DM status, we identified that patients with high fibrinogen and DM experienced the highest risk of all-cause mortality and cardiovascular mortality. Furthermore, the HRs for medium or high fibrinogen levels on mortality were higher in patients with DM. Notably, the HR for patients with medium fibrinogen and DM on all-cause mortality was even higher than that for patients with high fibrinogen but without DM. These findings suggest that the detrimental impact of fibrinogen on clinical outcomes in patients with ESRD and ACS appears to be more pronounced in the DM subgroup. These results are consistent with previous research to some extent. A study involving 411 ACS patients undergoing PCI demonstrated a positive association between fibrinogen and MACE in the entire study cohort, primarily in patients with DM rather than those without DM.[18] Similarly, two separate single-center cohort studies observed a notable correlation between high fibrinogen levels with adverse cardiovascular events in CAD patients with DM compared to those without DM, regardless of whether they have undergone PCI or not.[19,20] The underlying mechanism responsible for this phenomenon remains unknown. The existing literature illustrates the interaction and synergistic relationship between inflammation and DM status.[31] It is well-established that individuals with DM often present with elevated fibrinogen levels, which can be attributed to abnormalities in glycemic metabolism and insulin resistance.[16,17] Inflammation and insulin resistance are recognized pathological mechanisms in dialysis patients, which could further elevate the fibrinogen level.[13,32] Furthermore, elevated fibrinogen aggravates vascular inflammation and endothelial dysfunction, thereby contributing to diabetes-related complications and adverse clinical outcomes.[27,33,34] In addition, elevated fibrinogen levels may also compromise platelet inhibition with clopidogrel in patients with DM, potentially through direct interaction with the GP IIb/IIIa receptor rather than systemic inflammation.[35] Overall, our results help to bridge gaps in understanding the associations between elevated fibrinogen levels and adverse cardiovascular events. These results support that the potential utility of fibrinogen for assessing risk in patients with ESRD and ACS, especially for those with DM.

Many emerging quality data highlights the significant value of fibrinogen with or without other prognostic factors like albumin, uric acid, neutrophil percentage in predicting outcomes following CAD.[36–39] Recent studies have demonstrated the incremental value of combining fibrinogen and DM status in cardiovascular risk stratification in patients with stable CAD.[20] In our study, we extended this combined effect to patients with ESRD and ACS. The widely used GRACE score has proven to be a powerful tool for predicting adverse cardiovascular outcomes in ACS.[1,2,23] The present study reveals that the combination of fibrinogen and DM status significantly improved the predictive accuracy either of the GRACE score or of the baseline risk model for all-cause and cardiovascular mortality, surpassing the advancements achieved with any single biomarker. Fibrinogen, as a proinflammatory protein, can stimulate vascular inflammation and impair endothelial function by upregulating the synthesis of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor.[27] These inflammatory processes may contribute to the activation and rupture of vascular plaques.[7] Additionally, fibrinogen plays a significant role in the coagulation cascade. Previous studies consistently demonstrate a positive correlation between elevated fibrinogen levels with increased blood viscosity, peripheral resistance, and the subsequent heightened risk of thrombotic events and ischemic occurrences.[40,41] Thus, fibrinogen may not merely be a bystander in the inflammation and coagulation cascade; it likely plays a significant role in the development and prognosis of ACS. DM is a well-established risk factor for ACS.[34] Impaired glucose metabolism and insulin resistance contribute to oxidative stress, an inflammatory environment, coagulation activation, and accelerated progression of atherosclerosis.[42–44] Furthermore, ESRD exacerbates inflammation, hypercoagulability, insulin resistance, and oxidative stress.[13,32] Moreover, the synergistic effect of higher fibrinogen levels and DM, as aforementioned, may further increase the risk of cardiovascular events among dialysis patients with ACS.[27,33–35] Overall, these findings provide evidence supporting the prognostic value of combining fibrinogen and DM status in patients with ESRD and ACS, emphasizing the clinical significance of assessing both inflammatory-coagulative status and DM status for risk stratification in these patients. Further studies are necessary to investigate whether interventions targeting these potential pathophysiological mechanisms can lead to improved clinical outcomes in individuals affected by both ESRD and CAD.

Limitations

The current study has several limitations. Firstly, its retrospective nature raised concerns regarding potential confounding variables and selection bias, which might have exerted undue influence on the observed outcomes. Secondly, the

assessment of fibrinogen was only measured at baseline, potentially neglecting any clinically relevant changes during the subsequent follow-up period. The absence of a standardized laboratory sample collection protocol and measurement methods of fibrinogen, such as those provided by a central laboratory, might limit the generalizability of our findings, despite the widespread clinical application of fibrinogen measurement. In addition, our study lacked detailed information of heparinization, which might affect our findings. Furthermore, the definition of DM lacked the incorporation of oral glucose tolerance test results, as this examination is not routinely performed for dialysis patients with ACS. Nonetheless, it is important to acknowledge the widespread acceptance of HbA1c as a diagnostic and monitoring tool for DM, even encompassing ESRD patients requiring dialysis. Finally, the underlying mechanisms of the associations cannot be clarified in this observational study. Further dedicated prospective studies with larger sample sizes and more comprehensive data are needed to validate our findings.

Conclusions

In this cohort of patients with ESRD and ACS, elevated fibrinogen and DM were associated with an increased risk of all-cause mortality and cardiovascular mortality. Furthermore, the combined assessment of fibrinogen and DM status substantially enhanced the predictive accuracy for mortality, surpassing the improvements achieved with any single biomarker. Categorical classification of patients with fibrinogen levels and DM status could provide valuable information for risk stratification of these patients.

Data Sharing Statement

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of China-Japan Friendship Hospital, with a waiver of informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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