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ORIGINAL RESEARCH

Association Between Fibrinogen-to-Albumin Ratio and Long-Term Mortality in Senile Patients with Coronary Artery Disease: A Prospective 10-Year Follow-up Study

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Background: The synergistic effect of fibrinogen and albumin on long-term mortality remains unclear in senile patients with coronary artery disease (CAD). This study aimed to evaluate the association between fibrinogen-to-albumin ratio (FAR) and 10-year mortality, and to develop a model to predict survival probability in senile patients with CAD.

Methods: In total, 819 senile patients with CAD were enrolled on the basis of the China Geriatric Cardiovascular Comorbidity Study.

Results: Compared with patients in the lowest FAR (FAR-Q1) group, the median overall survival (OS) was 2631 days, and patients in the highest FAR (FAR-Q4) group had the shortest OS, with a median of 311 days ($p < 0.0001$). Multivariate Cox regression suggested FAR as a crucial factor affecting long-term mortality of patients with CAD (HR = 37.75, 95% CI = 4.10–347.98; $p < 0.05$). Five features associated with long-term mortality were selected using Least Absolute Shrinkage and Selection Operator (LASSO) regression: age, hemoglobin, albumin, FAR, and lnNT-proBNP. The area under the receiver operating characteristic curve (AUC) was 0.838 for multivariate Cox regression and 0.829 for LASSO regression. The restricted cubic spline curve showed a significant J-shaped relationship between FAR and mortality, with a cut-off point of 0.09 (p for nonlinear < 0.001). A time-dependent nomogram was constructed based on five features selected using LASSO regression. The time-dependent AUC remained in the range of 0.69–0.73, indicating the relatively stable power of this model.

Conclusion: FAR was independently associated with long-term mortality, and a prognostic model based on FAR may aid risk stratification in senile patients with CAD.

Plain Language Summary:

1. Coronary artery disease (CAD) is the principal cause of death worldwide and is a huge burden on medical care each year.
2. The synergistic effect of fibrinogen and albumin on long-term mortality remains unclear in senile patients with CAD.
3. This study aimed to evaluate the association between fibrinogen-to-albumin ratio (FAR) and 10-year mortality, and to develop a model to predict survival probability.

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4. FAR was independently associated with long-term mortality, with a nonlinear J-shaped relationship between FAR and mortality.
5. This study was the first to construct a prognostic model based on FAR for predicting long-term mortality in senile patients with CAD.

Keywords: coronary artery disease, fibrinogen-to-albumin ratio, J-shaped relationship, long-term mortality, senile patients

Introduction

Coronary artery disease (CAD) is the principal cause of death and disability worldwide, with a huge burden on medical care each year.[1] Considering high mortality of patients with CAD in parallel with population aging, early identification and prevention of risk factors are crucial for mitigating long-term mortality. Despite advanced preventive and therapeutic methods, cardiovascular death accounts for 32% of mortality.[2] Therefore, assessing the risk of CAD is an essential public health priority. Previous studies have demonstrated that atherosclerosis and inflammation play pivotal roles in the pathological processes of CAD.[3] Hypercoagulation and inflammation, characterized as a constellation of immune dysfunction, increase the risk of CAD.[4,5] Hemorheological indices including white cells and platelets have been calculated to be neutrophil-to-lymphocyte ratio (NLratio) and systemic immune-inflammation index as prognostic markers, while other inflammatory factors such as C-reactive protein (CRP) have been used to reflect adverse outcomes in patients with acute coronary syndromes (ACS). Fibrinogen, an acute-phase reactive protein synthesized by the liver, is a biochemical marker of systemic inflammation and thrombosis formation involved in the progression of atherosclerosis.[6] Recently, there has been evidence that high fibrinogen levels are closely associated with mortality in patients with CAD.[7] Albumin is an essential protein synthesized by the liver, and its reduction may indicate malnutrition, inflammation, or a hypercoagulable status. Previous studies have shown that low albumin levels are associated with an increased mortality in patients with CAD.[8] Patients with CAD have complex physiological processes, and inflammation is recognized as a crucial mechanism. Systemic inflammation has been found to be an initial driver of vascular endothelial injury in CAD.[9–11] Fibrinogen-to-albumin ratio (FAR), an inflammation-related marker, is an indicator used to predict the prognostic risk of CAD.[12–14] A recent study suggested that high FAR levels are positively associated with mortality in patients with CAD.[15] However, a nonlinear relationship between FAR and 10-year mortality has not been deeply explored for clinical application in senile patients, and long-term survival predictive models for Chinese senile patients with CAD are lacking for early development of effective therapeutic strategies. As an innovative direction, a nonlinear relationship has been used to analyze complex physiological mechanisms and clinical phenomena and guide precision medicine and personalized treatment. Emerging findings have reported that Least Absolute Shrinkage and Selection Operator (LASSO) regression is an extremely useful and effective algorithm for selecting the optimal features. A model based on FAR levels to conveniently predict long-term mortality should be developed by objectively integrating the patients' clinical features and auxiliary examinations selected using LASSO regression. Therefore, this study firstly aimed to evaluate the association between FAR and 10-year mortality, analyze their nonlinear relationship, develop a model to predict survival probability, and promote its clinical application in Chinese senile patients with CAD.

Methods

Population

This prospective study included 819 senile patients with CAD admitted in the Department of Geriatric Cardiology, Chinese PLA General Hospital, on the basis of the China Geriatric Cardiovascular Comorbidity Study (CGCCS). Patients were enrolled if they were (i) aged ≥ 80 years and (ii) diagnosed with CAD. Eligibility required a diagnosis of CAD based on the American College of Cardiology (ACC)/American Heart Association (AHA)/European College of Cardiology (ESC) guidelines. The final diagnosis of CAD was made by the chief physicians based on clinical histories, angina symptoms, laboratory tests, and auxiliary examinations (such as electrocardiogram, echocardiography, radionuclide imaging, computed tomography, and coronary angiography). Patients had comprehensive medical treatment and final death records at Chinese PLA General Hospital, which enabled long-term follow-up and accurate evaluation of

endpoints. Patients were excluded if they had (i) severe aortic stenosis, (ii) anticipated cardiovascular transplantation, (iii) a ventricular assist device, (iv) chronic liver and renal diseases, or (v) malignancy. This study was approved by the Ethics Committee of Chinese PLA General Hospital (Beijing, China) and was conducted in accordance with the tenets and provisions of the Declaration of Helsinki 1975 (revised 1983).

Feature

The following clinical features were extracted from patients: (i) general: age, sex, current smoker, heart rate, and body mass index (BMI), (ii) biochemistry: hemoglobin, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total protein (TP), albumin, fibrinogen, international normalized ratio (INR), serum creatinine (SCr), uric acid, logarithmic transformation of N-terminal pro-B-type natriuretic peptide (lnNT-proBNP), NLratio, and CRP, (iii) comorbidities: hypertension, diabetes, ACS, chronic heart failure (CHF), New York Heart Association (NYHA) classification III or IV, atrial fibrillation, and chronic kidney disease (CKD), and (iv) drugs: aspirin, clopidogrel, beta-receptor blockers, calcium channel blockers (CCBs), nitrates, angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and statins. FAR was calculated as follows: FAR = fibrinogen [g/L]/albumin[g/L].

Comorbidity

Comorbidities were determined by the chief physicians based on well-accepted clinical guidelines: (i) hypertension: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of anti-hypertensive medications, (ii) diabetes: FBG ≥ 7.0 mmol/L, 2-hour postprandial blood glucose ≥ 11.1 mmol/L, or use of oral hypoglycemic drugs or insulin, (iii) CHF: symptoms (dyspnea and/or fatigue), signs (edema and/or pulmonary rales), and cardiovascular structural and functional abnormalities. NYHA classification was determined by asking patients themselves or proxies to describe their symptoms, (iv) atrial fibrillation: history, symptomatology (palpitation), sign (arrhythmia), and electrocardiogram, and (v) CKD: estimated glomerular filtration rate < 60 mL/min/1.73 m^2 for ≥ 3 months.

Outcome

Considering the failure of multiple organs in senile population and the priority of all-cause mortality in prognostic study, the primary outcome of this study was all-cause mortality, and patient follow-up was started at the first medical discharge. Mortality was followed up and determined by professional telephone interviews and medical record judgement, with dead time, specific place, and other information collected from patients themselves or proxies.

Statistics

Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) depending on their distribution, while categorical variables are presented as frequency and percentage using the *Tableone* package. Analysis of variance, Kruskal–Wallis or Chi-square tests were used for descriptive analyses. The survival curve of quartile groups was plotted using Kaplan-Meier analysis and compared using Log rank test with the *survminer* and *survival* package. The *Coxph* package was used to investigate the association between FAR and mortality and to select the optimal risk factors using univariate and multivariate Cox regression analyses. Predictors were selected and integrated to clarify their association with long-term mortality using LASSO regression using the *glmnet* package. A prognostic nomogram with endpoints of the 1-year, 3-year, 5-year, and 10-year overall survival (OS) was constructed and visualized based on the covariates selected by multivariate analysis using the *nomogram* package. The restricted cubic spline (RCS) curve was constructed to present a nonlinear relationship between FAR and mortality using the *rms* package. Statistical analysis in this study was performed using the R language (version 4.3.2), with statistical significance considered when two-sided *p*-value was less than 0.05.

Results

Basic Feature

The median age was 87 [84–90] years, and 91.8% of study population were male. The demographic and clinical features of senile patients with CAD stratified by FAR quartiles are presented in Table 1. FAR levels were 0.092 [0.074–0.116],

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Table 1 The Demographic and Clinical Features of Senile Patients with CAD Stratified by FAR Quartiles

Features	Total	FAR-Q1	FAR-Q2	FAR-Q3	FAR-Q4	*p*
N	819	205	205	204	205	
Demographics						
Age (median [IQR], year)	87 [84–90]	86 [84–90]	87 [84–90]	88 [85–90]	88 [85–91]	0.009
Sex (male/female, %)	752/67 (91.8/8.2)	192/13 (93.7/6.3)	193/12 (94.1/5.9)	190/14 (93.1/6.9)	177/28 (86.3/13.7)	0.011
Current smoker (no/yes, %)	502/317 (61.3/38.7)	130/75 (63.4/36.6)	128/77 (62.4/37.6)	115/89 (56.4/43.6)	129/76 (62.9/37.1)	0.421
Heart rate (median [IQR], bpm)	72 [64–80]	70 [62–76]	70 [63–80]	72 [65–80]	78 [70–87]	<0.001
BMI (mean [SD], kg/m^2)	24.224 [3.641]	24.176 [3.216]	24.848 [3.649]	23.925 [3.838]	23.944 [3.779]	0.034
Tests						
Hemoglobin (median [IQR], g/L)	122 [107–135]	129 [115–140]	124 [113–140]	118 [107–131]	110 [97–128]	<0.001
FBG (median [IQR], mmol/L)	5.3 [4.8–6.1]	5.2 [4.8–5.7]	5.4 [4.9–6.0]	5.2 [4.7–5.9]	5.7 [4.9–7.0]	<0.001
TC (median [IQR], mmol/L)	3.8 [3.2–4.4]	3.8 [3.2–4.4]	3.7 [3.2–4.3]	3.9 [3.3–4.4]	3.8 [3.2–4.4]	0.587
TG (median [IQR], mmol/L)	1.2 [0.9–1.8]	1.2 [0.9–1.8]	1.2 [0.9–1.7]	1.2 [0.8–1.8]	1.4 [0.9–2.0]	0.158
HDL (median [IQR], mmol/L)	1.0 [0.8–1.2]	1.1 [0.9–1.3]	1.0 [0.9–1.2]	1.0 [0.8–1.2]	0.9 [0.7–1.1]	<0.001
LDL (median [IQR], mmol/L)	2.1 [1.7–2.6]	2.1 [1.6–2.6]	2.0 [1.7–2.7]	2.1 [1.7–2.6]	2.1 [1.7–2.6]	0.902
TP (median [IQR], g/L)	65.6 [61.6–69.4]	66.0 [61.8–69.8]	65.7 [62.7–69.7]	65.2 [61.7–69.4]	65.5 [60.4–69.0]	0.303
Albumin (median [IQR], g/L)	38.0 [35.0–40.2]	40.0 [37.6–42.0]	39.0 [36.9–40.9]	37.4 [35.2–39.3]	34.7 [31.7–37.5]	<0.001
Fibrinogen (median [IQR], g/L)	3.450 [2.850–4.200]	2.530 [2.240–2.770]	3.170 [2.970–3.380]	3.810 [3.538–4.130]	4.980 [4.480–5.840]	<0.001
FAR (median [IQR])	0.092 [0.074–0.116]	0.063 [0.058–0.069]	0.082 [0.078–0.086]	0.102 [0.096–0.109]	0.142 [0.125–0.173]	<0.001
INR (median [IQR])	1.08 [1.02–1.15]	1.07 [1.02–1.15]	1.06 [1.01–1.12]	1.07 [1.01–1.13]	1.12 [1.05–1.25]	<0.001
Scr (median [IQR], μmol/L)	92.0 [74.0–119.9]	86.1 [73.0–105.0]	93.6 [79.0–114.0]	93.6 [72.9–129.0]	98.0 [74.5–138.0]	0.004
Uric acid (median [IQR], μmol/L)	335.5 [255.5–415.6]	341.7 [262.5–411.4]	344.1 [266.3–412.1]	314.0 [251.8–417.2]	336.2 [231.2–441.7]	0.576
LnNT-proBNP (median [IQR], pg/mL)	6.053 [5.173–7.479]	5.576 [4.772–6.812]	5.726 [4.975–6.879]	6.371 [5.435–7.542]	6.879 [5.711–8.310]	<0.001
NLratio (median [IQR])	2.574 [1.797–4.060]	2.036 [1.458–2.938]	2.311 [1.697–2.939]	2.665 [1.939–4.114]	3.820 [2.424–7.000]	<0.001
CRP (median [IQR], mg/dL)	0.680 [0.185–2.665]	0.270 [0.080–1.150]	0.350 [0.130–1.000]	0.779 [0.235–2.423]	2.820 [1.190–7.370]	<0.001
Comorbidities						
Hypertension (no/yes, %)	163/656 (19.9/80.1)	31/174 (15.1/84.9)	44/161 (21.5/78.5)	49/155 (24.0/76.0)	39/166 (19.0/81.0)	0.137
Diabetes (no/yes, %)	483/336 (59.0/41.0)	124/81 (60.5/39.5)	124/81 (60.5/39.5)	124/80 (60.8/39.2)	111/94 (45.9/54.1)	0.451
ACS (no/yes, %)	604/215 (73.7/26.3)	153/52 (74.6/25.4)	155/50 (75.6/24.4)	149/55 (73.0/27.0)	147/58 (71.7/28.3)	0.815
CHF NYHA classification III or IV (no/yes, %)	652/167 (79.6/20.4)	174/31 (84.9/15.1)	179/26 (87.3/12.7)	165/39 (80.9/19.1)	134/71 (65.4/34.6)	<0.001
Atrial fibrillation (no/yes, %)	641/178 (78.3/21.7)	163/42 (79.5/20.5)	161/44 (78.5/21.5)	157/47 (77.0/23.0)	160/45 (78.0/22.0)	0.939
CKD (no/yes, %)	517/302 (63.1/36.9)	153/52 (74.6/25.4)	132/73 (64.4/35.6)	126/78 (61.8/38.2)	106/99 (51.7/48.3)	<0.001
Drugs						
Aspirin (no/yes, %)	450/369 (54.9/45.1)	113/92 (55.1/44.9)	106/99 (51.7/48.3)	109/95 (53.4/46.6)	122/83 (59.5/40.5)	0.426
Clopidogrel (no/yes, %)	352/467 (43.0/57.0)	79/126 (38.5/61.5)	78/127 (38.0/62.0)	92/112 (45.1/54.9)	103/102 (50.2/49.8)	0.037
Beta-receptor blockers (no/yes, %)	274/545 (33.5/66.5)	75/130 (36.6/63.4)	67/138 (32.7/67.3)	74/130 (36.3/63.7)	58/147 (28.3/71.7)	0.247
CCBs (no/yes, %)	293/526 (35.8/64.2)	54/151 (26.3/73.7)	80/125 (39.0/61.0)	86/118 (42.2/57.8)	73/132 (35.6/64.4)	0.006
Nitrates (no/yes, %)	136/683 (16.6/83.4)	37/168 (18.0/82.0)	29/176 (14.1/85.9)	38/166 (18.6/81.4)	32/173 (15.6/84.4)	0.582
ACEIs/ARBs (no/yes, %)	422/397 (51.5/48.5)	93/112 (45.4/54.6)	102/103 (49.8/50.2)	107/97 (52.5/47.5)	120/85 (58.5/41.5)	0.058
Statins (no/yes, %)	319/500 (38.9/61.1)	70/135 (34.1/65.9)	69/136 (33.7/66.3)	71/133 (34.8/65.2)	109/96 (53.2/46.8)	<0.001
OS (median [IQR], day)	1683 [286–3051]	2631 [1229–3310]	2220 [818–3207]	1256 [256–2715]	311 [72–1736]	<0.001

Abbreviations: CAD, coronary artery disease; FAR, fibrinogen-to-albumin ratio; IQR, interquartile range; BMI, body mass index; SD, standard deviation; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TP, total protein; INR, international normalized ratio; Scr, serum creatinine; lnNT-proBNP, logarithmic transformation of N-terminal pro-brain natriuretic peptide; NLratio, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; ACS, acute coronary syndrome; CHF, chronic heart failure; NYHA, New York Heart Association; CKD, chronic kidney disease; CCBs, calcium channel blockers; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; OS, overall survival.

ranging from 0.063 [0.058–0.069] in Q1, 0.082 [0.078–0.086] in Q2, 0.102 [0.096–0.109] in Q3 to 0.142 [0.125–0.173] in Q4. Compared with the lowest FAR (FAR-Q1) group, there were significantly and gradually reduced levels of hemoglobin, HDL, albumin, CKD, and OS and significantly and gradually increased levels of age, heart rate, Scr, lnNT-proBNP, fibrinogen, FAR, NLratio, and CRP in the higher FAR-Q2, FAR-Q3, and FAR-Q4 groups ($p < 0.05$). Significant differences were also observed in sex, BMI, FBG, INR, CHF NYHA classification III or IV, clopidogrel, CCBs, and statins ($p < 0.05$). In contrast, there were no statistical difference in current smoker, TC, TG, LDL, TP, uric acid, hypertension, diabetes, ACS, atrial fibrillation, aspirin, beta-receptor blockers, nitrates, or ACEIs/ARBs ($p > 0.05$).

Kaplan–Meier Plot

During the 10-year follow-up period, 650 patients died, with a long-term mortality of 79.4%. Patients were divided into groups based on FAR quartiles, and Kaplan-Meier analysis was used to curve their survival probability. Compared with patients in the lowest FAR (FAR-Q1) group, with a median OS of 2631 days, patients in the highest FAR (FAR-Q4) group had the shortest OS, with a median of 311 days ($p < 0.0001$; Figure 1A). This result revealed a significant correlation between FAR and OS.

Cox Regression

Univariate and multivariate Cox regression analyses were conducted to identify promising prognostic markers and to evaluate their impact on OS (Table 2). Multivariate Cox regression revealed that ten variables were significantly independent prognostic factors: age [hazard ratio (HR) = 1.08, 95% confidence interval (95% CI) = 1.06–1.10], hemoglobin (HR = 0.98, 95% CI = 0.98–0.99), HDL (HR = 0.67, 95% CI = 0.52–0.86), albumin (HR = 0.96, 95% CI = 0.93–0.98), FAR (HR = 37.75, 95% CI = 4.10–347.98), INR (HR = 1.40, 95% CI = 1.13–1.75), lnNT-proBNP (HR = 1.32, 95% CI = 1.24–1.40), CHF NYHA classification III or IV (HR = 1.37, 95% CI = 1.12–1.69), clopidogrel (HR = 0.85, 95% CI = 0.72–0.99), and ACEIs/ARBs (HR = 0.75, 95% CI = 0.64–0.88; $p < 0.05$; Figure 1B). This result suggested FAR as a crucial factor affecting long-term mortality of patients with CAD.

LASSO Regression

Given that the number of variables selected by multivariate Cox regression was excessive, five features associated with long-term mortality were further selected using LASSO regression, including age, hemoglobin, albumin, FAR, and lnNT-proBNP (Figure 1C and D). Collinearity matrix showed that all five features were less than 0.8, and their HR are presented using Forest plot (Figure 1E and F). The area under the receiver operating characteristic curve (AUC) was 0.838 (95% CI = 0.809–0.867) for multivariate Cox regression and 0.829 (95% CI = 0.798–0.860) for LASSO regression (Figure 1G). Considering the similar AUC of both regressions, LASSO regression with fewer variables was more suitable for clinical practice than Cox regression.

Adjusted Regression

As shown in Table 3, FAR as a continuous variable was significantly associated with an increased mortality in unadjusted Cox regression, and this association persisted in model 2 after adjusting for age and sex and in model 3 after adjusting for all covariates except albumin and fibrinogen ($p < 0.001$). Compared with the lowest FAR (FAR-Q1) group, FAR as a categorical variable was positively associated with mortality in model 1, with the HR (95% CI) of 1.33 (1.05–1.68), 1.98 (1.58–2.48), and 3.25 (2.59–4.07) in the higher FAR-Q2, FAR-Q3, and FAR-Q4 groups, respectively. Significant associations were observed in models 2 and 3 ($p < 0.05$). This result indicated FAR as an independent predictor of long-term mortality in patients with CAD.

Nonlinear Relationship

The RCS curve was constructed to explore whether there was a nonlinear relationship between FAR as a continuous variable and mortality. The RCS curve showed a significant J-shaped relationship between FAR and mortality, with a cut-off point of 0.09 (p for nonlinear < 0.001; Figure 2A), and this nonlinear relationship persisted even after adjusting for age and sex (p for nonlinear < 0.05; Figure 2B) and after adjusting for all covariates except albumin and fibrinogen (p for nonlinear < 0.05; Figure 2C).

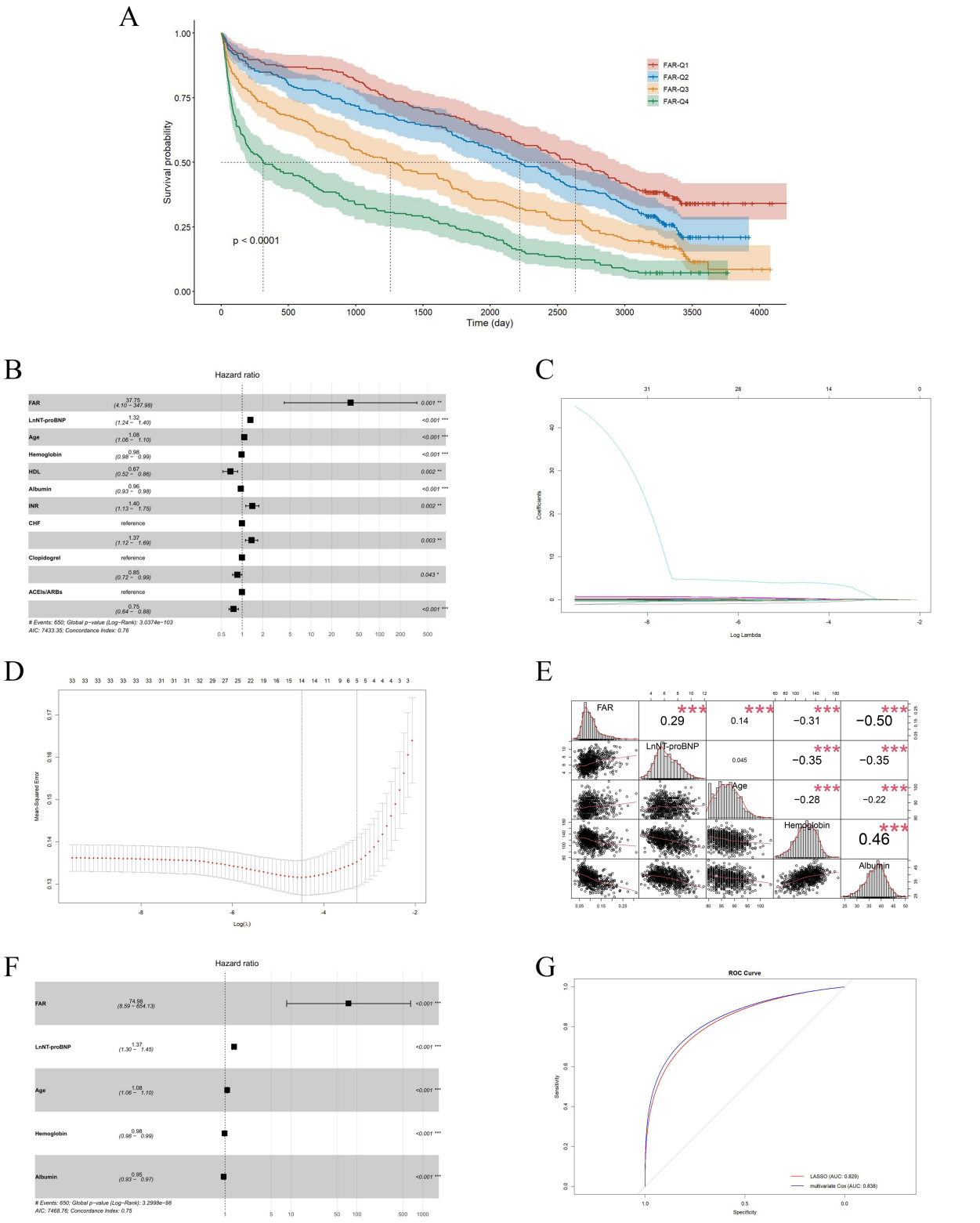

Figure 1 (**A**) Kaplan-Meier plot of survival probability based on fibrinogen-to-albumin ratio (FAR) quartiles. There was a significant difference in the survival probability between groups ($p < 0.0001$); (**B**) Ten independent prognostic factors by multivariate Cox regression. lnNT-proBNP, logarithmic transformation of N-terminal pro-brain natriuretic peptide; HDL, high-density lipoprotein; INR, international normalized ratio; CHF, chronic heart failure New York Heart Association classification III or IV; ACEIs/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; (**C**) Least absolute shrinkage and selection operator (LASSO) coefficient profiles; (**D**) Selection of appropriate features by LASSO; (**E**) Correlation coefficients between selected features using LASSO; (**F**) Forest plot of five features using LASSO; (**G**) The area under the receiver operating characteristic (ROC) curve (AUC) of both multivariate Cox and LASSO regression. Significance: *P < 0.05, **P < 0.01, ***P < 0.001.

Table 2 Univariate and Multivariate Cox Regression for OS in Senile Patients with CAD

Features	Univariate Cox Regression HR (95% CI, *p*)	Multivariate Cox Regression HR (95% CI, *p*)
Age	1.10 (1.08–1.12, $p < 0.001$)	1.08 (1.06–1.10, $p < 0.001$)
Sex		
Male	Reference	
Female	1.10 (0.83–1.45, $p = 0.508$)	
Current smoker		
No	Reference	
Yes	1.04 (0.89–1.22, $p = 0.598$)	
Heart rate	1.01 (1.01–1.02, $p < 0.001$)	
BMI	0.96 (0.94–0.98, $p < 0.001$)	
Hemoglobin	0.97 (0.96–0.97, $p < 0.001$)	0.98 (0.98–0.99, $p < 0.001$)
FBG	1.11 (1.06–1.16, $p < 0.001$)	
TC	0.95 (0.86–1.05, $p = 0.305$)	
TG	1.13 (1.05–1.21, $p < 0.001$)	
HDL	0.39 (0.30–0.52, $p < 0.001$)	0.67 (0.52–0.86, $p = 0.002$)
LDL	0.91 (0.81–1.02, $p = 0.110$)	
TP	1.00 (0.99–1.01, $p = 0.924$)	
Albumin	0.86 (0.84–0.88, $p < 0.001$)	0.96 (0.93–0.98, $p < 0.001$)
Fibrinogen	1.29 (1.22–1.37, $p < 0.001$)	
FAR	99,144 (15,744–624,319, $p < 0.001$)	37.75 (4.10–347.98, $p = 0.001$)
INR	1.67 (1.45–1.93, $p < 0.001$)	1.40 (1.13–1.75, $p = 0.002$)
Scr	1.00 (1.00–1.00, $p < 0.001$)	
Uric acid	1.00 (1.00–1.00, $p = 0.001$)	
LnNT-proBNP	1.49 (1.42–1.57, $p < 0.001$)	1.32 (1.24–1.40, $p < 0.001$)
NLratio	1.05 (1.04–1.07, $p < 0.001$)	
CRP	1.05 (1.04–1.07, $p < 0.001$)	
Hypertension		
No	Reference	
Yes	0.93 (0.77–1.13, $p = 0.468$)	
Diabetes		
No	Reference	
Yes	1.13 (0.97–1.32, $p = 0.118$)	
ACS		
No	Reference	
Yes	0.93 (0.78–1.11, $p = 0.401$)	
CHF		
NYHA classification I or II	Reference	
NYHA classification III or IV	2.29 (1.91–2.75, $p < 0.001$)	1.37 (1.12–1.69, $p = 0.003$)
Atrial fibrillation		
No	Reference	
Yes	1.22 (1.02–1.47, $p = 0.032$)	
CKD		
No	Reference	
Yes	1.67 (1.42–1.95, $p < 0.001$)	
Aspirin		
No	Reference	
Yes	0.83 (0.71–0.97, $p = 0.016$)	
Clopidogrel		
No	Reference	
Yes	0.75 (0.64–0.87, $p < 0.001$)	0.85 (0.72–0.99, $p = 0.043$)

(*Continued*)

Table 2 (Continued).

Features	Univariate Cox Regression HR (95% CI, *p*)	Multivariate Cox Regression HR (95% CI, *p*)
Beta receptor blockers		
No	Reference	
Yes	1.09 (0.93–1.29, $p = 0.293$)	
CCBs		
No	Reference	
Yes	0.85 (0.72–1.00, $p = 0.044$)	
Nitrates		
No	Reference	
Yes	1.23 (0.99–1.53, $p = 0.056$)	
ACEIs/ARBs		
No	Reference	
Yes	0.75 (0.64–0.87, $p < 0.001$)	0.75 (0.64–0.88, $p < 0.001$)
Statins		
No	Reference	
Yes	0.66 (0.57–0.78, $p < 0.001$)	

Notes: Multivariate Cox regression was adjusted for age, hemoglobin, high-density lipoprotein, albumin, fibrinogen-to-albumin ratio, international normalized ratio, logarithmic transformation of N-terminal pro-brain natriuretic peptide, chronic heart failure New York Heart Association classification III or IV, clopidogrel, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Abbreviations: OS, overall survival; CAD, coronary artery disease; HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TP, total protein; FAR, fibrinogen-to-albumin ratio; INR, international normalized ratio; Scr, serum creatinine; LnNT-proBNP, logarithmic transformation of N-terminal pro-brain natriuretic peptide; NLratio, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; ACS, acute coronary syndrome; CHF, chronic heart failure; NYHA, New York Heart Association; CKD, chronic kidney disease; CCBs, calcium channel blockers; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Table 3 Association Between FAR and Mortality in Senile Patients with CAD

Features	Model 1 HR (95% CI, *p*)	Model 2 HR (95% CI, *p*)	Model 3 HR (95% CI, *p*)
FAR (continuous)	99,144 (15,744–624,319, $p < 0.001$)	37,345 (5,819–239,654, $p < 0.001$)	243 (23.2–2,539, $p < 0.001$)
FAR (categorical)			
FAR-Q1	Reference	Reference	Reference
FAR-Q2	1.33 (1.05–1.68, $p < 0.001$)	1.32 (1.05–1.67, $p < 0.001$)	1.33 (1.05–1.70, $p = 0.019$)
FAR-Q3	1.98 (1.58–2.48, $p < 0.001$)	1.84 (1.47–2.31, $p < 0.001$)	1.58 (1.24–2.00, $p < 0.001$)
FAR-Q4	3.25 (2.59–4.07, $p < 0.001$)	3.08 (2.46–3.87, $p < 0.001$)	1.91 (1.47–2.47, $p < 0.001$)
	p for interaction < 0.001	p for interaction < 0.001	p for interaction < 0.001

Notes: Model 1: Cox regression was unadjusted; Model 2: Cox regression was adjusted for age and sex; Model 3: Cox regression was adjusted for age, sex, current smoker, heart rate, body mass index, hemoglobin, fasting blood glucose, total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, total protein, international normalized ratio, serum creatinine, uric acid, logarithmic transformation of N-terminal pro-brain natriuretic peptide, neutrophil-to-lymphocyte ratio, C-reactive protein, hypertension, diabetes, acute coronary syndrome, chronic heart failure New York Heart Association classification III or IV, atrial fibrillation, chronic kidney disease, aspirin, clopidogrel, beta-receptor blockers, calcium channel blockers, nitrates, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins.

Abbreviations: FAR, fibrinogen-to-albumin ratio; CAD, coronary artery disease; HR, hazard ratio; 95% CI, 95% confidence interval.

Time-Dependent Analysis

As shown in Figure 2D, a time-dependent nomogram was constructed based on five features selected by LASSO regression, and the 1-year, 3-year, 5-year, and 10-year survival probabilities were calculated based on a time-dependent nomogram for prediction and intervention. The time-dependent AUC remained in the range of 0.69–0.73, indicating the relatively stable power of this model (Figure 2E).

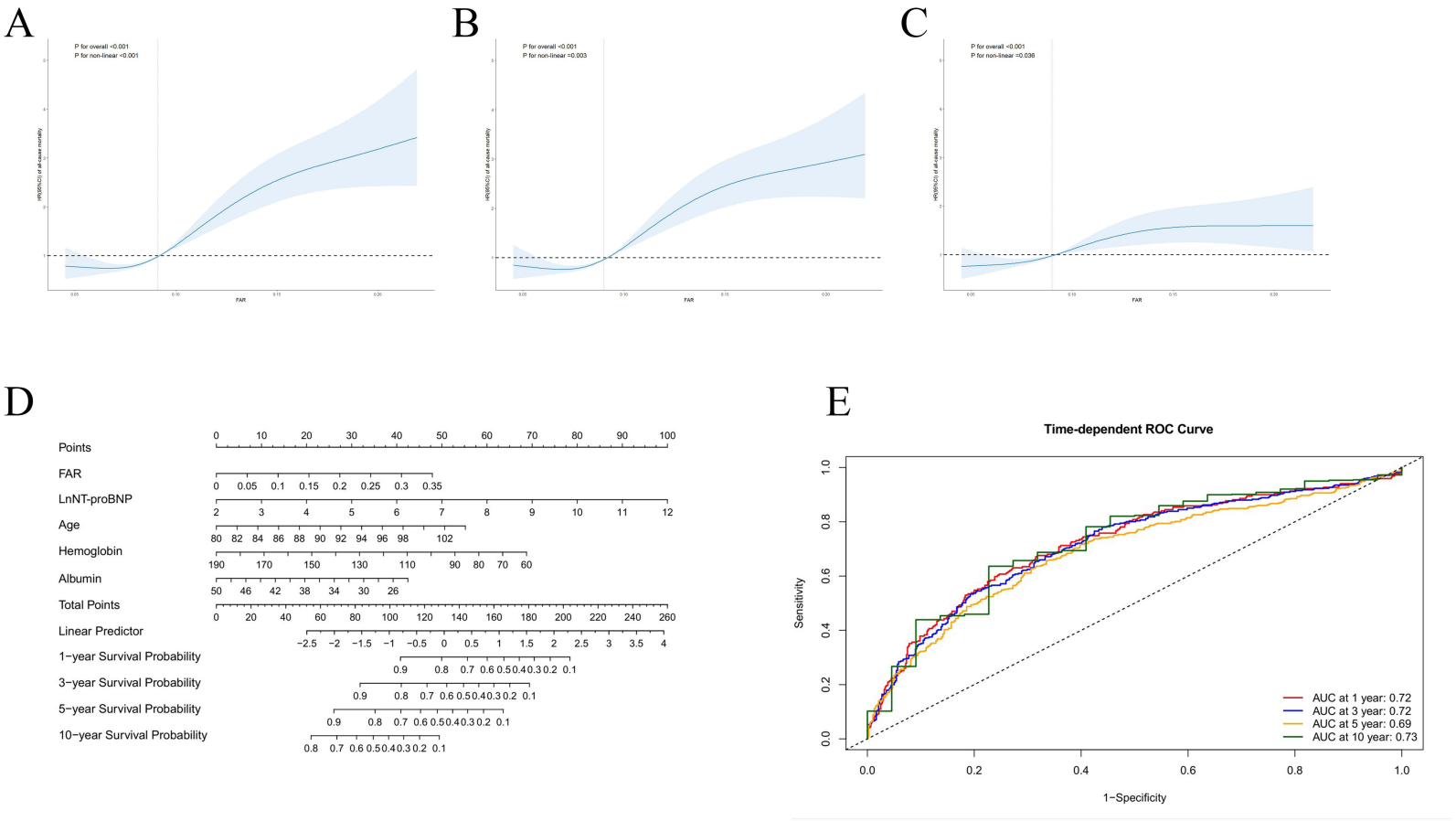

Figure 2 (**A**) Association between fibrinogen-to-albumin ratio (FAR) and mortality was evaluated by the restricted cubic spline (RCS) curve. HR, hazard ratio; 95% CI, 95% confidence interval; (**B**) Association between FAR and mortality was evaluated by the RCS after adjusting for age and sex; (**C**) Association between FAR and mortality was evaluated by the RCS after adjusting for all covariates except albumin and fibrinogen; (**D**) Construction of a time-dependent nomogram. lnNT-proBNP, logarithmic transformation of N-terminal pro-brain natriuretic peptide; (**E**) The time-dependent area under the receiver operating characteristic (ROC) curve (AUC).

Discussion

This study explored prognostic role of FAR in senile patients with CAD and found a significant association between FAR and long-term mortality. Promisingly precise risk management of high FAR levels should be established to reduce long-term mortality in senile patients with CAD. Cumulative mortality was significantly higher in CAD patients with high FAR levels than in those with low FAR levels. FAR is an independent prognostic factor in CAD and can be used as a reliable predictor even after adjusting for confounding parameters by analyzing CAD patients aged ≥ 80 years. Moreover, the RCS curve revealed a significant nonlinear relationship between FAR and mortality, with a turning point of 0.09. An optimal nomogram model was established to predict long-term mortality for early risk stratification and clinically efficient intervention among senile patients with CAD. The optimal predictors were integrated into this model to visualize the predictive survival probability.

CAD is a progressive disease initially caused by the gradual stenosis of blood vessels, providing oxygen to the myocardium, with durative inflammation playing a pivotal role in the occurrence of vascular atherosclerosis.[16] Previous studies have suggested that elevated inflammatory factors are strongly associated with long-term mortality in patients with CAD.[17,18] Fibrinogen is important in promoting thrombin formation, preventing continuous bleeding, and driving wound healing in many physiological processes.[2] Disruption of the balance between fibrinogen transformation and product degradation can lead to diseases in various manners.[19] Fibrinogen is closely associated with many diseases including CAD.[20,21] Previous studies have revealed that high fibrinogen levels are positively associated with CAD severity.[7,22–24] High fibrinogen levels may result from coagulation disturbance or inflammatory status caused by the underlying pathology, thereby causing local inflammation or triggering lipid deposition, driving the generation, destabilization, and rupture of atherosclerotic plaques.[25] Albumin is a crucial factor in physiological processes, with anti-inflammatory and anti-thrombotic functions against atherosclerotic development.[8] Recent findings have indicated that low albumin levels caused by fluid overload lead to an imbalance between inflammation and thrombosis, and are strongly associated with an increased mortality in diseases, especially CAD.[26,27] Therefore, fibrinogen and albumin are easily obtained to reflect inflammatory and thrombotic status, and their ratio has been found to be an innovative inflammatory marker.

FAR integrates two opposing biological pathways. Fibrinogen can activate endothelial cell receptors, promote monocyte chemokine release, accelerate monocyte migration to vascular intima, transform them into macrophages phagocytozing lipids, and form lipid core of atherosclerotic plaques. After the rupture of atherosclerotic plaques in patients with CAD, fibrinogen can promote platelet aggregation and thrombus contraction by binding to glycoprotein IIb/IIIa receptor on the surface of platelets, further strengthening thrombus. Meanwhile, albumin plays an antithrombotic role by maintaining hemorheological stability and combining with procoagulant substances and affects inflammatory process in patients with CAD through antioxidant and immune regulation. Recent studies have reported that FAR has received increasing attention and has predicted CAD development.[12,28–31] The synergistic effect of fibrinogen and albumin is more effective than fibrinogen or albumin alone in the clinical evaluation of patients with CAD.[32–34] Additional studies have shown that FAR is a more convenient and rapid marker and is related to the severity of CAD, which may contribute to stratifying high-risk individuals in CAD and provide long-term strategies for predicting CAD mortality.[35,36] This study found that FAR was positively associated with long-term mortality among patients with CAD aged ≥ 80 years. FAR was demonstrated to be a risk factor for senile patients with CAD during a 10-year follow-up, and there was a J-shaped relationship between FAR and mortality, with a cut-off point of 0.09.[37]

LASSO regression revealed that five features were associated with long-term mortality. Previous studies have suggested that age is an important risk factor for patients with CAD because vascular wall becomes stiffer and less elastic with aging.[38] Long-term mortality in senile patients with CAD remains largely unknown, which warrants urgent exploration of its changes with the progression of aging. The current observation showed that age was closely linked to overall survival in patients with CAD, and for every 1 year elevated in age, death risk increased by 8% after adjusting for confounding parameters. The relationship between hemoglobin and mortality remains controversial, with studies revealing its effect on the clinical evaluation of patients with CAD.[39–42] However, studies have also suggested that the association between hemoglobin and mortality is not significant after adjusting for confounding parameters. This study found that hemoglobin was a prognostic factor associated with long-term mortality in patients with CAD. Previous studies have shown that NT-proBNP, a peptide hormone secreted by the heart, is an early predictor of mortality in

patients with CAD.[43–45] This study reported that elevated NT-proBNP levels were associated with an increased mortality among senile patients with CAD who were more likely to experience further exacerbation of CAD development.

This study has several limitations that should be acknowledged. Firstly, generalizability was limited due to the male-dominant and single-center cohort. Secondly, high HR with wide CI for FAR indicated potential statistical instability, caused by population bias, data collinearity and skewed distribution. Thirdly, clinical applicability would be strengthened with external validation as our future study direction.

Conclusions

This study demonstrated that FAR was significantly and independently associated with long-term mortality and revealed a nonlinear J-shaped relationship between FAR and mortality in senile patients with CAD during a 10-year follow-up period. This study was the first to construct a prognostic model based on FAR for predicting long-term mortality in senile patients with CAD. In combination with these valuable findings, new insights may be provided to achieve effective stratification, clinical intervention, and prognostic improvement in CAD through early utility, timely monitoring, and precise control of FAR. For high-risk patients identified by this model, a comprehensive treatment strategy, combining dynamic FAR monitoring, targeted anti-inflammatory therapy and aggressive comorbidity management, should be explored in clinical practice to improve adverse outcomes.

Data Sharing Statement

Datasets used or analyzed during this study are available from the corresponding author (Shihui Fu, xiaoxiao0915@126.com) upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Chinese PLA General Hospital (Beijing, China) and was conducted in accordance with the tenets and provisions of the Declaration of Helsinki 1975 (revised 1983). Participants provided informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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