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Relationship Between the Fibrinogen-to-Albumin Ratio and SYNTAX Score in Patients with Non-ST-Elevation Myocardial Infarction

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ABSTRACT

Background: Despite the association of fibrinogen-to-albumin ratio (FAR) with the extent, severity, and complexity of coronary artery disease (CAD) in patients with ST-elevation myocardial infarction (STEMI) and stable CAD, no studies to date have specifically addressed this issue in patients with non-STEMI (NSTEMI). **Objectives:** This study aimed to evaluate whether a relationship exists between FAR and the SYNergy between Percutaneous Coronary Intervention with TAXus (SYNTAX) score in patients with NSTEMI. **Methods:** In this prospective cross-sectional study, 330 patients with NSTEMI who had undergone coronary angiography in an academic medical center were divided into two groups: those with an intermediate/high (≥23) SYNTAX score (241 patients) and those with a low SYNTAX score <23 (89 patients). SYNTAX score was computed by two highly experienced cardiologists (who were blinded to the study data) using an online SYNTAX calculator. Fibrinogen and albumin levels were measured in all patients, and FAR was calculated. **Results:** Multivariate logistic regression analysis showed that FAR (odds ratio [OR]: 1.478, 95% confidence interval [CI]: 1.089-2.133, p = 0.002), low-density lipoprotein (OR: 1.058, 95% CI: 1.008-1.134, p = 0.026), and troponin I (OR: 1.219, 95% CI: 1.015-1.486, p = 0.031) were independent predictors of the SYNTAX score. In a receiver operating characteristics analysis, a cutoff FAR value of 95.3 had an 83% sensitivity and an 86% specificity (area under the curve [AUC]: 0.84, p < 0.001) for the prediction of SYNTAX scores ≥23 in NSTEMI patients. **Conclusion:** These results indicate that FAR is a useful tool to predict intermediate-high SYNTAX scores in NSTEMI patients. (REV INVEST CLIN. 2021;73(3):XX-XX)

Key words: Fibrinogen-to-albumin. SYNergy between percutaneous coronary intervention with TAXus score. Non-ST-elevation myocardial infarction.

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INTRODUCTION

Coronary artery disease (CAD) occurs through complex pathophysiological mechanisms. Inflammatory markers play a major role in the onset and progression of processes associated with CAD[1]. Prior studies have demonstrated that various inflammatory biomarkers are associated with both the severity and prognosis of CAD[2]. Hypoalbuminemia has been identified as a risk factor for incident myocardial infarction (MI) in patients with CAD[3]. Several studies have reported an association between low serum albumin levels and increased risk of cardiovascular mortality and morbidity[4]. Fibrinogen, a short half-life protein, is an indicator of procoagulant state and a biomarker for inflammatory responses. It has been proposed that baseline plasma fibrinogen levels can predict cardiovascular events in the general population[5]. Moreover, a recent study showed that elevated fibrinogen levels are linked to the presence and severity of CAD[6]. The SYNergy between Percutaneous Coronary Intervention with TAXus (SYNTAX) score, a lesion-based angiographic scoring system, has been widely used to grade the complexity of CAD. A vast number of non-ST-elevation MI (NSTEMI) patients have multivessel disease[7], and SYNTAX score is crucial in determining the selection of optimal revascularization strategy. A previous study found that the fibrinogen-to-albumin ratio (FAR) was useful in predicting SYNTAX score in patients with stable angina pectoris[8]. Another study has demonstrated that FAR is associated with SYNTAX score and related to no-reflow after primary percutaneous intervention in ST-elevation MI (STEMI) patients[9]. However, to our knowledge, no previous studies have investigated the association between FAR and SYNTAX score in NSTEMI patients. Thus, the current study aims to investigate whether FAR, as a new inflammatory index, is associated with the extent and severity of CAD in patients with NSTEMI.

METHODS

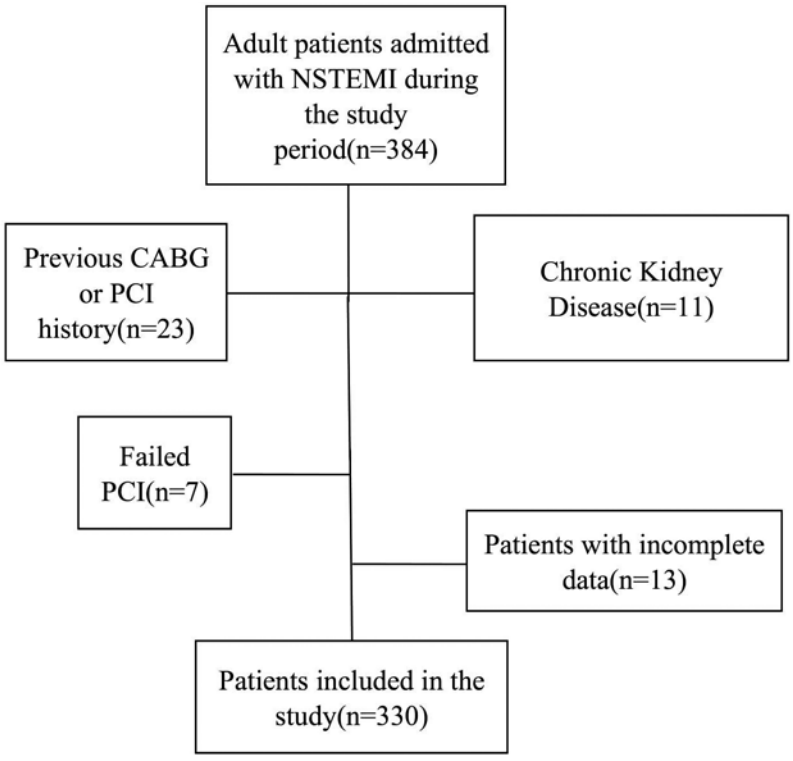
Study population

This prospective cross-sectional single-center study investigated the relationship between serum FAR and SYNTAX score in patients with NSTEMI admitted to our cardiology clinic. A total of 384 NSTEMI patients underwent coronary angiography (CAG) between August 2019 and September 2020. NSTEMI was defined if patients had typical angina pain lasting 30 min, a positive troponin-I level (defined in our clinical laboratory as >0.01 ng/mL), and no evidence of ST segment elevation on 12-lead electrocardiogram[10]. The study exclusion criteria encompassed characteristics that may have affected the systemic and local inflammatory response: a history of congestive heart failure, previous percutaneous coronary intervention (PCI), coronary artery bypass grafting, active infectious disease, inflammatory or immunologic disease, cirrhosis, intermittent claudication or critical ischemia of the lower limbs, chronic obstructive pulmonary disease, chronic kidney disease, malignancy, cardiogenic shock on admission, and the inability to achieve thrombolysis in MI 3 flow after PCI. After screening for these eligibility criteria, the final cohort of the study population consisted of 330 patients with NSTEMI. The flow chart of the study population is presented in figure 1. The study was conducted in accordance with the general principles stated in the Declaration of Helsinki. Written informed consents of all patients were taken and the local research ethics committee approved the study protocol.

PCI procedure

All study patients were treated according to the latest evidence-based guidelines from the European Society of Cardiology[10]. Once NSTEMI was confirmed, patients were given a loading dose of antiplatelet medication (600 mg clopidogrel, 60 mg prasugrel, or 180 mg ticagrelor) with 300 mg aspirin. Eligible NSTEMI patients underwent emergent CAG using the standard Judkins technique through the femoral or radial artery. The infarct-related artery was defined in different image planes by cine angiography visualization, and PCI was performed on the culprit lesion. In all NSTEMI patients with very high-risk criteria, CAG was carried out within 2 h. The remaining NSTEMI patients were referred to CAG within 24 h. In addition, all patients without contraindications were initiated on statin therapy in addition to a beta-blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker. SYNTAX score was computed with an online SYNTAX score calculator (http://www.syntaxscore.com/calculator/start.htm) by two highly experienced cardiologists who were blinded to the study data. Coronary lesions with >50% diameter narrowing in vessels of >1.5 mm diameter were identified, scored,

Figure 1. Flowchart of the study population.



and summed to obtain the final SYNTAX score. If scoring between the cardiologists differed, the final score was calculated as the average of the two scores. The study population was divided into two groups according to SYNTAX score: there were 241 patients in the low SYNTAX score (<23) group and 89 patients in the intermediate/high SYNTAX score (≥23) group.

Clinical and demographic data

The following clinical and demographic parameters were acquired from patients' medical records: age, sex, hypertension (defined as known hypertension treated with antihypertensive drugs or two or more blood pressure recordings >140/90 mmHg), diabetes mellitus (defined as known diabetes treated with diet or drugs or a fasting serum glucose measurement of >126 mg/dL), and hypercholesterolemia (defined as known hypercholesterolemia treated with cholesterol-lowering medication or a measured fasting or non-fasting serum cholesterol concentrations >200 mg/dL). Current cigarette smoking was defined as active smoking within the past 12 months. Body mass index (BMI) was determined by the following formula: BMI=weight (kg)/height^2 (m^2).

Laboratory measurements

When patients were first admitted to the emergency room or coronary care unit, 3 mL samples of peripheral venous blood were collected from the antecubital vein and analyzed for the measurement of complete blood count, troponin levels, liver enzymes, kidney function tests, bleeding profile, serum albumin, and plasma fibrinogen. Serum albumin concentrations were measured using the Abbott C8000i analyzer automatic photometry kit (Abbott Park, Illinois). Plasma fibrinogen levels were measured by the Clauss method with Stago Compact (Diagnostica Stago, Asnieres sur Seine, France) and a coagulation AutoAnalyzer (Diagnostica Stago Inc, Paris, France). Echocardiography was performed by two experienced cardiologists who were blinded to other data. All measurements were performed in accordance with the latest guidelines[11]. Left ventricular ejection fraction

(LVEF) was calculated according to the biplane modified Simpson's method.

Statistical analysis

All statistical calculations were performed using SPSS version 22.0 (SPSS Inc, Chicago, Illinois). The distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Accordingly, the Student's t-test or Mann–Whitney U test were used to compare continuous variables according to the distribution of the data. Chi-square or Fisher's exact tests were used to compare categorical variables. Continuous variables were presented as mean ± standard deviation, whereas categorical variables were presented as counts and percentages. Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity with 95% confidence interval (CI) of FAR for predicting SYNTAX values. The Spearman correlation coefficient was used for correlation analysis. Association of different variables with low (≥23) SYNTAX score were calculated in univariate analysis. Logistic regression analysis was used to determine independent predictors of low SYNTAX score. In this analysis, variables that differed between groups with a $p < 0.25$ were included in the study. $p < 0.05$ were considered statistically significant. We calculated that a minimum of 113 participants should be sampled in order to obtain 99% power at an alpha level of 0.05 (R 3.0.1. open-source program).

RESULTS

Table 1 summarizes the baseline characteristics of the low SYNTAX and intermediate/high SYNTAX groups. No statistical difference was observed between the groups in terms of sex, hypertension, smoking, and family history. Patients in the intermediate/high SYNTAX group had lower LVEF ($p = 0.011$), lymphocyte count ($p = 0.046$), and albumin levels ($p = 0.01$) compared to the low SYNTAX group. The following were higher among patients with intermediate/high SYNTAX vs. low SYNTAX: age (59.2 ± 5.1 vs. 61.8 ± 5.6; $p = 0.037$), diabetes mellitus (67 [26.4%] vs. 45 [51%]; $p = 0.032$), low-density lipoprotein (LDL) (152.1 ± 43.4 vs. 120.8 ± 27.5; $p < 0.001$), fibrinogen (265.8 ± 72.9 vs. 350.7 ± 124.2; $p = 0.011$), FAR (66.9 ± 21.5 vs. 126.3 ± 44.7; $p < 0.001$), and troponin I peak (11.3 ± 8.9 vs. 19.5 ± 14.7 ng/dL, $p < 0.001$).

Univariate logistic regression analysis identified that FAR, LDL-cholesterol (LDL-C), admission troponin I levels, LVEF, age, and diabetes mellitus were significantly associated with intermediate/high SYNTAX score (Table S1). Multivariate logistic regression analysis showed that FAR (odds ratio [OR]: 1.478, 95% CI: 1.089-2.133, $p = 0.002$), LDL (OR: 1.058, 95% CI: 1.008-1.134, $p = 0.026$), and troponin I (OR: 1.219, 95% CI: 1.015-1.486, $p = 0.031$) were the independent predictors of intermediate/high SYNTAX score (Table S1).

In ROC curve analysis, the value for FAR to detect intermediate/high SYNTAX score with a sensitivity of 83% and specificity of 86% was 95.3 in NSTEMI patients (Fig. 2). The area under the curve was 0.84. FAR had a stronger correlation with intermediate/high SYNTAX score compared to low SYNTAX score (Fig. 3). The R^2 linear correlation coefficient was 0.442 for FAR ($p < 0.001$). The correlations between several study parameters are shown in Table 2. Spearman correlation analysis revealed a moderate positive correlation between FAR and intermediate/high SYNTAX score ($r = 0.548$, $p < 0.001$).

DISCUSSION

To the best of our knowledge, the current study is the first to demonstrate the relationship between FAR and SYNTAX score in patients with NSTEMI. We also report that a higher FAR may also be an independent predictor of SYNTAX score in NSTEMI patients, in addition to LDL and troponin I.

Inflammation and hemorheological markers are factors underlying the development of atherosclerosis and its complications. Albumin regulates plasma oncotic pressure and also acts as a transport vehicle for a variety of substances and plays a role in both acute and chronic inflammatory processes[12]. Moreover, serum albumin has antioxidant and anti-inflammatory effects[13]. Hartopo et al. identified low SA as a risk factor for the in-hospital adverse outcomes in acute coronary syndrome (ACS)[14]. Furthermore, Acet et al. showed that low serum albumin levels at the time of hospital admission predict the development of the

Table 1. Baseline characteristics of the patients

Variable	Low SYNTAX score n = 241	Intermediate-high SYNTAX score n = 89	p-value
Age (year)	59.2 ± 5.1	61.8 ± 5.6	0.037
Gender			
Male (%)	151 (63.6)	67 (75.2)	0.265
Hypertension, n (%)	93 (38)	41 (45.4)	0.446
DM, n (%)	67 (26.4)	45 (51)	0.032
Smoking, n (%)	88 (35.7)	43 (47.3)	0.325
Family history, n (%)	53 (21.9)	29 (31.8)	0.282
Heart rate, per minute	71 ± 10	78 ± 13	0.295
Creatinine, mg/dL	0.94 ± 0.23	1.05 ± 0.28	0.113
WBC,/μL	10.2 ± 2.6	10.9 ± 3.1	0.359
Hemoglobin, g/dL	13.5 ± 1.9	12.9 ± 1.3	0.163
Platelet count, 10^3/μL	227 ± 55	240 ± 63	0.432
Neutrophil count, 10^3/μL	6.9 ± 2.5	7.5 ± 3.9	0.365
Lymphocyte count, 10^3/μL	2.2 ± 0.8	1.7 ± 0.7	0.046
Total cholesterol, mg/dL	187.7 ± 43.8	201.0 ± 49.1	0.257
LDL-C, mg/dL	120.8 ± 27.5	152.1 ± 43.4	0.001
HDL-C, mg/dL	41.4 ± 10.7	38.2 ± 9.3	0.317
Triglyceride, mg/dL	185.6 ± 117.9	204.8 ± 135.2	0.654
Fibrinogen, mg/L	265.8 ± 72.9	350.7 ± 124.2	0.011
Albumin, g/L	3.73 ± 0.45	3.35 ± 0.32	0.009
FAR	66.9 ± 21.5	126.3 ± 44.7	0.001
LVEF, %	48.6 ± 6.2	43.7 ± 5.4	0.011
Troponin I peak (ng/dL)	11.3 ± 8.9	19.5 ± 14.7	0.001

DM: diabetes mellitus; LVEF: left ventricular ejection fraction; FAR: fibrinogen-to-albumin ratio; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SYNTAX: SYNergy between Percutaneous Coronary Intervention with TAXus.

no-reflow phenomenon after primary PCI in patients with STEMI[15]. As a result, lower serum albumin levels are closely associated with CAD[16,17].

Fibrinogen, one of the most important coagulation factors, contributes to blood viscosity, platelet aggregation, and fibrin formation and modulates coagulation activation, clot properties, and fibrinolysis[18]. Elevated fibrinogen levels have been found to be related to an increased risk of CAD[18,19]. High circulating levels of fibrinogen as a risk factor for premature CAD in patients <55 years was first reported by Pineda et al.[19]. De Luca et al. demonstrated that plasma fibrinogen levels are an independent predictor of the severity and extent of CAD in the Italian population, as estimated by both the numbers of the diseased vessels and the Gensini score[18].

It has been suggested that a combined measure of albumin and fibrinogen may have enhanced predictive value for clinical outcomes in gallbladder and non-small cell lung cancer patients[20,21]. However, there is insufficient literature on the relationship between FAR and cardiovascular events. Sapmaz et al. found that significantly higher FAR values may be associated with increased risk of cardiovascular events and hypothesized that hemorheological factors such as fibrinogen and albumin could influence blood viscosity and play a crucial role in the development of pathological vascular thrombosis[22]. Sapmaz et al. also

Figure 2. Receiver operating characteristics curve analysis indicating the discriminating ability of fibrinogen-albumin ratio.

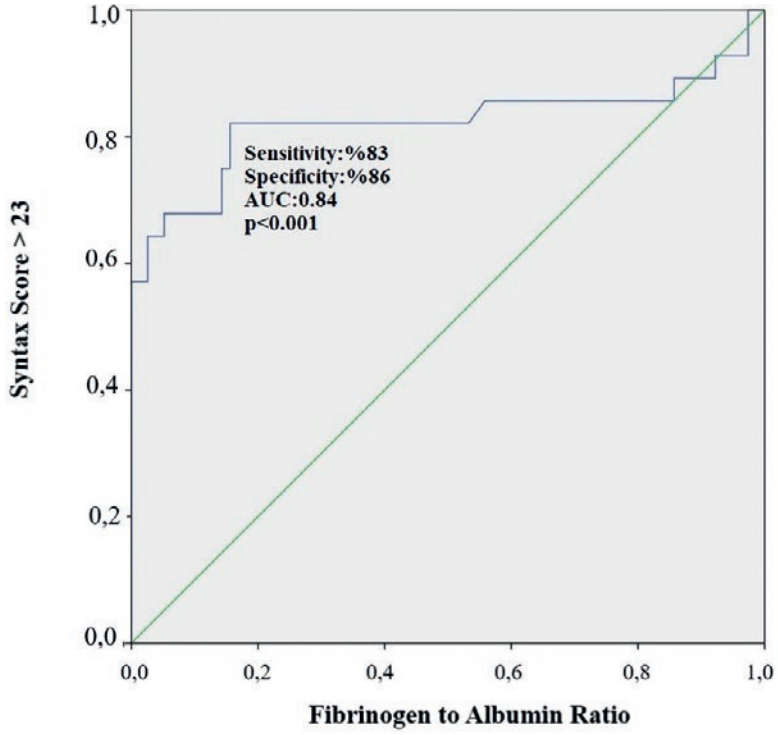


Figure 3. Correlation between fibrinogen-albumin ratio and SYNergy between Percutaneous Coronary Intervention with TAXus score.

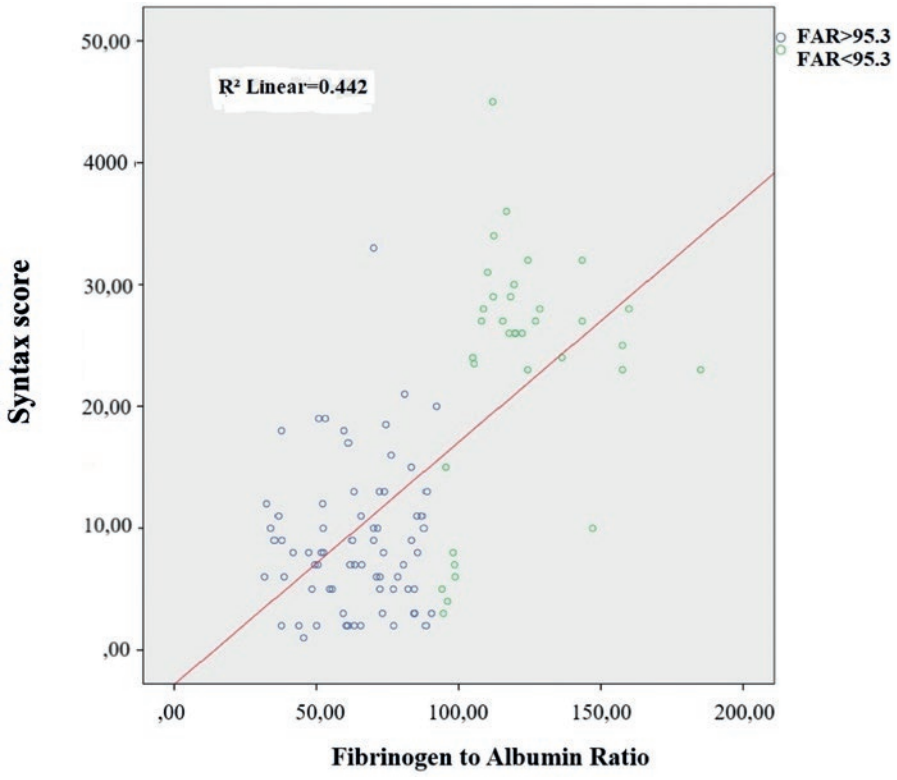


Table 2. Correlation of baseline characteristics and SYNTAX score

Variable	r	p-value
Age	0.253	0.010
LVEF	−0.232	0.017
LDL	0.721	0.001
Troponin I	0.268	0.009
Fibrinogen	0.423	0.001
Albumin	−0.241	0.012
FAR	0.522	0.001

LVEF: left ventricular ejection fraction; FAR: fibrinogen-to-albumin ratio; LDL-C: low-density lipoprotein cholesterol; SYNTAX: SYNergy between Percutaneous Coronary Intervention with TAXus.

speculated that fibrinogen and albumin levels should be evaluated together to clarify the pathophysiology of cardiovascular events[22]. Several studies have indicated that FAR may predict the severity and prognosis of atherosclerosis in patients with STEMI. Xiao et al. reported that elevated FAR is an independent predictor of poor prognosis in STEMI patients undergoing primary PCI[23]. Similarly, Zhao et al. showed that elevated FAR is significantly associated with no-reflow and short-term mortality in patients with STEMI undergoing primary PCI[24].

Even though the 6-month mortality rates of STEMI and NSTEMI are similar, patients with NSTEMI have a two-time- higher 4-year mortality rate than those with STEMI[25]. Therefore, risk stratification and appropriate management of patients with NSTEMI in both the acute phase and over long-term follow-up are crucial to prevent increased mortality and morbidity. Previous studies have reported that up to 80% of NSTEMI patients have multivessel disease, and the complexity of CAD in NSTEMI tends to be much greater than in STEMI[26,27]. Moreover, with higher SYNTAX scores, adverse cardiovascular outcomes occur more frequently and CAD becomes more complicated[28]. This study's use of SYNTAX score, an angiographic tool employed to grade CAD complexity was crucial since this measure reflects the complexity of coronary artery lesions, particularly in NSTEMI patients.

A small number of studies have investigated the relationship between FAR and SYNTAX score in patients with CAD. Karahan et al. demonstrated that a FAR of >87 was the cutoff point for predicting an intermediate/high SYNTAX score in patients with STEMI, with a sensitivity and specificity of 70%[9]. Celebi et al. determined that a FAR of >82 was the cutoff point for predicting an intermediate/high SYNTAX score in patients with stable CAD, with a sensitivity of 82% and a specificity of 88.3%[8]. However, to our knowledge, the association of FAR with SYNTAX score has not been adequately researched in NSTEMI. In our study, we found that a FAR of >95.3 was the cutoff point for predicting an intermediate/high SYNTAX score in patients with NSTEMI, with a sensitivity of 83% and a specificity of 86%. Our reported that FAR cutoff value was higher compared to what has been previously reported in the STEMI population by Celebi et al.,[8] and in the stable CAD population by Karahan et al.[9] A possible explanation for this observation is that NSTEMI represents a more complicated disease as a result of chronic inflammation. The association between FAR and SYNTAX score can help advance our understanding of the inflammatory process of atherosclerosis. Early recognition of CAD severity using FAR may help to stratify patients according to the most appropriate revascularization method and anti-ischemic/antiaggregant treatment regimen upon hospital admission.

This study has several limitations, including a relatively small number of patients and that it was conducted in a single center. In addition, FAR is a dynamic index and could differ from day to day. Therefore, analyses based on a single FAR measurement may not reflect the long-term relationship between FAR and SYNTAX score. Another limitation is the lack of data on cardiovascular outcomes, including re-intervention rates and mortality. Although we have used a multivariable model to adjust for potential confounders, there may remain unmeasured or residual confounding because of the limited sample size. Large-scale prospective studies are needed to clarify the relationship between FAR, SYNTAX score, pathophysiological mechanisms, and clinical outcomes.

In conclusion, FAR, an easily measurable laboratory index, is significantly associated with SYNTAX score for predicting the extent and severity of CAD in patients with NSTEMI. This association is independent of LDL and troponin I. A higher cutoff value of FAR was found to detect an intermediate/high SYNTAX score in patients with NSTEMI, indicating more

complex disease compared to STEMI and stable CAD. Further studies are needed to evaluate the differential and prognostic role of FAR on the severity and extent of CAD in patients with other forms of ACS such as unstable angina pectoris.

SUPPLEMENTARY DATA

Supplementary data are available at Revista de Investigación Clínica online (www.clinicalandtranslationalinvestigation.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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