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Prognostic value of age, creatinine, and left ventricular ejection fraction risk score in patients evaluated with fractional flow reserve: a cross-sectional study

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SUMMARY

OBJECTIVE: In this study, we investigated the relationship between age, creatinine, and left ventricular ejection fraction risk score and the severity of coronary lesions detected by applying fractional flow reserve in the patient group presenting with chronic coronary syndrome. Also, we presented long-term follow-up results in patients whose age, creatinine, and left ventricular ejection fraction score was evaluated by the fractional flow reserve procedure.

METHODS: This study was planned retrospectively and in two centers. For this purpose, 114 patients who met the study criteria and who underwent elective fractional flow reserve between January 2014 and January 2019 were included in the study. Age, creatinine, and left ventricular ejection fraction was calculated as age/left ventricular ejection fraction +1 (if estimated glomerular filtration rate<30 mL/min).

RESULTS: They were divided into two groups according to the cutoff value of the age, creatinine, and left ventricular ejection fraction score. A total of 76 patients had an age, creatinine, and left ventricular ejection fraction score of ≤1.17 (Group I) and 38 patients had an age, creatinine, and left ventricular ejection fraction score of >1.17 (Group II). The number of patients with severe lesions in fractional flow reserve was significantly higher in Group II compared with Group I (60.5 vs. 32.9%, p=0.005). According to the Kaplan-Meier analysis, a significant increase was observed in major adverse cardiac events and mortality during the follow-up period in the group with a high-risk score (Log Rank: 15.01, p<0.001 and Log Rank: 8.51, p=0.004, respectively).

CONCLUSION: In light of the data we obtained from our study, we found a correlation between the severity of the lesion detected in fractional flow reserve and the age, creatinine, and left ventricular ejection fraction scores. In addition, we found that patients with high age, creatinine, and left ventricular ejection fraction scores had higher mortality and major adverse cardiac events rates during follow-up.

KEYWORDS: Stable angina pectoris. Myocardial fractional flow reserve. Major adverse cardiac events. Creatinine. Ventricular ejection fractions.

INTRODUCTION

Coronary angiography (CAG) is the gold standard method in the diagnosis and treatment of coronary artery lesions. However, sometimes, quantitative measurements are needed to evaluate the severity of the lesion detected in the coronary arteries. It is important to measure fractional flow reserve (FFR) in the coronary arteries, especially when the stenosis level is evaluated as 40–70% (i.e., moderate). FFR is a reliable method, especially for the functional assessment of lesion severity[1]. The development and progression of coronary atherosclerosis can be influenced by many clinical factors[2]. In addition, it is important to predict the short- and long-term prognosis of coronary artery patients. For this purpose, various risk-scoring systems have been developed. One of these scores is the ACEF score, which consists of three independent factors such as age, creatinine, and left ventricular ejection fraction (LVEF). The ACEF score was first used by Ranucci et al. in patients undergoing elective coronary artery bypass surgery (CABG)[3]. It has been reported that this scoring may be a similar or better predictive value for mortality compared with more complex risk scores[3]. Also, it is thought that this risk score may be an alternative predictive value to EuroSCORE[3]. Wykrzykowska et al., in the LEADERS study, reported that ACEF score was a predictor of mortality and myocardial infarction (MI) risk in the group of patients who underwent percutaneous coronary intervention (PCI)[4]. Similarly, it has been reported to be a good prognostic marker in high-risk patients who underwent PCI for lesions such as bifurcation lesions and chronic coronary total occlusion[5,6]. Studies on the ACEF risk score in the literature mostly focused on the patient group presenting with acute coronary syndrome (ACS). Studies on the long-term predictive value of the ACEF risk score in the patient group presenting with chronic coronary syndrome (CCS) are insufficient.

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In this study, we investigated the relationship between the ACEF risk score and the severity of coronary lesions detected by applying FFR in the patient group presenting with CCS. Also, we presented long-term follow-up results in patients whose ACEF score was evaluated by the FFR procedure.

METHODS

Study population

This study was planned retrospectively and in two centers. For this purpose, a total of 121 consecutive patients who underwent elective FFR between January 2014 and January 2019 were analyzed. Seven patients who did not meet the inclusion criteria were excluded from the study. A total of 114 patients were included in the study. Inclusion criteria for the study were as follows: it was determined as the patients who were evaluated as CCS and underwent the FFR procedure under elective conditions. Exclusion criteria for the study were as follows: ACS, severe arrhythmia, hemodynamic instability, high risk of bleeding (i.e., active internal bleeding, hemorrhagic stroke, intracranial neoplasm, arteriovenous malformation or aneurysm, and ischemic stroke in last 3 months), patients with CABG in last 3 months, moderate/severe heart valve pathology, acute decompensated and/or severe heart failure, liver failure, active infection, malignancy, hematologic diseases, patients receiving steroid therapy, familial history of hyperlipidemia, rheumatologic disease, life expectancy <1 year, and ages between <18 and >90 years. The study was designed in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the local ethics committee before starting the study.

Definitions and age, creatinine, and left ventricular ejection fraction score

A detailed medical history was taken from all patients at the time of admission. Hypertension was defined as systolic blood pressure≥140 mmHg or diastolic blood pressure (DBP)≥90 mmHg or using antihypertensive medication. Diabetes mellitus (DM) was defined as a fasting glucose level of 126 mg/dL or the use of antidiabetic agents or HbA1c>7%. Dyslipidemia was defined as a total cholesterol level>200 mg/dL or a low-density lipoprotein level>130 mg/dL. Smoking was defined as current smoking. Peripheral vascular disease was defined as >50% stenosis in peripheral arteries. LVEF was evaluated from the apical four- and two-chambered views using the biplane Simpson method[7]. The ACEF score was calculated as follows: ACEF=age/left ventricular ejection fraction+1 [if estimated glomerular filtration rate (GFR) <30 mL/min][8]. The equation obtained from the Modification of Diet in Renal Disease (MDRD) study was used, and estimated GFR was calculated considering the initial serum creatinine value[9].

Coronary angiography and fractional flow reserve

Selective CAG was performed on the patients with a right-left femoral or radial approach, using 6F or 7F catheters with the Judkins technique. CAG images were evaluated by two experienced cardiologists, who were unaware of the laboratory values and clinical features of the patients. The degree of stenosis in the coronary arteries was decided based on the projection showing the greatest stenosis. Evaluation by applying the FFR is left to the discretion and discretion of the cardiologists. After an intra-arterial bolus of 5,000 units of heparin, the coronary arteries were visualized using a guide catheter without side holes. A 0.014 inch pressure monitoring guidewire (PrimeWire, Volcano, San Diego, CA, USA) was placed distal to the stenosis after calibration. Before FFR measurements, 200 μg bolus nitroglycerin was administered intracoronally. Initially, distal intracoronary pressures of the patients were recorded. Hyperemia was triggered by administering gradually increasing doses of intracoronary adenosine until the last value where the FFR value decreased. FFR value was determined as the ratio between the mean distal intracoronary pressure and the mean aortic pressure, at which time the highest level of hyperemia was observed. FFR value<0.80 was defined as functionally significant. Patients with a critical FFR were treated as recommended in the European Society of Cardiology guidelines[10].

Major adverse cardiac event

All-cause death and MI were considered major adverse cardiac events (MACE). All tracking data, hospital epicrisis, national data recording system, patients' families, or family doctors (face-to-face or telephone interview) were reached by interviewing. Follow-up period was defined as the time from the time of admission to our clinic for CAG until death from any cause. The study was terminated at the end of the 96-month follow-up period.

Statistical analysis

SPSS (IBM, USA, version 25) was used for statistical analysis. The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed as mean±standard deviation (mean±SD) or median (interquartile range) in case of skewed distribution. Continuous variables between two independent groups were analyzed using the Student's t-test or Mann-Whitney U test as

appropriate. Categorical variables were presented as percentages (%), and their statistical analysis was performed using the chi-square test or Fisher's exact test. Cox proportional hazards model analysis was used to determine the potential risk factors for MACE, and the results were presented as hazards ratio and 95% confidential interval (CI). Discrimination performance of ACEF score for FFR severity was accessed by receiver operating characteristic (ROC) curve analysis, and their areas under the curve (AUC) were compared using a nonparametric approach. Kaplan-Meier curve with Log Rank test was applied to detect the difference in event-free survival rates between the two groups. A univariable and multivariable analysis for predictors of ACEF score was applied and also plotted in a graph. Variables with a p-value of <0.05 were considered significant.

RESULTS

Baseline characteristics

They were divided into two groups according to the cutoff value of the ACEF score. A total of 76 patients had an ACEF score of ≤1.17 (Group I) and 38 patients had an ACEF score of >1.17 (Group II). The mean age in Group II was significantly higher than in Group I (62.89±7.12 vs. 54.74±8.62 years, p<0.001). Compared with Group I, in Group 2, DM (55.3 vs. 34.2%, p=0.031), cerebrovascular disease (13.2 vs. 2.6%, p=0.040), chronic kidney disease (10.5 vs. 1.3%, p=0.042) was significantly higher. LVEF was significantly higher in Group I (57.64±4.97 vs. 48.39±8.86%, p<0.001) (Table 1). Other clinical and demographic characteristics are summarized in Table 1.

The mean creatinine was higher in Group II compared with Group I, but no significant difference was found (0.87 vs. 0.85, p=0.467) (Table 2). The results of other hemogram and biochemical parameters are summarized in Table 2.

Fractional flow reserve and follow-up data

The mean FFR was higher in Group I compared with Group II (82.47±6.06 vs. 78.47±7.47%, p=0.003). In addition, the number of patients with severe lesions in FFR was significantly higher in Group II compared with Group I (60.5 vs. 32.9%, p=0.005). Mortality (15.8 vs. 2.6%, p=0.016) and MACE (26.3 vs. 3.9%, p=0.001) rates were significantly higher in Group II compared with Group I (Table 1).

Table 1. Demographic, baseline characteristic, and clinical endpoints results.

Parameters	All patients (n=114)	Group I (n=76)	Group II (n=38)	p-Value
Age (years)	57.46±8.99	54.74±8.62	62.89±7.12	**<0.001**
Gender, male, n (%)	76 (66.7)	52 (68.4)	24 (63.2)	0.574
Body mass index (kg/m^2)	26.72±3.08	27.06±3.17	26.03±2.80	0.093
Hypertension, n (%)	65 (57)	39 (51.3)	26 (68.4)	0.082
Diabetes mellitus, n (%)	47 (41.2)	26 (34.2)	21 (55.3)	**0.031**
Hyperlipidemia, n (%)	61 (53.5)	39 (51.3)	22 (57.9)	0.507
Smoking, n (%)	45 (39.5)	33 (43.4)	12 (31.6)	0.223
Cerebrovascular disease, n (%)	7 (6.1)	2 (2.6)	5 (13.2)	**0.040**
COPD, n (%)	18 (15.8)	11 (14.5)	7 (18.4)	0.586
CKD, n (%)	5 (4.4)	1 (1.3)	4 (10.5)	**0.042**
PVD, n (%)	6 (5.3)	3 (3.9)	3 (7.9)	0.317
LVEF (%)	54.56±7.83	57.64±4.97	48.39±8.86	**<0.001**
Mortality	8 (7.0)	2 (2.6)	6 (15.8)	**0.016**
Myocardial infarction in follow-up	3 (2.6)	1 (1.3)	2 (5.3)	0.257
Revascularization	2 (1.8)	0	2 (5.3)	0.109
MACE	13 (11.4)	3 (3.9)	10 (26.3)	**0.001**
FFR value (%)	80.74±6.98	82.47±6.06	78.47±7.47	**0.003**
Critical lesion (FFR value ≤0.80)	48 (42.1)	25 (32.9)	23 (60.5)	**0.005**

COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PVD: peripheral vascular disease; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; FFR: fractional flow reserve; Group I: ACEF score≤1.17 (low risk); Group II: ACEF score>1.17 (high risk). Bold indicates statistically significant values.

Table 2. Hemogram and biochemical parameter results.

Parameters	All patients (n=114)	Group I (n=76)	Group II (n=38)	p-Value
Urea, mg/dL	34.22±11.64	33.26±11.09	36.14±12.60	0.214
Creatinine, mg/dL	0.86 (0.30)	0.85 (0.20)	0.87 (0.28)	0.467
Uric acid, mg/dL	5.40±0.78	5.35±0.76	5.51±0.81	0.306
Total cholesterol, mg/dL	188.09±41.34	183.15±38.08	197.97±46.14	0.071
Triglyceride, mg/dL	157.75±49.08	153.51±45.90	166.21±54.54	0.194
HDL, mg/dL	39.88±9.72	40.18±9.53	39.28±10.19	0.645
LDL, mg/dL	116.66±38.50	112.27±35.32	125.44±43.36	0.085
Hemoglobin, g/dL	13.53±1.48	13.68±1.52	12.98±1.27	**0.017**
Platelet, $\times10^3/\mu L$	260.95±56.18	264.51±58.70	253.84±50.75	0.341
Leukocyte, $\times10^3/\mu L$	8.08±1.67	7.93±1.72	8.37±1.54	0.194
MPV, fL	8.41±0.91	8.38±0.90	8.49±0.94	0.533
Neutrophil, $\times10^3/\mu L$	5.14±1.54	5.10±1.52	5.20±1.59	0.749
Monocyte, $\times10^3/\mu L$	0.87±0.23	0.88±0.25	0.85±0.20	0.635
Lymphocyte, $\times10^3/\mu L$	2.35±0.77	2.40±0.79	2.24±0.73	0.286
Fasting glucose, mg/dL	100.31±15.66	98.61±10.58	103.71±22.45	0.102
TSH, μIU/mL	1.87 (1.71)	1.88 (2.05)	1.85 (1.38)	0.568
T4, ng/dL	1.28 (0.51)	1.30 (0.60)	1.26 (0.29)	0.469
AST, U/L	21.0 (12.5)	21 (13)	22.5 (12.2)	0.269
ALT, U/L	20.0 (10.5)	21 (14)	19 (7.25)	0.415

HDL: High-density lipoprotein; LDL: low-density lipoprotein; MPV: mean platelet volume; TSH: thyroid-stimulating hormone; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Group I: ACEF score≤1.17 (low risk); Group II: ACEF score>1.17 (high risk). Bold indicates statistically significant values.

According to the Kaplan-Meier analysis performed to examine the relationship between ACEF score and MACE and mortality during the follow-up period, a significant increase was observed in MACE and mortality during the follow-up period in the group with a high-risk score (Log Rank: 15.01, p<0.001 and Log Rank: 8.51, p=0.004, respectively).

In the cox regression analysis; we found that ACEF (OR:15.58; 95%CI: 4.79–50.64, p<0.001) and FFR (OR:6.64; 95%CI: 1.37–32.21, p=0.019) parameters were independent predictors of mortality (Figure 1).

In the multivariable regression analysis performed among all causes affecting the ACEF score, we found that MACE (OR: 5.89; 95%CI: 1.23–28.09, p=0.026) and DM (OR:2.49; 95%CI: 1.02–6.07, p=0.044) parameters are independent predictors (Figure 1).

ROC analysis was used to evaluate the power of the ACEF score to predict MACE rates. ACEF predicted MACE rates with 62.5% sensitivity and 66.7% specificity (AUC: 0.708; 95%CI: 0.615–0.802, p<0.001).

DISCUSSION

In our study, we found a correlation between patients with a high ACEF risk score and the severity of the lesion detected in FFR. We found that patients with high ACEF scores had significantly higher mortality and MACE rates in the long-term follow-up. In addition, we showed that the severity of the lesion detected in FFR may be an independent predictor of mortality in the long-term follow-up. Studies on the ACEF score in the literature have generally focused on ACS patients. However, the majority of patients who underwent CAG are CCS patients. Studies examining the effect of the ACEF score on CCS patients are limited. Therefore, in our study, we examined patients who applied with CCS and were evaluated with FFR. In this respect, we wanted to examine its effect on quantitative data, and to the best of our knowledge, this is the first study in the literature. In a study, it was reported that the ACEF risk score was a better predictor than other risk scores in patients with non-ST-elevation MI in whom all treatment strategies were applied[11]. In another study, it was reported that the ACEF value at

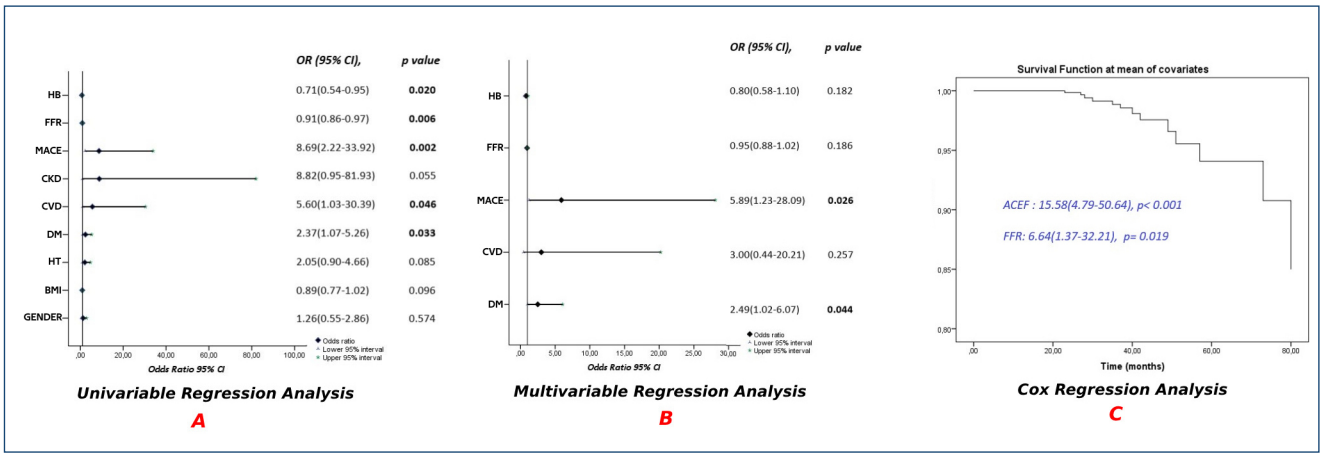

Figure 1. Forest plot of univariable **(A)** and multivariable **(B)** analyses showing correlation of parameters with age, creatinine, and left ventricular ejection fraction risk score. Cox regression analysis **(C)** examining the effect of age, creatinine, and left ventricular ejection fraction and fractional flow reserve parameters on mortality.

admission could predict the 1 month and 1 year cardiac mortality rate after emergency PCI in STEMI patients aged ≥75 years[12]. In contrast, Chichareon et al. stated that the ACEF score may be a better predictive marker in ACS patients compared with CCS patients[13]. The ACEF score, which consists of three vital parameters: age, creatinine, and LVEF, is simple and easy to calculate[3]. Advanced age and renal insufficiency can lead to a deterioration in diastolic parameters and a long-term decrease in LVEF. In addition, the probability of development of calcified stable atheroma plaques is high. Symptoms may not always develop due to silent ischemia and collateral development. Therefore, we want to emphasize that ACEF score can be a prognostic marker not only in ACS patients but also in CCS patients that may cause critical stenosis. Pyxaras et al. showed that the ACEF score can predict MACE rates in the 1 year follow-up of severe calcific coronary lesions undergoing PCI[14]. In a study conducted on CCS patients, it was reported that the ACEF score is a predictor of mortality and MACE rates in the long-term follow-up[15]. However, in our study, we also evaluated the severity of lesions in CCS patients with FFR and conducted our research on quantitative values. This is a strong aspect of our work.

The relationship between inflammatory parameters and cardiovascular diseases has been frequently investigated. However, there are serious limitations regarding such parameters. More powerful and generalizable clinical scoring systems have been investigated in order to determine the prognosis. For this purpose, the ACEF score is one of the simplest prognostic models in the field of cardiology. Therefore, it can be easily calculated in the vast majority of patients, especially in CCS patients undergoing elective percutaneous coronary procedures. Identifying a patient group at high risk of mortality and incorporating ACEF score calculation into routine clinical practice may help improve postprocedural clinical management. In patients considered to be at high risk according to the ACEF score, applications such as cardioverter-defibrillator implantation may be beneficial for more frequent monitoring of kidney and cardiac functions, strict adherence to guidelines in terms of medical treatments, and prevention of sudden death[15].

Limitations

Our study has some limitations. The sample size was relatively small and this was a retrospective study. Prospective studies with larger patient groups are needed. The ACEF score at the time of admission to the hospital was taken into account. The effect of changes in the ACEF score during the follow-up period could not be excluded. In this study, we only looked at the prognostic value of the ACEF score, we did not use other scoring systems. In addition, some data were obtained from the hospital system and national data recording systems. Errors may have occurred in this respect.

CONCLUSION

In light of the data we obtained from our study, we found a correlation between the severity of the lesion detected in

FFR and ACEF scores. In addition, we found that patients with high ACEF scores had higher mortality and MACE rates during follow-up. It may be beneficial to increase the frequency of follow-up in high-risk patients, especially in terms of changeable parameters.

AUTHORS' CONTRIBUTIONS

AA: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **TG**: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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