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ORIGINAL ARTICLE

Usefulness of fibrinogen-to-albumin ratio to predict no-reflow and short-term prognosis in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Abstract
No-reflow is one of the major complications of primary percutaneous coronary artery intervention (pPCI) in the treatment of acute ST-segment elevation myocardial infarction (STEMI). Fibrinogen-to-albumin ratio (FAR) has currently emerged as a novel inflammatory marker to predict inflammation in chronic diseases. This study aimed to investigate whether admission FAR values predicts angiographic no-reflow and short-term prognosis in all STEMI patients. A total of 510 consecutive STEMI patients who underwent successful pPCI between September 2016 and May 2018 were included in this study. Patients were divided into groups based on thrombolysis in myocardial infarction (TIMI) flow grades after pPCI. No-reflow was defined as a post-PCI TIMI flow grade of 0, 1, or 2. Angiographic success was defined as TIMI flow grade 3. Fibrinogen, hs-CRP, and admission FAR values were significantly higher among patients with no-reflow. On multivariate analysis, admission FAR was an independent predictor of angiographic no-reflow ($p < 0.001$). Receiver-operating characteristics analysis revealed the cut-off value of admission FAR was a predictor of no-reflow with a sensitivity of 79.59% and a specificity of 69.42%. In multivariable Cox regression models adjusted for potential confounders, admission FAR values, and LVEF, hs-CRP was independently and positively associated with the 30-day all-cause mortality. Admission FAR was associated independently and significantly with angiographic no-reflow and short-term mortality in patients with STEMI undergoing pPCI.

Keywords ST-segment elevation myocardial infarction · Thrombus grade · Primary percutaneous coronary intervention · Fibrinogen-to-albumin ratio

Introduction

ST-segment elevation myocardial infarction (STEMI) is a common form of acute myocardial infarction (AMI). Percutaneous coronary intervention (PCI) is performed as soon as possible within 12 h of onset to open the infarct-related coronary artery, which has been recommended as the preferred method of reperfusion [1]. Slow coronary flow or no-reflow is a serious complication of reperfusion in patients with STEMI, which lead to poor prognosis and increased mortality [2, 3]. Some experimental models have found that neutrophil accumulation, reactive oxygen species, and the coagulation cascade via endothelial dysfunction and microvascular constriction are associated with slow or no-reflow [4]. However, the pathophysiological mechanisms of coronary no-reflow are not fully understood. Inflammation plays an important role in the development, progression, and

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evolution of atherosclerosis. Previous studies have shown a relationship between no-reflow phenomenon and increased inflammatory activity, for instance, neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) have been reported as independent predictors of no-reflow among STEMI patients treated with primary PCI [5, 6].

Recently, fibrinogen-to-albumin ratio (FAR) has been reported as a new inflammatory marker closely related to a variety of diseases, including cardiovascular diseases. For example, FAR has been shown to provide a reliable inflammatory index to be used in predicting the severity of coronary artery disease in patients with STEMI. However, there are no data regarding the prognostic value of FAR in the prediction of postprocedural no-reflow among STEMI patients undergoing primary PCI. Therefore, the purpose of this study was to explore the relationship between FAR and no-reflow phenomenon and short-term prognosis in patients with acute STEMI undergoing direct PCI.

Methods

This retrospective analytic-cross sectional study used the data of 510 consecutive patients from September 2016 to May 2018 who were admitted to our cardiovascular center with a diagnosis of acute STEMI and underwent primary PCI within 12 h from symptom onset. The definition of STEMI was based on the criteria of the classic symptoms of coronary ischemia and detection of a 1-mm ST-segment elevation in the inferior lead, or a 2-mm ST-segment elevation in the anterior chest lead occurring in two contiguous leads, or on the presence of a new (or presumably new) left bundle branch block. Patients with culprit lesion in left main coronary artery, left main stenosis over 50%, previous coronary artery bypass surgery, cardiogenic shock, pain to balloon time over 12 h, treatment with fibrinolytic, active infectious or inflammatory diseases, presence of any chronic inflammatory–autoimmune disease including rheumatologic disorders, hematologic diseases, end-stage liver and renal failures, and known malignancy were excluded from the current study. Patients on the following medications were also excluded from the study: glycoprotein IIb/IIIa receptor blockers, corticosteroids, cytotoxic drugs, and diuretics. The study protocol was approved by the Second Affiliated Hospital of Zhengzhou University Ethics Committee. Written informed consent was obtained from all patients.

All participants that underwent coronary angiography performed in multiple orthogonal projections were using Judkins technique. Patients who were candidates for primary PCI received 300 mg of aspirin and a single loading dose of 600 mg clopidogrel or 180 mg ticagrelor at the time of diagnosis of STEMI coronary angiography was performed using standard technique. Immediately after the decision of coronary intervention, 50–70 unit/kg of intravenous bolus dose of unfractionated heparin was administered to the patients who were not treated with enoxaparin before the coronary angiography. The TIMI flow grades were analyzed by two interventional cardiologists blinded to patient clinical data and the frame rate of cine images was 30 frames per seconds. Analysis of cineangiography was performed using an Axiom (Siemens Medical Solution, Erlangen, Germany) workstation. TIMI flow grade three for the treated coronary vessel with a residual stenosis under 20% was considered as a successful pPCI. The no-reflow phenomenon was identified in patients with anterograde flow less than or equal to second level for TIMI and in the absence of dissection, thrombus, spasm, or distal embolization in the final angiogram [7]. Accordingly, the patients were subdivided into normal-reflow group and no-reflow group. Multivessel disease was defined as the presence of more than or equal to one lesion with over 50% stenosis in more than or equal to one major epicardial coronary artery or its major branches remote from the IRA.

All patients received venous blood samples from the antecubital veins after admission, which was performed prior to coronary angiography. Plasma levels of albumin were measured using an automated chemistry analyzer (AU5400, OLYMPUS, JAPAN). Plasma fibrinogen levels were measured using an automatic coagulation analyzer (STA Compact Max, STAGO, FRANCE). F/A ratios were calculated by loading all the data to the statistical program used. Standard methods were used to measure the serum level of glucose, glycated hemoglobin, hemoglobin, uric acid, hs-CRP, and lipid profile. Cardiac troponin T (cTnT), creatine kinase (CK), and CK-MB were measured using a Hitachi modular E-170 (Roche Diagnostics GmbH, Mannheim, Germany). All echocardiographic measurements were made immediately after obtaining the blood samples, using a GE ViVidE7 ultrasound machine (GE Healthcare, Piscataway, USA) with a 3.5-MHz transducer. Left ventricular ejection fraction (LVEF) was measured using the Simpson method according to the recommendations of the American Society of Echocardiography.

Statistical analysis was performed using the SPSS 22.0 Statistical Package Programmed for Windows (SPSS, Inc., Chicago, Illinois). A two-sided p value of < 0.05 was considered significant. Distribution of continuous variables was assessed with the one-sample Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation for normally distributed variables and as the median (25th–75th percentiles) for non-normally distributed variables. The differences between groups were tested by independent samples t test or Mann–Whitney U test. Categorical variables were summarized as percentages and

Table 1 Baseline patient characteristics of the study patients

	Normal reflow ($n=412$)	No-reflow ($n=98$)	p value
Age (years)	60.44 ± 10.96	64.09 ± 11.53	0.004
Male sex	325 (78.9%)	67 (68.4%)	0.026
Diabetes mellitus	113 (27.4%)	37 (37.8%)	0.044
Smoking	229 (55.6%)	62 (63.3%)	0.167
Hypertension	196 (47.6%)	51 (52.0%)	0.426
Family history	78 (18.9%)	24 (24.5%)	0.216
Previous CAD	113 (27.4%)	33 (33.7%)	0.219
Admission LVEF (%)	51.18 ± 4.91	50.41 ± 5.05	0.169
Systolic blood pressure (mmHg)	132.76 ± 21.45	134.94 ± 20.61	0.362
Diastolic blood pressure (mmHg)	73.11 ± 13.85	76.08 ± 12.05	0.051
Heart rate (bpm)	80.13 ± 12.40	82.40 ± 11.12	0.097
Preprocedural medications			
Stain	256 (62.1%)	54 (55.1%)	0.200
Beta-blocker	276 (67.0%)	61 (62.2%)	0.372
ACEI/ARB	291 (70.6%)	64 (65.3%)	0.303
Aspirin	342 (83.0%)	81 (82.7%)	0.121
P_2Y_{12} inhibitor use			
Ticagrelor	187 (45.4%)	37 (37.8%)	0.171
Clopidogrel	235 (54.6%)	61 (62.2%)	

CAD coronary artery disease, *LEVF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

compared with the χ^2 test. Multivariant stepwise logistic regression, including covariates found to have a significant association with no-reflow in univariate analysis, was used to identify independent predictors of no-reflow. The receiver-operating characteristic (ROC) curve was used to determine the cut-off value of FAR values to predict the no-reflow. A multivariate Cox proportional-hazards regression model was used to find the independent predictors of the primary endpoint. Factors entered into the multivariate model included those with p value < 0.05 from the univariate analysis and variables with known prognostic value. The 30-day survival curves for FAR groups were analyzed using the Kaplan–Meier method, and statistical assessment was performed using the log-rank test.

Results

Among the 510 patients of STEMI (mean age 61.14 ± 11.15 years, 78.9% male), the incidence of angiographic no-reflow was 19.2%. Study participants were divided into two groups according to TIMI flow grades after pPCI. No-reflow group with flow grades 0 to 2 ($n=98$, 67 men, mean age 64.09 ± 11.53 years) and the normal-reflow group with flow TIMI grade 3 ($n=412$, 325 men, mean age 60.44 ± 10.96 years). Demographic, clinical, laboratory, and procedural characteristics in individual groups are listed in Table 1.

Compared to normal-reflow group, patients in the no-reflow group were older (64.09 ± 11.53 vs. 60.44 ± 10.96 years, $p=0.004$, Table 1) and prevalence of diabetes mellitus was significantly higher in them (37.8% vs. 27.4%, $p=0.044$, Table 1). Besides, more men were in the reflow group (78.9% vs. 62.4%, $p=0.026$, Table 1).

The comparison of admission hematological parameters of both groups is presented in Table 2. The patients in the no-reflow group had significantly higher fibrinogen, FAR and hs-CRP levels when compared to those in reflow patients. The comparison of angiographic and echocardiographic characteristics of the two groups showed no statistically significant differences apart from chest pain to balloon time, initial TIMI flow, and the presence of multivessel disease (Table 2). Pain to balloon time in the no-reflow group was longer than that of the patients in the reflow group, as presented in Table 2 (5.0 h vs. 4.0 h, $p=0.018$). There were more patients with multivessel disease in the no-reflow group compared to that of the reflow group (48.8% vs. 65.3%, $p<0.001$). In both study groups, the left anterior descending coronary artery is the most common IRA. The percentage of stent implantation, stent length, and diameter in the two groups were similar (Table 2).

Effects of the variables with an unadjusted $p<0.05$ in logistic regression analysis and clinically important variables on the no-flow were analyzed using univariate and multivariate logistic regression analyses. Male (OR 0.45; 95% confidence interval [CI] 0.23–0.87; $p=0.017$, Table 3),

Table 2 Laboratory data and angiographic characteristics of the study patients

	Normal reflow ($n=412$)	No-reflow ($n=98$)	p value
Serum glucose (mg/dL)	6.30 ± 2.50	6.55 ± 2.61	0.380
Glycated hemoglobin (mg/dL)	7.11 ± 1.57	6.83 ± 1.44	0.099
Hemoglobin (g/dL)	141.05 ± 15.84	139.47 ± 17.85	0.386
TC (mg/dL)	187.51 (156.62–223.38)	189.48(159.59–222.85)	0.891
TG (mg/dL)	120.01 (104.08–131.38)	115.79(107.34–123.77)	0.271
LDL-C (mg/dL)	111.92 (96.81–125.72)	109.84(89.50–125.57)	0.286
HDL-C (mg/dL)	41.13 (33.02–49.30)	39.59(33.89–48.66)	0.854
Peak cTnI (U/L)	8.37 ± 3.71	8.72 ± 3.78	0.402
Peak CK-MB (U/L)	89.82 (66.07–111.80)	96.31(72.11–111.68)	0.314
UA (mg/dL)	296.89 (250.32–348.42)	310.75(264.97–344.93)	0.448
Fibrinogen (μg/mL)	354.73 (290.46–434.92)	480.40(401.85–542.18)	< 0.001
Albumin (g/L)	37.13 ± 5.21	36.59 ± 5.51	0.360
FAR	9.72 (8.02–11.57)	13.31(11.32–15.28)	< 0.001
Hs-CRP (mg/dL)	7.98 ± 3.70	9.02 ± 3.56	0.012
Number of narrowed vessel			< 0.001
Single vessel	211 (51.2%)	34 (34.7%)	
Multivessel	201 (48.8%)	64 (65.3%)	
Initial TIMI flow			< 0.001
	0	248 (60.2%)	81 (82.7%)
	1	106 (25.7%)	12 (12.2%)
	2	47 (11.4%)	3 (3.1%)
	3	11 (2.7%)	2 (2.0%)
Infarct-related artery			0.213
LAD	159 (38.6%)	47 (48.0%)	
RCA	153 (37.1%)	29 (29.6%)	
CFX	100 (26.3%)	22 (22.4%)	
PCI procedure			0.447
Balloon angioplasty	29 (7.0%)	10 (10.2%)	
Balloon + stenting	329 (79.9%)	73 (74.5%)	
Primary stenting	54 (13.1%)	15 (15.3%)	
Pain to balloon time (h)	4.0 (2.0–6.0)	5.0 (3.0–6.0)	0.018
Stent diameter (mm)	3.22 ± 0.29	3.25 ± 0.25	0.282
Stent length (mm)	17.73 ± 3.90	18.24 ± 4.51	0.239

TC total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *cTnI* cardiac troponin I, *UA* uric acid, *CK-MB* creatine kinase myocardial band, *TIMI* thrombolysis in myocardial infarction, *LAD* left anterior descending artery, *CFX* circum flex coronary artery, *RCA* right coronary artery, *PCI* percutaneous coronary intervention

Initial TIMI flow(OR 0.56; 95% CI 0.37–0.85; $p=0.007$, Table 3), FAR (OR: 1.80; 95% CI 1.57–2.07; $p<0.001$, Table 3), multivessel disease (OR 0.46; 95% CI 0.26–0.79; $p=0.005$, Table 3), hs-CRP (OR 1.08; 95% CI 1.00–1.17; $p=0.041$, Table 3) were observed to be independent predictors for the development of no-reflow phenomenon.

ROC statistical analyses showed that FAR above 10.89 had 79.59% sensitivity and 69.42% specificity for the development of no-reflow status (95% CI 0.786–0.852, $p<0.001$, Fig. 1).

In the multivariate Cox regression model, procedural success, FAR, LVEF, and hs-CRP at admission were independent predictors of 30-day mortality after pPCI (Table 4). Moreover, Kaplan–Meier curves between patients with FAR < 10.89 and ≥ 10.89 for 30-day mortality revealed worse outcomes in patients with high FAR ($p<0.001$) (Fig. 2).

Discussion

To our knowledge, this is the first study to report the relationship among the FAR, no-reflow and short-term mortality in patients with STEMI undergoing pPCI. The results of this study showed that FAR, fibrinogen, and hs-CRP values

Table 3 Effects of various variables on no-reflow in univariate and multivariate logistic regression analyses

	Univariate analysis		Multivariate analysis	
	Odds ratio, 95% CI	*p* value	Odds ratio, 95% CI	*p* value
Age	1.03 (1.01–1.05)	0.004		
Sex (male)	1.73 (1.06–2.81)	0.028	0.45 (0.23–0.87)	0.017
DM	0.62 (0.39–0.99)	0.045		
Smoking	0.73 (0.46–1.15)	0.168		
Family history	0.72 (0.43–1.21)	0.218		
Hypertension	0.84 (0.54–1.30)	0.427		
Previous CAD	1.34 (0.84–2.15)	0.220		
Initial TIMI flow	0.49 (0.33–0.73)	<0.001	0.56 (0.37–0.85)	0.007
Multivessel disease	1.83 (1.10–3.04)	0.020	0.46 (0.26–0.79)	0.005
Pain to balloon time	1.09 (1.00–1.18)	0.036		
FAR	1.67 (1.49–1.86)	< 0.001	1.80 (1.57–2.07)	<0.001
Fibrinogen	1.01 (1.00–1.01)	< 0.001		
Albumin	0.98 (0.94–1.02)	0.359		
hs-CRP	1.08 (1.02–1.15)	0.012	1.08 (1.01–1.17)	0.041

DM diabetes mellitus, *CAD* coronary artery disease, *CI* confidence interval

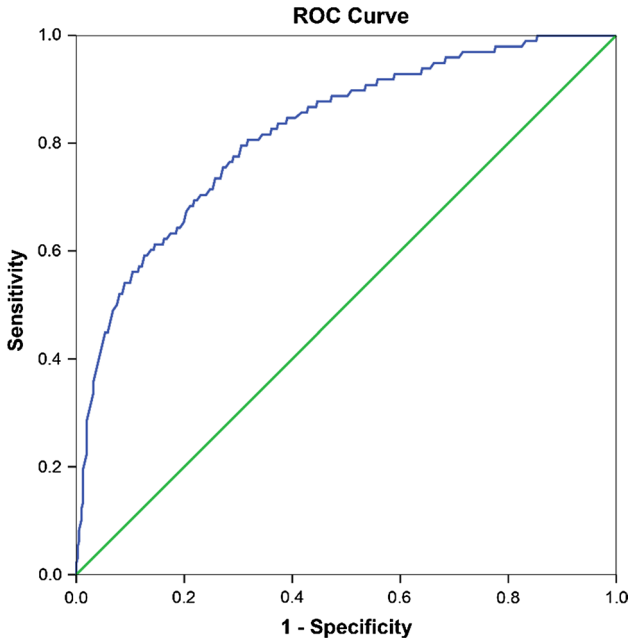

Fig. 1 ROC curves of FAR for prediction of no-reflow phenomenon after pPCI in patients with STEMI

independent predictors of no-reflow after pPCI on multivariate analysis in this study. Furthermore, FAR was an independent factor for 30-day mortality in these patients.

Primary PCI is the preferred revascularization method for most patients with STEMI, but the performance of primary PCI fails to normalize the coronary flow and myocardial perfusion in some of these patients [8]. This phenomenon described as no-reflow is significantly associated with poor outcome and increased mortality after pPCI [9]. Therefore, early identification of patients with high risk of coronary angiography no-reflow can enable physicians to choose the best treatment strategy.

Previous studies have found that no-reflow is associated with a variety of pathological factors, including endothelial dysfunction, reactive oxygen species, ischemia–reperfusion injury, platelet aggregation, micro-thrombosis, distal embolization, and vasomotor dysfunction, but the exact mechanism of no-reflow is still unclear [4, 10, 11]. Celik et al. [12] suggested that distal embolization plays an important role in the mechanism of no-reflow after pPCI. Several high-risk factors, such as high thrombotic load in the coronary artery, right coronary artery lesions, and women (parallel structure), have been found to predict the risk of distal coronary thrombosis in STEMI patients [12–15]. Recent studies have shown that higher inflammation status play an important role in the occurrence of the no-reflow phenomenon in STEMI patients after pPCI [13]. Akpek et al. [14] reported that neutrophil-to-lymphocyte ratio and CRP had a positive correlation with no-reflow in patients with STEMI undergoing pPCI. Oduncu et al. [15] showed that patients with no-reflow who underwent PCI have higher baseline CRP levels.

Serum albumin is the major protein in human serum, maintains the permeability of the capillary membrane, and participates in the acute and chronic inflammatory response [16, 17]. In addition, serum albumin is an important inhibitor of platelet activation and aggregation and is an important mediator of platelet induction [18, 19]. Recent studies have shown that the serum albumin levels are closely related to the occurrence, development and prognosis of coronary heart disease. It has been suggested that serum albumin levels lower than 3.5 g/dl on admission were one of the independent predictors of new heart failure and in-hospital

Table 4 Univariate and multivariate Cox regression analyses model revealing the predictors of 30-day mortality after primary percutaneous coronary intervention

	Univariate analysis		Multivariate analysis	
	Hazard ratio, 95% CI	*p* value	Hazard ratio, 95% CI	*p* value
Age	0.988 (0.956–1.022)	0.489		
Male	1.517 (0.691–3.332)	0.299		
Family history	1.189 (0.454–3.117)	0.724		
Previous CAD	0.418 (0.202–0.865)	0.019	0.659 (0.303–1.433)	0.292
Hypertension	1.160 (0.558–2.411)	0.691		
DM	1.091 (0.483–2.464)	0.833		
Smoking	1.080 (0.519–2.245)	0.837		
Multivessel vessel	0.656 (0.310–1.389)	0.271		
Hemoglobin	0.983 (0.960–1.006)	0.139		
Glycated hemoglobin	0.779 (0.612–0.992)	0.043	0.925 (0.729–1.174)	0.520
LVEF	0.736 (0.672–0.806)	< 0.001	0.701 (0.629–0.780)	< 0.001
Hs-CRP	1.248 (1.130–1.377)	< 0.001	1.312 (1.179–1.461)	< 0.001
TG	0.985 (0.968–1.003)	0.110		
TC	1.002 (0.995–1.009)	0.602		
LDL-C	0.997 (0.982–1.013)	0.707		
HDL-C	1.014 (0.985–1.045)	0.338		
UA	1.001 (0.997–1.006)	0.585		
FAR	1.409 (1.347–1.473)	<0.001	1.191 (1.039–1.365)	0.012
Stent diameter	1.045 (0.291–3.748)	0.946		
Stent length	1.032 (0.943–1.129)	0.495		

CAD coronary artery disease, *DM* diabetes mellitus, *LEVF* left ventricular ejection fraction, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *UA* uric acid, *CI* confidence interval

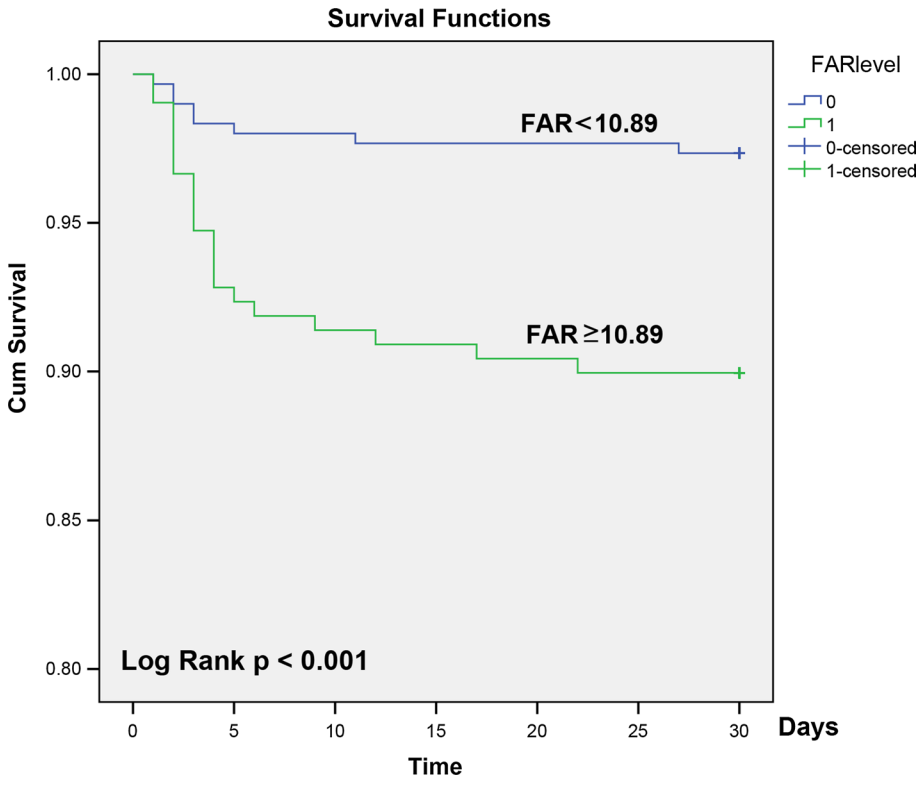

Fig. 2 Kaplan–Meier curves between patients with FAR < 10.89 and ≥ 10.89 for 30-day mortality

mortality in patients with acute coronary syndrome [20]. Kurtul et al. [21] showed that albumin was associated with coronary artery SYNTAX scores and the incidence of adverse events during hospitalization in patients with ACS. Meanwhile, fibrinogen is also a biomarker of chronic inflammation, which is known to be a precursor to fibrin and accelerates platelet aggregation [22]. In the Atherosclerosis Risk in Communities Study, elevated fibrinogen levels have been shown to be one of the risk factors for coronary heart disease. However, in healthy adults, the role of predicting coronary events is weaker than traditional risk factors [23]. Gao et al. [24] showed that fibrinogen levels were associated with coronary artery Gensini scores in men under 35 years of age. Kurtul et al. [25] showed that fibrinogen levels in patients with the acute coronary syndrome were positively correlated with coronary SYNTAX scores.

Based on the previous research results, both higher fibrinogen levels and lower serum albumin levels were reported to be associated with adverse cardiovascular outcomes in the setting of STEMI. Its relation with inflammation has been investigated some previous clinical studies. It has been found that there is a positive correlation between FAR and coronary SYNTAX score in patients with STEMI, and FAR can be used as an independent predictor of higher SYNTAX Score in patients with STEMI [26]. Karahan et al. [27] showed that FAR levels are related to the clinical classification and severity of chronic venous insufficiency. Yang et al. [28] have found that the albumin-to-fibrinogen ratio (AFR) is associated with disease activity in patients with rheumatoid arthritis (RA). AFR may serve as two novel inflammatory markers for monitoring disease activity in RA patients. Furthermore, several studies have shown that the FAR has been used frequently to predict outcomes in several types of human cancers [29–32]. Our results showed that FAR levels were significantly higher in the no-reflow group compared with the normal-reflow group. We also found an optimal cut-off point for FAR of at least 10.89. It predicted the no-reflow with good sensitivity and specificity. In multivariate Cox regression, FAR, LVEF, and hs-CRP at admission were independent predictors of 30-day mortality after pPCI. One of the mechanisms by which higher levels of FAR cause no-reflow may be that low albumin levels promotes fibrinolysis, thereby inhibiting the physiological fibrinolytic system and reducing the spontaneous dissolution of the thrombus [33]. In addition, the bioavailability of prostacyclin (PGI2), an effective platelet aggregation inhibitor, also depends on serum albumin levels [16, 34]. On the other hand, serum albumin inhibits the expression of vascular cell adhesion molecule-1(VCAM-1) induced by tumor necrosis factor A(TNF-a), thereby reducing apoptosis of endothelial cells [35]. The deposition of fibrinogen can change the permeability of vascular endothelium, promote the aggregation and oxidation of low-density lipoprotein under the endothelium, further stimulate the proliferation and migration of vascular smooth muscle cells to the intima, and eventually lead to the formation of atherosclerotic plaque [36].

In summary, we believe that FAR, as a readily available and cheaper marker, may help clinicians in predicting the development of no-reflow and short-term mortality after pPCI. Therefore, FAR is considered to be a new marker of inflammation in STEMI patients. It may be used as a component in accurate risk stratification when a patient is a candidate for pPCI. However, the occurrence of no-reflow appears to involve many mechanisms, of which only a few may have been illuminated. Therefore, further clinical research is needed in the future to better understand the specific mechanism of this phenomenon. Our study has some limitations. First, the sample size is very small, and the results shown in this study should be verified in larger clinical trials. Second, there are multiple risk factors for the no-reflow that we did not assess them and it might have affected our multivariate analysis. Finally, FAR has confined clinical utility, because when performing pPCI, the surgeon usually does not know the results of fibrinogen and albumin.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

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