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Predictive value of the combination of age, creatinine, and ejection fraction (ACEF) score and Fibrinogen in patients with acute coronary syndromes undergoing percutaneous coronary intervention

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Abstract

Background: The purpose of this study was to explore whether the FIB can improve the predictive value of ACEF in patients with ACS.

Methods: A total of 290 ACS patients were enrolled in this study. The clinical characteristics and MACE was recorded.

Results: Multivariate logistic regression analysis revealed that the level of FIB (Odds Ratio =7.798, 95%CI,3.44-17.676, P<0.001) and SYNTAX score (Odds Ratio =1.034, 95%CI,1.001-1.069, P=0.041) emerged as independent predictors for MACE. On the

basis of the regression coefficient of FIB, the ACEF-FIB was developed. The area under the ROC of the ACEF-FIB scoring system in predicting MACE after PCI was 0.753 (95%CI 0.688-0.817, P<0.001), higher than the ACEF score, SYNTAX score and Grace score (0.627, 0.637 and 0.570 respectively).

Conclusion: Compared with other risk scores, the ACEF-FIB also had better discrimination ability based on ROC curve analysis, net reclassification improvement and integrated discrimination improvement.

Keywords: Acute coronary syndrome; ACEF score; Fibrinogen; Percutaneous coronary intervention; Major adverse cardiovascular events

Introduction

Acute coronary syndrome (ACS) is one of the most critical cardiovascular diseases and the main contributor leading to the death of patients with cardiovascular disease. ACS includes ST segment elevation myocardial infarction (STEMI) with non-ST segment elevation myocardial infarction (STEMI) and unstable angina (UA). Although the proportion of ACS patients receiving percutaneous coronary intervention (PCI) is increasing, the occurrence of adverse cardiovascular events are inevitable[1]. A previous study reported that the incidence of major adverse cardiovascular events (MACE) in ACS patients treated with PCI was approximately 10% within 1 year [2]. Thus, early risk stratification for ACS patients after PCI has important clinical significance to reduce the occurrence of adverse events after PCI.

The ACEF score is composed of three factors: age, serum creatinine and ejection fraction. And This risk score, used to predict the operative mortality of patients

undergoing coronary artery bypass grafting(CABG), was first developed and validated by Ranucci et al. in 2009 [3].The advantage of this simplified risk model is to avoid the “overfitting” problem of many independent variables. Wykrzykowska et al. evaluated the ACEF score of the patients receiving PCI in the LEADERS trial, indicating that ACEF score may be a simple method for predicting the risk of myocardial infarction and mortality in patients treated with PCI[4]. However, considering the results from previous study that the risk score combined with clinical variables can provide more reliable predictive accuracy for clinical outcomes of patients after PCI[5].

Fibrinogen (FIB) is an important component of the clotting pathway, which binds to the receptors on the platelet membrane to form acute coronary thrombosis[6]. Peng et al. reported that plasma fibrinogen level at admission was an independent predictor of cardiac mortality in patients with coronary artery disease (CAD)[7]. Ang et al. and Mahmud et al. showed that, as a reactant in the acute phase of inflammation, elevated FIB baseline level was associated with long-term MACE after PCI[8,9]. In conclusion, the purpose of our reaserch was to determine whether the ACEF score combined with FIB can improve the prognostic value of patients with ACS after PCI.

Methods

Study populations and study design

All patients were enrolled in the Heart Center of Beijing Chaoyang Hospital, Capital Medical University. A total of 290 patients who underwent angiography for ACS were recruited between May 2019 and December 2019. The diagnostic criteria

for ACS were clinical symptoms, elevated cardiac biomarkers (troponin-I or creatine kinase MB), typical electrocardiogram changes and coronary angiography. The exclusion criteria were as follows: 1) patient age < 18 years old; 2) patients with a history of coronary artery bypass grafting or received hybrid coronary-revascularization during this hospitalization; 3) patients have contraindications or are not suitable for PCI; 4) incomplete data to calculate ACEF score.

The blood samples were collected from each patient under fasting state in the first morning after admission. All laboratory indices, including FIB, leukocytes, platelets, troponin I, creatine kinase-MB (CK-MB), type b natriuretic peptide (BNP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, creatinine, high-density lipoprotein cholesterol(HDL-c), low-density lipoprotein cholesterol (LDL-c) and triglyceride were determined at the clinical laboratory center. All patients were examined by echocardiography. All the subjects underwent coronary angiography and optimized treatments. The baseline and clinical characteristics were gathered from the medical record systems.

The ACEF score was calculated according to the following formula: age/left ventricular ejection fraction+1 (if creatinine was > 2.0 mg/dL). The SYNTAX score is Calculated from coronary angiography and can be a useful tool for assessing the severity of coronary artery lesions(http://syntaxscore.com/). The GRACE risk score is a practical tool for risk assessment tool for in-hospitals outcomes (http://www.outcomes-umassmed.org/GRACE/).

Statistical analysis

Categorical variables were given as frequencies (percentage) and Continuous variables were as mean ± standard deviation or median and interquartile range (25, 75 percentiles). Categorical variables were performed using chi-square test or Fisher's exact test. Continuous variables were tested for the differences with one-way ANOVA or the Kruskal-Wallis H test. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test.

All patients were systematically followed up by medical record or telephone call. The primary clinical endpoint was the occurrence of MACE, including all-cause death and rehospitalization for cardiovascular diseases. All relevant clinical factors for MACE were included into the logistic regression analysis. We aimed to assess whether ACEF score combined FIB increase prognostic value. Receiver operating characteristic (ROC) curves were constructed to assess the prognostic value of the risk scores to predict MACE. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to compare the ability of the new risk score with other scores to reclassify the risk of MACE. Cumulative event rates were calculated based on Kaplan-Meier survival curves and compared by log-rank test. For all tests, $P<0.05$ was considered statistically significant. All the statistical analyses were performed using IBM-SPSS version 24.0 (IBM, Armonk, NY, USA) and R. (version 4.03).

Results

Baseline characteristics

Patients were divided according to the tertile level of ACEF score: Low ACEF group (ACEF≤0.899， N=97), mid ACEF group (0.899<ACEF<1.130, N=100) and high ACEF group (ACEF≥1.130，N=93). The overall patient characteristics are shown in Table1. Regarding demographic characteristics, the age, gender proportion, body mass index, medical history of myocardial infarction, diabetes mellitus, arrhythmia and stroke among three groups reach statistical significance. In the laboratory measurement, people in the higher ACEF score groups were characterized by higher level of troponin I, CK-MB, BNP, CRP, ESR, fast glucose, D-dimer and FIB. Conversely, they were associated with lower level of hemoglobin, platelets and serum albumin. In the evaluation of cardiac function using echography, patients with higher ACEF had lower left ventricular ejection fraction (LVEF). Meanwhile, the patients with higher ACEF score also have higher GRACE score and SYNTAX score.

Table 1. Basic clinical, laboratory and MACE in ACS Patients according to ACEF score groups.

	low group (N=97)	mid group (N=100)	high group (N=93)	P
Demography				
Age, years	51（49,52）	64（62,65）	71（69,73）	<0.001
Male, n,	84（86.6%）	67（67.0%）	69（74.2%）	0.005
BMI, kg/m2	26.6±3.4	25.5±2.9	25.2±3.4	0.048
Heart rate, bpm	74±12	72±13	75±13	0.167
Systolic blood pressure, mmHg	131±17	130±17	129±22	0.427
Diastolic blood pressure, mmHg	78±12	74±11	72±11	0.001
Previous MI, n, %	13（13.4%）	15（15.0%）	32（34.4%）	<0.001
Previous PCI, n, %	23（23.7%）	32（32.0%）	33（35.5%）	0.191
Current smoker, n, %	58（59.8%）	36（36.0%）	25（26.9%）	<0.001
Hypertension, n, %	61（62.9%）	56（56.0%）	60（64.5%）	0.432
Diabetes mellitus,	32（33.0%）	37（37.0%）	46（50.0%）	0.045

n, %				
Previous arrhythmia, n, %	5（5.2%）	6（6.0%）	21（22.6%）	<0.001
Previous stroke, n, %	11（11.3%）	5（5.0%）	16（17.2%）	0.026
Laboratory findings				
WBC, ×109/L	8.9±3.1	7.7±2.5	8.6±3.3	0.024
Hemoglobin, g/L	142.2±14.3	133.8±15.2	131.0±18.9	<0.001
Platelets, ×109/L	218(193,268)	202(175,240)	202（164,244）	0.003
Serum albumin, g/L	41.6±4.7	40.4±5.0	39.0±6.4	<0.001
Total cholesterol, mmol/L	4.3±1.1	4.0±0.9	4.2±1.3	0.093
HDL, mmol/L	0.96(0.78,1.10)	0.96(0.82,1.12)	0.90(0.77,1.03)	0.177
LDL, mmol/L	2.7±1.0	2.3±0.8	2.6±1.2	0.082
Triglycerides, mmol/L	1.8（1.2,2.3）	1.3（1.0,1.9）	1.3（0.9,1.9）	0.002
Troponin-I, ng/mL	0.23(0,.00,19.15)	0.10(0.00,14.63)	4.40(0.03,41.22)	0.004
CK-MB, ng/mL	2.0（0.7,31.8）	1.7（0.8,22.9）	6.6（1.5,76.4）	0.002
BNP, pg/mL	36.0（18.0,95.0）	58.0（26.0,108.3）	258.0（100.0,556.0）	<0.001
ESR, mm/h	5.0（2.0,11.5）	6.5（2.0,15.0）	11.0（5.0,21.0）	0.001
C-reactive protein, mg/L	2.4（0.9,5.9）	3.2（1.0,9.8）	4.4（1.7,23.7）	0.024
Serum creatinine, μmol/L	67.1（60.8,74.8）	64.1（56.4,76.2）	77.4（64.6,99.3）	<0.001
BUN, mmol/L	4.9（4.3,6.1）	5.3（4.3,6.4）	6.4（5.2,8.3）	<0.001
K+, mmol/L	3.9（3.7,4.1）	3.9（3.7,4.1）	4.0（3.8,4.3）	0.021
sTSH, uIU/ml	1.2（0.7,2.2）	1.3（0.6,2.1）	1.4（0.7,2.4）	0.812
D-dimier, mg/L	0.19（0.17,0.26）	0.23（0.19,0.50）	0.44（0.22,0.81）	<0.001
Fibrinogen, mg/dL	261.6（227.6,306.4）	276.2（230.7,312.5）	312.5（258.9,386.3）	<0.001
SYNTAX score	20.4±8.7	19.9±9.3	27.1±9.3	<0.001
GRACE score	117.7±22.0	139.2±22.5	170±27.4	<0.001
Echocardiography				
Left atrial diameter, mm	35.5±4.5	36.4±4.2	38.7±4.5	<0.001
LVEDD, mm	47.3±3.5	47.1±4.1	49.8±6.7	0.004
LVESD, mm	28.9±3.5	29.9±4.7	35.0±7.7	<0.001
LVEF, %	67.6±5.8	63.5±6.8	52.0±11.5	<0.001
MACE	15(15.5%)	19(19.0%)	28(30.1%)	0.037

MACE, major adverse cardiovascular events; BMI, body mass index; WBC, White blood count; HDL, high-density lipoprotein; CK-MB, creatine kinase MB; LDL, low-density lipoprotein; BNP, brain natriuretic peptide; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; sTSH, thyroid stimulating hormone; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection.

Follow up

During a median follow-up of 14 (12, 16) months, the rates of MACE were 15.5% of low group, 19.0% of mid group and 30.1% of high group (P=0.037). ROC was utilized to derive the cut-off value of the FIB for predicting MACE. The cut-off point of 291.1mg/dl for FIB had a sensitivity of 87.1% and a specificity of 58.3% in predicting MACE. The patients were divided into two groups according to the cut-off point of FIB (lower group, FIB≤291.1mg/dl; and higher group, FIB > 291.1mg/dl).

Regression analysis

Table 2 shows the univariate and multivariate logistic regression analyses of MACE for all patients. In univariate analysis, several potential risk factors were identified, including FIB, BNP, creatinine, left atrial diameter (LAD), left ventricular end systolic diameter (LVESD), LVEF, SYNTAX score, diabetes and previous arrhythmia (P<0.05). However, after multivariate adjustment, only the level of FIB (Odds Ratio =7.798, 95%CI,3.44-17.676, P<0.001) and SYNTAX score (Odds Ratio =1.034, 95%CI,1.001-1.069, P=0.041) emerged as independent predictors for MACE.

Table 2. Logistic regression analysis of clinical parameters for MACE prediction.

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P	OR (95%CI)	P
Male	0.39 (0.15,0.95)	0.038		
Diabetes mellitus	2.02 (1.08,3.77)	0.028		
Previous arrhythmia	2.55 (1.12,5.80)	0.025		
BNP	1.00 (1.00,1.10)	0.021		
Serum creatinine	1.00 (1.01,1.20)	0.031		
Fibrinogen>291.1	9.11 (4.41,20.03)	<0.001	7.80 (3.44, 17.68)	<0.001
SYNTAX score	1.05 (1.02,1.08)	0.002	1.03 (1.00,1.07)	0.041
LAD	1.09 (1.02,1.16)	0.014		
LVESD	1.05 (1,00,1.09)	0.049		

LVEF	0.95 (0.93,0.98)	0.001

OR, odds ratio; CI, confidence interval; BNP, brain natriuretic peptide; LAD, left atrial diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction.

The new model

On the basis of the regression coefficient of FIB, the ACEF-FIB was developed. The score was derived by attributing integer numbers to the variables retained in the multivariable model. We used ROC curves to estimate the prognostic value of ACEF-FIB and other risk scores. The area under the ROC curve of the ACEF-FIB scoring system in predicting MACE after PCI was 0.753 (95%CI 0.688-0.817, P<0.001), higher than the ACEF score, SYNTAX score and Grace score (0.627, 0.637 and 0.570 respectively) (Fig 1). Compared with other risk scores, the ACEF-FIB also had better discrimination ability based on NRI and IDI (Table 3).

Table 3. Reclassification of MACE by ACEF-FIB versus other scores.

	NRI or IDI [95% confidence interval]	P value
ACEF-FIB score versus ACEF score		
NRI	0.788[0.554,1.023]	<0.001
IDI	0.101[0.066,0.136]	<0.001
ACEF-FIB score versus SYNTAX score		
NRI	0.735[0.487,0.983]	<0.001
IDI	0.097[0.057,0.137]	<0.001
ACEF-FIB score versus GRACE score		
NRI	0.891[0.681,1.102]	<0.001
IDI	0.134[0.099,0.168]	<0.001

MACE, major adverse cardiovascular event; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

Kaplan-Meier estimates of MACE according to the ACEF score are shown in Fig 2. And best cut-off for ACEF-FIB for MACE was 1.87, with a sensitivity of 88.7% and a specificity of 56.6%. The new risk score was dichotomized based on a cutoff

determined by the Youden index: lower group < 1.87 and higher group ≥1.87. Kaplan-Meier survival analysis showed that patients of lower group had an increased event-free survival rate compared with higher group and the log-rank was P<0.001(Fig 2).

Discussion

This study demonstrates that the ACEF score combined with FIB predicts MACE in patients presenting with ACS after PCI. When FIB and ACEF are jointly used to evaluate MACE, the AUC of the combined prognostic model increased significantly. In addition, the integration of FIB significantly improved the discriminatory capacity, and reclassification of ACEF scoring. Therefore, this new score may provide a novel tool for clinical practice to stratify the risk of ACS patients.

With the rapid expansion of PCI indications and the increase of clinical complexity of patients[1], risk assessment of the overall incidence of MACE after these procedures, especially mortality, has become a very important aspect of daily clinical decision making. Some of risk scores, such as SYNTAX score and GRACE score, have been widely used in daily clinical practice to stratify the risk of patients with ACS[10,11]. However, the SYNTAX score is based on anatomic information and only indirectly combined with clinical characteristics, as older patients with renal insufficiency generally have more calcified vessels and a wider range of diseases[4,12]. Besides, GRACE score contains too many variables, resulting in inaccuracy and the overfitting associated with them and the lack of some important predictors of mortality, such as the LVEF[13]. The study by Wu et al. showed that LVEF after acute

STEMI is a reliable and most commonly used functional marker of severity of potential myocardial damage[13].

ACEF score consists of three risk factors, all of which are objective measurement variables[3]. These risk factors represent three important prognostic indicators, namely age, renal function, and cardiac function, which accurately reflect the burden of comorbidities and cardiovascular disease in ACS patients[13-15]. The patients receiving PCI treatment in the LEADERS trial demonstrated that a significant correlation between the increased ACEF score and an elevated risk of adverse events after coronary revascularization[4]. The predictive power of the ACEF score has been characterized in high-risk patients, such as those with chronic total occlusions, left main artery disease, and heavily calcified lesions [16-18]. Our results were consistent with previous studies. We found that patients with a higher ACEF score were more likely to develop MACE, and the elevated ACEF scores were significantly associated with the poor prognosis in all patients.

Fibrinogen is a serum glycoprotein with dimeric molecular structure synthesized by the liver and is the first clotting factor.[19]Inflammation is a common precursor of atherosclerosis[20] and FIB plays an important role in inflammation and tissue repair[21]. Previous studies have confirmed that FIB could enhance systemic or local vascular inflammation, secondary vascular endothelial injury, and further promote the accumulation and oxidation of subendothelial low-density lipoprotein, and eventually promote the proliferation and migration of vascular smooth muscle cells[21]. These reactions ultimately led to the formation and vulnerability of atherosclerotic

plaques[24]. In addition to being an acute phase reactant of inflammation, FIB is converted into insoluble fibrin by thrombin and expose to polymerization sites that promote thrombus formation during activation of the coagulation cascade, platelet aggregation, and thrombosis[25].In addition, blood viscosity and peripheral resistance have been reported to increase with plasma FIB levels, resulting in disrupted blood oxygen transport, slow blood flow, and aggregation of red blood cell, thereby increasing the risk of thrombosis[26]. Verdoia et al. found that high fibrinogen level was an independent predictor of the presence and severity of CAD[27]. In the ERFC study, Kaptoge et al. found that evaluating FIB concentrations was associated with a significant improvement in the prediction of cardiovascular advent events[28].

In our study, FIB levels were higher in the high ACEF group than in the low ACEF group. It is not surprising that FIB predicted worse clinical outcomes in our ACS cohort. And the predictive performance of the ACEF-FIB score was similar to that of the SYNTAX score. Moreover, the new ACEF-FIB model does not violate its original simple principles. In clinical practice, it may be reasonable to use the ACEF-FIB score as a reliable and updated tool for risk stratification after PCI. But far from replacing the original ACEF score or claiming to be superior to the other existing scores, the new model needs to be validated by mandatory external verification.

Limitation

This study had several limitations. First, this study was a single center study and thus had a low level of evidence. Second, the sample size of this study was small,

which need further validation in a larger cohort of patients. Finally, the follow-up period is short and needs to be further extended in the future.

Conclusion

This study supports that the ACEF score along with FIB may serve as a convenient effective to predict the prognosis and to improve risk stratification in ACS patients after PCI.

Declarations

Consent for publication: Not applicable.

Ethics approval and consent to participate: The study protocol was in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Beijing Chao-Yang Hospital of Capital Medical University. And all patients signed the informed consent.

Competing interests: The authors declare no conflicts of interest.

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Table 1. Basic clinical, laboratory and MACE in ACS Patients according to ACEF score groups.

Table 2. Logistic regression analysis of clinical parameters for MACE prediction.

Table 3. Reclassification of MACE by ACEF-FIB versus other scores.

Figure captions and legends

Figure 1. Receiver operating characteristic curve analysis for risk scores in predicting MACE.

Figure 2. Kaplan-Meier curves in patients with ACS for MACE during Follow-up.