

Predictive value of the combination of age, creatinine, and ejection fraction score and diabetes in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention

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Background: This study investigated whether the age, creatinine, and ejection fraction (ACEF) score [age (years) /ejection fraction (%) +1 (if creatinine>176μmol/L)] could predict 1-year outcomes following ST-segment elevation myocardial infarction after percutaneous coronary intervention, and whether accuracy could be improved by establishing novel ACEF-derived risk models.

Methods: A total of 1146 patients were included. The study endpoint was 1-year major adverse cardio-cerebrovascular events, including all-cause death, nonfatal myocardial infarction, unplanned revascularization, and nonfatal stroke. Accuracy was defined with area under the curve by receiver-operating characteristic curve analysis.

Results: The incidence of 1-year major adverse cardio-cerebrovascular event increased with the rising age, creatinine, and ejection fraction score tertiles (4.8%, 8.4%, and 15.2%, $P < 0.001$ for all). Higher ACEF score was significantly associated with an increased risk of the endpoint in overall (odds ratio = 3.75, 95% confidence interval, 2.44–5.77, $P < 0.001$) and in subgroups (all $P < 0.05$). The accuracy of the ACEF score was equivalent to the other complex risk scores. The combination of ACEF, and diabetes (ACEF-diabetes score) yielded a superior discriminatory ability than the original ACEF score (increase in C-statistic from 0.67 to 0.71, $P = 0.048$;

continuous net reclassification improvement = 51.9%, 95% confidence interval, 33.4–70.5%, $P < 0.001$; integrated discrimination improvement = 0.020, 95% confidence interval, 0.011–0.030, $P < 0.001$).

Conclusions: The simplified ACEF score performed well in predicting 1-year outcomes in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. The novel ACEF-diabetes score provided a better predictive value and thus may help stratify high-risk patients and potentially facilitate decision making. *Coron Artery Dis* 31: 109–117 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Acute coronary syndrome (ACS) remains a leading contributor to high mortality and morbidity worldwide. Patients with ST-segment elevation myocardial infarction (STEMI) are particularly at high risk to develop future major cardiac and cerebrovascular events (MACCE) even in the setting of optimal medical therapy and successful reperfusion after percutaneous

coronary intervention (PCI) [1–3]. Therefore, accurate and early risk stratification are of crucial necessity and profound implication in the management of STEMI. Till now, many risk scores have been introduced and are currently in use. Of these, the age, creatinine, and ejection fraction (ACEF) score limited to 3 risk factors is a simple and extremely user-friendly tool. It was initially proposed and validated to predict mortality risk in patients who underwent elective cardiac surgeries [4,5] and was later proved to be of vital predictive value for ACS [6]. Following its good accuracy and clinical applicability, the European Society of Cardiology guideline on myocardial revascularization has included the ACEF score for risk stratification (Class IIB) in 2010[7] and further confirmed its utility in patients undergoing PCI in the 2014[8] and 2018 update [9]. However, data on the

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prognostic power of the ACEF score in STEMI patients treated with PCI are scarce. In the present study, we investigated the predictive performance of the ACEF score for 1-year MACCE in STEMI patients after PCI as compared with the other recommended risk scores. Moreover, we established a novel ACEF-derived risk model and further evaluated its incremental prognostic value beyond the original ACEF score.

Methods

Study population

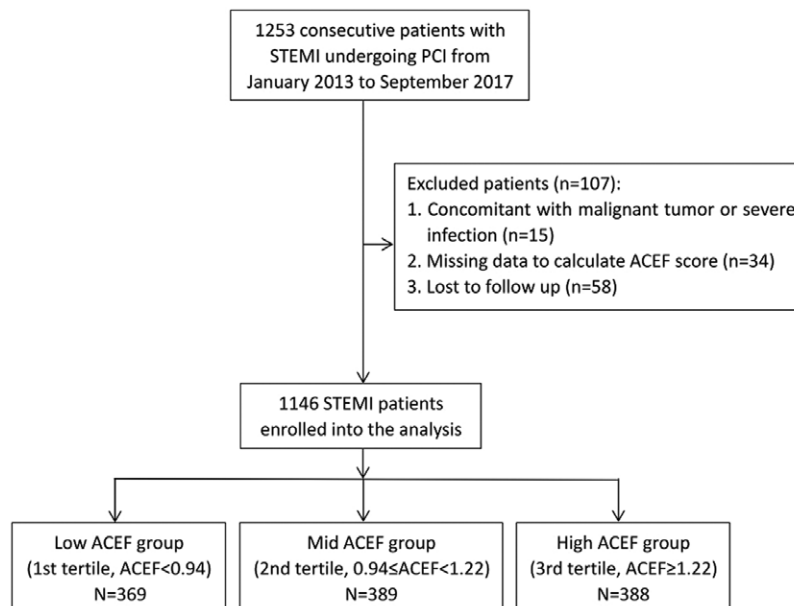
A total of 1253 consecutive patients with STEMI undergoing PCI were admitted to Beijing Friendship Hospital between January 2013 and September 2017. Exclusion criteria included (1) life expectancy less than 1 year due to severe concomitant non-cardiac diseases, such as tumor or infection; (2) inability to give written informed consent; (3) incomplete data to calculate ACEF score; and (4) lost to follow-up. Finally, 1146 patients were enrolled into the analysis (flowchart of the study was shown in Fig. 1). All patients received evidence-based optimal therapy of medication and coronary revascularization according to current guidelines and recommendations [1,2]. All interventional procedures and strategies such as balloon angioplasty, the second-generation drug-eluting stent implantation, aspiration thrombectomy, and the usage of intra-aortic balloon pump were performed at the expert operator's discretion using standard techniques. Of note, if patients failed to receive primary PCI in 12 hours after the onset of symptom, delayed PCI was initiated subsequently during hospitalization. Medications like aspirin,

clopidogrel or ticagrelor, low-molecular-weight heparin, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and β -blocker were routinely prescribed in all patients and were continued after discharge unless there were contraindications. After stent implantation, all patients were advised to take dual anti-platelet therapy with aspirin and clopidogrel or ticagrelor for at least 12 months. Patients were regularly followed up at clinics or by telephone contact. All adverse events of interest within 1 year after PCI were checked with telephone questionnaires or medical documents by a team of independent research physicians blinded with the clinical treatment. This study was approved by the Ethics Committee of Beijing Friendship Hospital and was conducted in accordance with the Declaration of Helsinki.

Data collection

The data were from Cardiovascular Center Beijing Friendship Hospital Database (CBD BANK) where the baseline demographic, clinical, laboratory, and angiographic characteristics were collected from in-person interviews and medical records. The left ventricular ejection fraction (LVEF) was calculated by echocardiography using the standard biplane Simpson method. In case of multiple LVEF values available, the lowest LVEF value was considered. Fasting blood glucose and blood lipid index, such as total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol, were tested using standardized biochemical assay. Glycated hemoglobin (HbA1c) was

Fig. 1



Flowchart of the study. ACEF, age, creatinine, and ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

measured using the liquid chromatography analyzer. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Creatinine (CKD-EPI_{Cr}) equation. Peak values of N-terminal B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (TnI) were recorded. The ACEF score was calculated as follows: age (years)/LVEF (%) + 1 (if creatinine > 176 μmol/L) [4]. As previously described, the global registry of acute coronary event (GRACE) score [10] and the thrombolysis in myocardial infarction (TIMI) score [11] were calculated since admission. Coronary angiogram was analyzed by two expert cardiologists, and the Gensini score system [12] was used to evaluate the severity and complexity of coronary artery lesion. Discrepancies were solved by consensus. Detailed definition and components of the above risk scores were shown in Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/MCA/A282>.

Outcomes and study definitions

The follow-up time of the present study was 1 year after the index procedure. The study endpoint was a composite of MACCE, including all-cause death, nonfatal myocardial infarction (MI), unplanned revascularization, and nonfatal stroke. The study endpoint was assessed by time to first event. Reinfarction was diagnosed according to the updated fourth universal definition of MI [13]. Unplanned revascularization was defined as revascularization for recurrent myocardial ischemia due to coronary stenosis or occlusion, including PCI or coronary artery bypass graft, and it was not identified as a staged procedure to be performed within 60 days since the index procedure [14]. Stroke was defined as an episode of neurological dysfunction persisting > 24 hour or until death due to disabling vascular brain injury caused by cerebral ischemia or hemorrhage [14].

In accordance with the 2018 revised American Diabetes Association criteria [15], diabetes was defined as having a history of diabetes or having newly diagnosed diabetes with fasting plasma glucose \geq 7.0 mmol/L, HbA1c \geq 6.5%, or 2-hour plasma glucose \geq 11.1 mmol/L in the oral glucose tolerance test. Dyslipidemia was defined as LDL-C concentrations \geq 3.4 mmol/L (130 mg/dl), high-density lipoprotein cholesterol concentrations < 1.0 mmol/L (40 mg/dl), triglyceride concentrations \geq 1.7 mmol/L (150 mg/dl), or patients who were taking lipid-lowering medication [16].

Statistical analysis

Continuous variables were expressed as mean \pm SD or median with interquartile range in case of skewed distribution. Categorical variables were presented as numbers with corresponding percentages. Differences were analyzed using Mann-Whitney *U* test for continuous variables and Pearson's χ^2 test for categorical variables.

Logistic regression analysis was used to identify potential risk factors and risk scores for 1-year MACCE. Crude

and adjusted odds ratio (OR) with 95% confidence interval (CI) were calculated. Multivariate adjustment was not performed when comparing outcomes in groups with ACEF score tertiles due to the limited number of events in each group (18 events in first tertile, 33 in second tertile, and 59 in third tertile). The subgroup analysis was used to determine whether the ACEF score was still associated with the risk of subsequent MACCE in specific subsets of patients. The clinically relevant covariates were tested for their possible prognostic effects, including age, sex, body mass index (BMI), hypertension, diabetes, dyslipidemia, previous MI, prior PCI, previous stroke, LVEF, log₁₀(NT-proBNP), peak TnI, and eGFR. Each variable with a significant *P*-value on univariate analysis was further enrolled into the multivariate model to ascertain its independent contribution to the outcomes. The ACEF-diabetes model was generated by adding diabetes into the original ACEF score based on multivariate logistic regression.

Predictive values of the risk scores were evaluated for their discrimination (or accuracy), calibration, and reclassification. Discrimination was defined with area under the curve (AUC) by receiver-operating characteristic curve analysis. The AUC values were interpreted as follows: negligible (\leq 0.55), small (0.56–0.63), moderate (0.64–0.70), and strong (\geq 0.71) [17]. Differences of AUC values were appraised using the DeLong's test [18] with MedCalc V.11.4 (MedCalc Inc., Ostend, Belgium). Calibration was assessed by the Hosmer-Lemeshow goodness of fit test, in which Chi-square statistics were calculated and *P* > 0.05 indicated the calibration was significant. Reclassification described how well a risk model could correctly reclassify events by use of continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) with the PredictABEL package in R V.3.5.1. The IDI was defined as the increase in discrimination slope that combined average change in probabilities among events and among nonevents [19]. The continuous NRI was a non-parametric analogue of the IDI and was equal to twice the difference between fractions of correct and incorrect movements of mean predicted probabilities among events and nonevents [20].

All tests were 2-tailed and *P* < 0.05 was considered statistically significant except for the Hosmer-Lemeshow test. Unless stated otherwise, most of the analyses were performed with statistical package SPSS V.20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

Patients were divided according to the tertile level of ACEF score: Low ACEF group (ACEF < 0.94, *n* = 369), mid ACEF group (0.94 \leq ACEF < 1.22, *n* = 389), and high ACEF group (ACEF \geq 1.22, *n* = 388). As shown in Table 1,

patients with increased ACEF score were more likely to be female and nonsmokers. They had lower BMI, lower prevalence of dyslipidemia, and higher frequent presence of hypertension, diabetes, and previous stroke. As expected, patients with elevated ACEF score tended to have higher GRACE score and TIMI score, they also had higher Killip class and higher levels of fasting blood glucose, HbA1c, NT-proBNP, and peak TnI but lower values of triglyceride, LDL-C and eGFR. Of note, the prevalence of multivessel disease, the Gensini score and the usage of intra-aortic balloon pump were all significantly higher in patients with higher ACEF score. In this regard, the ACEF score approximately mirrors the general cardiovascular risk profile in terms of the burden of comorbidities and coronary lesion.

Relationship between the age, creatinine, and ejection fraction score and 1-year major cardiac and cerebrovascular event

Patients with higher tertile level of ACEF score had more incidence of MACCE within 1 year post-PCI (4.8%, 8.4%, and 15.2%, respectively; $P < 0.001$ for all; Table 2). The unadjusted risk for MACCE also increased in parallel with the ACEF score tertiles (the first tertile as reference; second tertile: OR = 1.80, 95% CI, 0.99–3.27, $P = 0.050$; third tertile: OR = 3.49, 95% CI, 2.02–6.05, $P < 0.001$). The univariate logistic regression analysis (Fig. 2) indicated that a higher ACEF score was significantly associated with an increased risk for 1-year MACCE in all STEMI patients after PCI (OR = 3.75, 95% CI, 2.44–5.77, $P < 0.001$). Furthermore,

Table 1 Baseline characteristics and 1-year outcomes of three groups

	Low ACEF score (n=369)	Mid ACEF score (n=389)	High ACEF score (n=388)	P-value
Male, n (%)	321 (86.9%)	313 (80.4%)	256 (65.9%)	< 0.001
Age, y	50.8 ± 7.8	63.0 ± 8.3	72.4 ± 9.6	< 0.001
BMI, kg/m ²	26.0 ± 3.3	25.5 ± 3.3	24.8 ± 3.6	< 0.001
Cardiovascular risk factors				
Hypertension	197 (53.3%)	212 (54.4%)	257 (66.2%)	< 0.001
Diabetes	138 (37.3%)	170 (43.7%)	194 (50.0%)	0.002
Dyslipidemia	171 (46.3%)	178 (45.7%)	140 (36.0%)	0.005
Previous MI	26 (7.0%)	36 (9.2%)	36 (8.2%)	0.451
Prior PCI	31 (8.4%)	42 (10.7%)	39 (10.0%)	0.525
Previous stroke	23 (6.2%)	44 (11.3%)	78 (20.1%)	< 0.001
Smoking	287 (77.7%)	259 (66.5%)	196 (50.5%)	< 0.001
Killip class ≥ 2, n (%)	25 (6.7%)	30 (7.7%)	80 (20.6%)	< 0.001
LVEF (%)	63.2 ± 6.1	58.9 ± 7.1	49.3 ± 8.8	< 0.001
Clinical risk scores				
ACEF score	0.80 ± 1.10	1.07 ± 0.07	1.55 ± 0.34	< 0.001
TIMI score	2.28 ± 1.24	3.27 ± 1.68	5.16 ± 1.92	< 0.001
GRACE score	129.07 ± 20.50	150.92 ± 21.14	174.28 ± 29.51	< 0.001
Laboratory assessment				
FBG, mmol/L	6.80 ± 2.80	7.07 ± 2.96	7.28 ± 3.06	0.005
HbA1c, %	6.38 ± 1.56	6.46 ± 1.45	6.48 ± 1.42	0.004
TC, mmol/L	4.69 ± 1.07	4.48 ± 1.04	4.41 ± 1.04	0.457
TG, mmol/L	1.65 (1.24, 2.50)	1.41 (1.05, 1.92)	1.26 (0.95, 1.69)	< 0.001
LDL-C, mmol/L	2.75 ± 0.77	2.61 ± 0.79	2.56 ± 0.77	0.001
HDL-C, mmol/L	1.03 ± 0.22	1.06 ± 0.25	1.07 ± 0.26	0.123
eGFR, mL/(min×1.73 m ²)	92.83 ± 16.37	83.16 ± 16.76	69.72 ± 2.26	< 0.001
NT-proBNP, pg/mL	738 (362, 1447)	1827 (796, 3013)	4493 (2056, 9735)	< 0.001
Peak TnI, ng/mL	15.84 ± 16.01	18.78 ± 17.86	22.47 ± 19.31	< 0.001
Interventional characteristics				
Primary PCI	223 (60.4%)	247 (63.5%)	224 (57.7%)	0.259
No. of diseased vessel				< 0.001
Single vessel	47 (12.7%)	24 (6.1%)	18 (4.6%)	
Two vessels	74 (20.0%)	65 (16.7%)	40 (10.3%)	
Three vessels	248 (67.2%)	300 (77.1%)	330 (85.0%)	
Culprit artery				< 0.001
LM artery	3 (0.8%)	6 (1.5%)	12 (3.1%)	
LAD artery	162 (44.0%)	177 (45.5%)	226 (58.2%)	
LCX artery	57 (15.4%)	58 (15.0%)	39 (10.1%)	
RCA artery	147 (39.8%)	148 (38.0%)	111 (28.6%)	
Gensini score	52.48 ± 27.51	61.08 ± 32.21	70.60 ± 33.43	< 0.001
No. of stents	1.53 ± 0.87	1.65 ± 1.03	1.55 ± 0.94	0.386
Usage of IABP	3 (0.8%)	11 (2.8%)	22 (5.6%)	0.001
Thrombus aspiration	95 (25.7%)	105 (26.9%)	84 (21.6%)	0.197
1-year outcomes				
MACCE	18 (4.8%)	33 (8.4%)	59 (15.2%)	< 0.001
All-cause death	3 (0.8%)	9 (2.3%)	35 (9.0%)	< 0.001
Nonfatal MI	5 (1.3%)	7 (1.7%)	13 (3.3%)	0.140
Revascularization	13 (3.5%)	19 (4.8%)	18 (4.6%)	0.622
Nonfatal stroke	1 (0.2%)	3 (0.7%)	5 (1.2%)	0.115

Low ACEF group: ACEF < 0.94, mid ACEF group: 0.94 ≤ ACEF < 1.22, high ACEF group: ACEF ≥ 1.22. primary PCI: time from symptom onset to PCI less than 12 h. ACEF, age, creatinine, and ejection fraction; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LM, left main artery; LVEF, left ventricular ejection fraction; MACCE, major cardiac and cerebrovascular event; MI, myocardial infarction; NT-proBNP, N-terminal B-type natriuretic peptide; PCI, percutaneous coronary intervention; RCA, right coronary artery; TC, total cholesterol; TG, triglyceride; TnI, Troponin I.

elevated ACEF score remained a strong predictor of poor prognosis in subgroups of patients stratified by the age, sex, hypertension, diabetes, dyslipidemia, smoking, timing of PCI, and the Gensini score (all $P < 0.05$).

Logistic regression analysis of risk factors for 1-year major cardiac and cerebrovascular event

At univariate analysis (Table 3), several potential risk factors were identified, including age, BMI, diabetes, previous stroke, LVEF, Ln NT-proBNP, and eGFR ($P < 0.05$). However, after multivariate adjustment, only the age (OR = 1.02; 95% CI, 1.00–1.04, $P = 0.040$), diabetes (OR = 2.64; 95% CI, 1.67–4.16, $P < 0.001$), and LVEF (OR = 0.06; 95% CI, 0.01–0.80, $P = 0.033$) emerged as independent predictors for 1-year MACCE.

Table 2 Association between the tertile level of ACEF score and 1-year MACCE

Groups	1-year MACCE incidence		Univariate logistic analysis	
	N (%)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Low ACEF	18 (4.8%)	...	1 (reference)	...
Mid ACEF	33 (8.4%)	0.048	1.80 (0.99–3.27)	0.050
High ACEF	59 (15.2%)	< 0.001	3.49 (2.02–6.05)	< 0.001

Low ACEF group: ACEF < 0.94, mid ACEF group: $0.94 \leq \text{ACEF} < 1.22$, and high ACEF group: ACEF ≥ 1.22 . ACEF, age, creatinine, and ejection fraction; CI, confidence interval; MACCE, major cardiac and cerebrovascular event; OR, odds ratio.

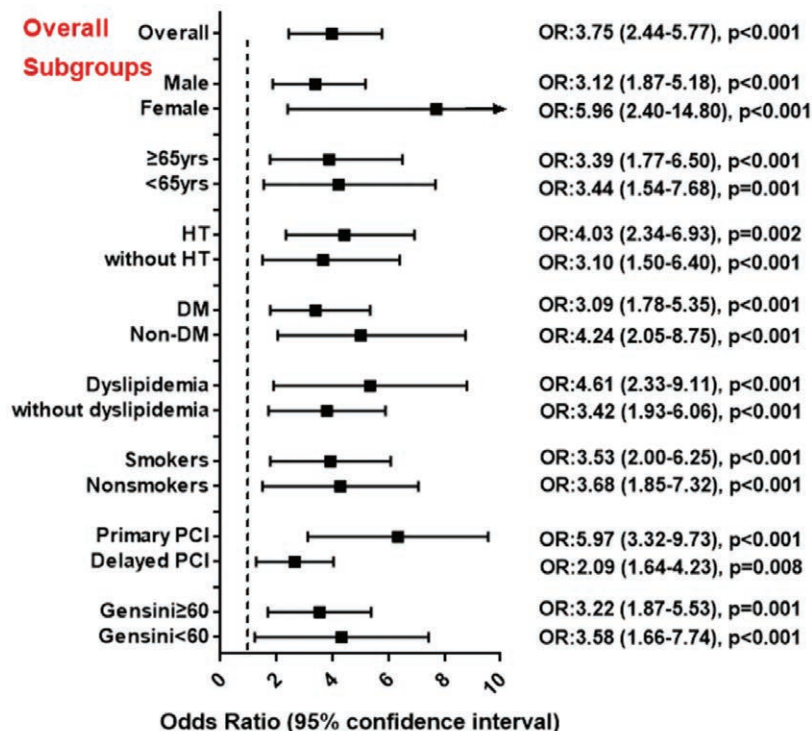
Predictive values of the age, creatinine, and ejection fraction score versus other risk scores for 1-year major cardiac and cerebrovascular event

At receiver-operating characteristic curve analysis, the ACEF score had similar discriminatory power in predicting 1-year MACCE (AUC 0.67) when compared with the Gensini score (AUC 0.63), TIMI score (AUC 0.62), and GRACE score (AUC 0.69) (Table 4, Fig. 3). There were no significant differences of discrimination between the ACEF score and the other 3 complex risk scores (all $P > 0.05$ by DeLong's test). The Hosmer-Lemeshow test indicated that all these scores had satisfactory calibration (all $P > 0.05$), among them, the best calibration was achieved by the ACEF score.

Model improvement of the age, creatinine, and ejection fraction-diabetes risk score in predicting 1-year major cardiac and cerebrovascular event

Except for age and LVEF, diabetes status was also proved to be a robust predictor for the outcomes, we thus generated a combined ACEF-diabetes score and found that its accuracy (AUC 0.71) was superior to the original ACEF score (AUC 0.67). The difference of AUC was statistically significant by DeLong's test ($P=0.048$) (Table 4). As shown in Table 5, the reclassification was significantly improved by incorporating

Fig. 2



Prognostic effect of the age, creatinine, and ejection fraction (ACEF) score at subgroup analysis. The odds ratio (OR) and 95% confidence interval (CI) was calculated by univariate logistic regression analysis. The dotted line indicated the OR value of 1. DM, diabetes.

Table 3 Logistic regression analysis of clinical risk factors for 1-year MACCE

Variables	Univariate logistic analysis		Multivariate logistic analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.04 (1.03–1.06)	< 0.001	1.02 (1.00–1.04)	0.040 ^a
Female	1.48 (0.96–2.30)	0.075	NA	...
BMI	0.92 (0.87–0.98)	0.009	0.96 (0.90–1.02)	0.235
Hypertension	1.37 (0.90–2.07)	0.133	NA	...
Diabetes	2.92 (1.92–4.43)	< 0.001	2.64 (1.67–4.16)	< 0.001 ^a
Dyslipidemia	1.07 (0.72–1.60)	0.720	NA	...
Previous MI	1.08 (0.54–2.16)	0.809	NA	...
Prior PCI	1.28 (0.69–2.37)	0.429	NA	...
Previous stroke	1.87 (1.13–3.10)	0.014	1.47 (0.84–2.58)	0.177
LVEF	0.01 (0.00–0.08)	< 0.001	0.06 (0.01–0.80)	0.033 ^a
Ln NT-proBNP	2.69 (1.88–3.86)	< 0.001	1.17 (0.66–2.06)	0.587
Peak Tnl	1.00 (0.99–1.01)	0.598	NA	...
eGFR	1.01 (1.00–1.02)	< 0.001	0.99 (0.98–1.01)	0.779

Statistically significant variables with univariate analysis were enrolled in the multivariate model. OR stands for per 1 SD increase in each continuous variable, for being female and for having hypertension, diabetes, dyslipidemia, previous MI, prior PCI and previous stroke. NT-proBNP was natural logarithmically transformed to Ln NT-proBNP. ACEF, age, creatinine, and ejection fraction; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MACCE, major cardiac and cerebrovascular event; NA, not assessed; NT-proBNP, N-terminal B-type natriuretic peptide; OR, odds ratio; PCI, percutaneous coronary intervention; Tnl, Troponin I.

^aThe independent predictors for 1-year MACCE after multivariate adjustment.

Table 4 Predictive value of the ACEF score versus other scores for 1-year MACCE

Risk scores	ROC curve analysis			H-L test	
	AUC (95% CI)	Δ AUC	P-value	Chi-square	P-value
ACEF score	0.67 (0.62–0.72)	Reference	...	11.60	0.170
Gensini score	0.63 (0.57–0.68)	−0.04	0.188	3.52	0.897
TIMI score	0.62 (0.57–0.68)	−0.05	0.081	1.01	0.961
GRACE score	0.69 (0.63–0.74)	0.02	0.412	7.41	0.493
ACEF-DM score	0.71 (0.66–0.76)	0.04	0.048 ^a	10.68	0.220

P-value of ΔAUC is calculated by DeLong's test. H-L test: Hosmer-Lemeshow goodness of fit test. ΔAUC, difference of the AUC values; ACEF, age, creatinine, and ejection fraction; AUC, area under the curve; GRACE, global registry of acute coronary event; MACCE, major cardiac and cerebrovascular event; ROC, receiver-operating characteristic curve analysis; TIMI, thrombolysis in myocardial infarction.

^aSignificant improvement of accuracy in the combined ACEF-DM score.

diabetes into the ACEF score (continuous NRI = 51.9%, 95% CI, 33.4–70.5%, $P < 0.001$; IDI = 0.020, 95% CI, 0.011–0.030, $P < 0.001$).

Discussion

Our major findings

In the present study, we tested the clinical performance of the ACEF score in STEMI patients after PCI and found that this simple and user-friendly score had a similar predictive value compared with other complex risk scores. Moreover, we proved that a novel ACEF-diabetes score could improve the risk stratification and enable a more accurate prediction of prognosis.

Validation of the age, creatinine, and ejection fraction score in patients with acute coronary syndrome

The ACEF score was first created by Ranucci in 2009 in order to assess mortality risk in elective cardiac operations [4] and was updated to the ACEF II risk score in 2018 [21]. Although it was originally designed for cardiac surgery patients, several studies later confirmed the prognostic power of ACEF score in ACS patients or in 'all-comer' patients treated with PCI, proving that the elevated ACEF score was significantly associated with

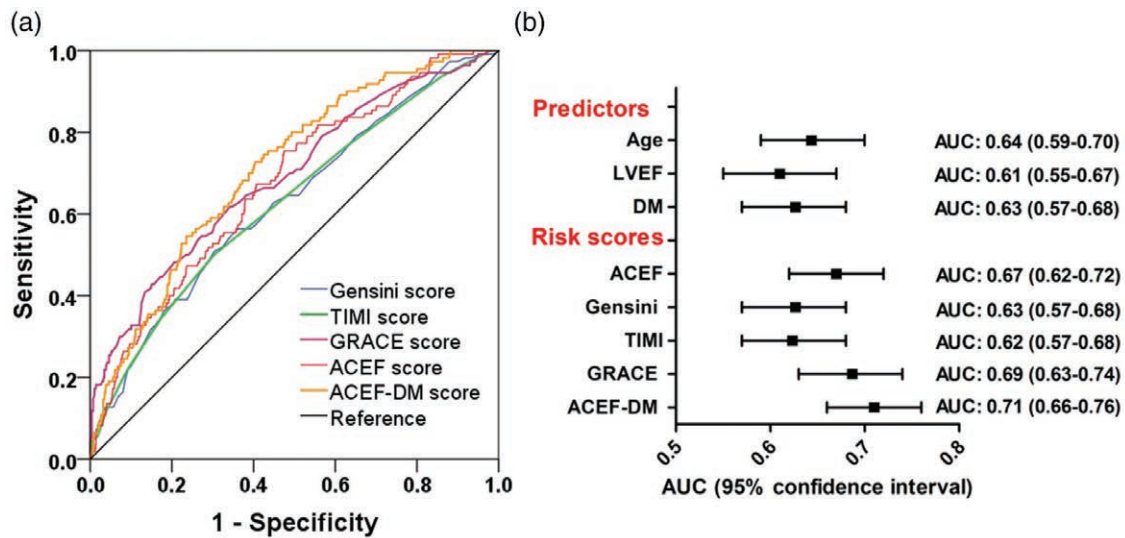
an increased risk of subsequent adverse events after coronary revascularization [6,22,23]. It was also reported that the ACEF score could predict myocardial microvascular injury after STEMI as assessed by cardiac magnetic resonance [24]. The ACEF score also performed well in identifying high-risk patients undergoing PCI for complex coronary lesions, including bifurcation lesion [25], heavily calcified stenosis [26], and chronic total occlusion [27].

Our results were consistent with previous studies. In fact, we focused on STEMI patients who received evidence-based optimal medical therapy and PCI in a Chinese tertiary hospital. At the end of 1-year follow-up, we found that patients with higher ACEF score were more likely to develop MACCE, and the increased ACEF score was significantly associated with the poor prognosis in all patients and in subgroups.

Predictive value of the age, creatinine, and ejection fraction score versus other recommended risk scores

The GRACE and TIMI risk score are well-established tools for risk stratification in ACS patients and they are still widely used in daily clinical practice. The Gensini

Fig. 3



Predictive value of the risk factors or risk scores for 1-year major cardiac and cerebrovascular event (MACCE). a, Receiver operating characteristic curves. The risk scores were Gensini score (light purple line), thrombolysis in myocardial infarction (TIMI) score (green line), global registry of acute coronary event (GRACE) score (dark purple line), age, creatinine, and ejection fraction (ACEF) score (red line), and the combined ACEF-diabetes (DM) score (orange line). b, C-statistics of the predictors and risk scores for 1-year MACCE. C-statistics were expressed as area under the curve (AUC) with 95% confidence interval (CI). Predictors were age, left ventricular ejection fraction (LVEF), and DM. Risk scores were ACEF score, Gensini score, TIMI score, GRACE score, and ACEF-DM score.

Table 5 Model improvement for the ACEF score in combination with diabetes

		P-value
Events, n (%)	110 (9.6%)	
Nonevents, n (%)	1036 (90.4%)	
Continuous NRI statistics (%)		
cNRI-event	34.5	
cNRI-nonevent	17.4	
cNRI	51.9 (95% CI, 33.4–70.5)	< 0.001
IDI statistics		
ΔP-event	0.018	
ΔP-nonevent	0.002	
IDI	0.020 (95% CI, 0.011–0.030)	< 0.001

cNRI is equal to the cNRI for events and nonevent. ΔP-event, increase in mean predicted probability of events; ΔP-nonevent, decrease in mean predicted probability of nonevents; ACEF, age, creatinine, and ejection fraction; cNRI, continuous net reclassification improvement; IDI, integrated discrimination improvement.

score system was used to roughly assess the severity of coronary lesion. Though the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score has been highly recommended to describe the coronary anatomy and lesion characteristics [28], we still adopted the easier applicable Gensini score in view of the heavy workload on precisely calculating the complicated SYNTAX score. Interestingly, we demonstrated that the ACEF model limited to 3 risk factors showed similar accuracy and good calibration as compared with the other risk scores.

It was not our intention to conclude that a new simplified risk score is superior to those existing risk scores. Instead, they have been verified and used for

years, and they all have a good reputation for statistical soundness and clinical usefulness. Even the ACEF score was readily usable and it performed equivalently to a more complex model, this simple tool still needs the long-term validation studies in different population, different hospitals and different countries. The ACEF score, as Ranucci puts it [4], follows the philosophical concept of the law of parsimony, that is, risk factors must not be multiplied beyond necessity. In fact, there are often too many independent variables existing in risk models trying to yield a better accuracy. Like SYNTAX II risk score [29], it includes both 12 angiographic characteristics (the original SYNTAX score) and 6 clinical factors (age, sex, creatinine clearance, LVEF, peripheral artery disease, and chronic obstructive pulmonary disease). This may cause the problem of overfitting and multicollinearity among risk factors in the model. Besides, many categorical variables need a definition (e.g. Killip class in both GRACE score and TIMI score). Sometimes, different practitioners may have different interpretation and, therefore, conclude different risk scores, which may possibly increase the risk of information bias. However, the above problems are absent in the ACEF model because the risk factors (age, LVEF, and creatinine) are continuous variables. They all had standardized assessment and no intercorrelation was found.

Hence, the clinical utility of the ACEF score is promising for its good effectiveness and applicability. The ACEF

score may help physicians to stratify high-risk STEMI patients at the early stage after PCI, and thus potentially facilitate pre-emptive clinical decision making.

Incremental prognostic power of the new age, creatinine, and ejection fraction-derived risk score

The accuracy of the original ACEF score was still moderate, so we updated the score with the inclusion of diabetes as an additional risk factor. It turned out that this new combined ACEF-diabetes score provided better accuracy and good calibration properties. We further used novel statistical metrics to confirm the model improvement in discrimination. A category-free, continuous NRI (>0) showed that a net 17.4% of the patients without events were reclassified into lower risk and a net 34.5% of patients with events were reclassified into higher risk, thus leading to a net 51.9% of appropriate reclassification for patients' risk. The IDI also indicated a significant average separation of events from nonevents by adding diabetes into the model.

Since diabetes has been repeatedly confirmed to be an independent strong predictor for adverse events following STEMI, it is not surprising that the combined score has incremental prognostic value in MACCE prediction. Besides, the novel ACEF-diabetes model does not betray its original parsimonious principle, and there are clear diagnostic criteria on diabetes, which may minimize the information bias due to the imprecise interpretation of variables in the risk model. In clinical practice, it might be reasonable to use the ACEF-diabetes score as a simplified, reliable, and updated tool for risk stratification after PCI. But far from replacing the original ACEF score or claiming superiority to the other existing scores, this new model still needs to be verified by the imperative external validation.

Limitations

There were several limitations in the present study. First, this was a single-center observational study and the number of patients was relatively small. The prognostic value of the ACEF score, especially the updated ACEF-diabetes score, needs to be further validated by multicenter and larger cohort studies. Second, despite multivariate adjustment and subgroup analysis were performed, there were possibly potential confounding factors which may affect the outcomes. For instance, we also enrolled STEMI patients who received delayed PCI. It is hard to calculate the exact time from symptom onset to balloon, and the effect of reperfusion time was not analyzed. Third, we only analyzed patients with STEMI who underwent PCI, so our findings remain to be proven in patients with stable angina pectoris and NSTEMI-ACS.

Conclusions

The ACEF score is a readily useful and effective tool to identify STEMI patients at high risk of developing

subsequent MACCE after PCI. The combined ACEF-diabetes score allows the inclusion of diabetes and appears to provide more accurate prognostic information.

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Conflicts of interest

There are no conflicts of interest.

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