Predictive Value of Fibrinogen-to-Albumin Ratio for Post-Contrast Acute Kidney Injury in Patients Undergoing Elective Percutaneous Coronary Intervention

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Background:
Post-contrast acute kidney injury (PC-AKI) is a contributor to adverse outcomes after percutaneous coronary intervention (PCI). This study aimed to investigate whether fibrinogen-to-albumin ratio (FAR), a novel inflammation-based risk index, can predict the occurrence of PC-AKI in patients undergoing elective PCI.

Material/Methods:
We retrospectively enrolled 291 patients who underwent elective PCI from June 2017 to June 2019. PC-AKI was defined as an increase in serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L), or ≥1.5 times baseline within 48 to 72 hours after PCI. The area under the receiver-operating characteristic curve (AUC), continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated to make comparison for PC-AKI prediction.

Results:
PC-AKI occurred in 43 patients (14.8%). FAR showed an AUC of 0.691 (95% confidence interval: 0.64–0.74; $P<0.001$) in predicting PC-AKI. In stepwise multivariable logistic regression, FAR was independently associated with the occurrence of PC-AKI along with hypertension, diabetes, hemoglobin, estimated glomerular filtration rate, and left ventricular ejection fraction. FAR significantly improved PC-AKI prediction over Mehran risk score in the continuous NRI and IDI, but not AUC.

Conclusions:
FAR is independently associated with the occurrence of PC-AKI, and can significantly improve PC-AKI prediction over Mehran risk score in patients undergoing elective PCI.

MeSH Keywords:
Acute Kidney Injury • Biological Markers • Coronary Artery Disease • Percutaneous Coronary Intervention

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Background

Acute kidney injury (AKI) that follows intravascular administration of iodine-based contrast media is a common complication with an overall incidence of approximate 3% to 15% after percutaneous coronary intervention (PCI) [1,2]. The European Society of Urogenital Radiology (ESUR) [3] has recently updated their guidelines and recommends that the term post-contrast acute kidney injury (PC-AKI) should replace the older term of contrast-induced nephropathy to describe a decrease in renal function after the use of contrast media. Common risk factors of PC-AKI include primary renal insufficiency, diabetes, anemia, heart failure, and high contrast volume [4]. Although PC-AKI is generally transient and reversible, it remains a serious clinical problem due to its high incidence and association with adverse outcomes. Patients with PC-AKI generally confer prolonged hospitalization, high economic burden, high risk of the requirement for dialysis, and increased mortality [1,2,5,6].

Although the pathological mechanisms underlying PC-AKI are complicated and multifactorial, it has been shown that active inflammation with an excessive response of cytokines and reactive oxygen radicals plays a key role in promoting the occurrence of PC-AKI [7–9]. Elevated systemic inflammatory status can enlarge local inflammation response and aggravate the renal injury. Emerging evidence suggests that systemic inflammatory biomarkers are associated with the occurrence of PC-AKI independent of the conventional risk factors [10,11]. Fibrinogen-to-albumin ratio (FAR), a novel inflammation-based risk index, has been found to be valuable in predicting the poor outcomes in cancers [12,13] and cardiovascular diseases [14–16]. Recently, studies have shown that preprocedural FAR levels are associated with PC-AKI occurrence in patients after carotid angiography [17] and emergency PCI [18]. However, to date, no study has investigated the potential association between the FAR and the risk for PC-AKI in non-acute patients undergoing elective PCI.

Mehran risk score is a classical model for predicting PC-AKI which has been proven useful in the clinical setting over a decade [19,20]. In this study, we aimed to evaluate the predictive value of FAR for PC-AKI, and investigate whether FAR can improve PC-AKI prediction over Mehran risk score in patients undergoing elective PCI.

Material and Methods

Study population

We retrospectively enrolled 291 patients who underwent elective PCI in the First Affiliated Hospital of Guangxi Medical University from June 2017 to June 2019. Patients without sufficient baseline clinical data or repeat measurement of serum creatinine within 72 h after the procedure were excluded. In addition, patients with acute myocardial infarction, acute decompensated heart failure, autoimmune diseases, inflammatory or infectious diseases, end-stage renal disease, cancers, use of contrast media within 1 week, and AKI by other causes were also excluded. Standard medications were used at the time of hospitalization. All patients received drug-eluting stent placement, and the used dosage of contrast volume during the operation was recorded. The study protocol was reviewed and approved by the Human Research Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Approval number: 2020. KY-E-025). Given the retrospective design of our study, written informed consent was not required.

Data collection and related definition

The baseline clinical and laboratory data were acquired from the hospital's database. Fasting blood samples were taken in the first morning at admission, and analyzed in the laboratory department of our institution. Plasma fibrinogen was measured using immune turbidity method. Serum albumin was measured using bromcresol green colorimetric method. Neutrophil to lymphocyte ratio was calculated as the ratio of neutrophil count to lymphocyte count. The FAR was calculated as the ratio of fibrinogen to the albumin level multiplied by 100. Mehran risk scores were calculated according to the corresponding algorithm [19].

PC-AKI was defined as an increase in serum creatinine ≥0.3 mg/dL (≥26.5 μmol/L), or ≥1.5 times baseline within 48 to 72 hours after PCI according to the 2018 guidelines of the ESUR [3]. Estimated glomerular filtration rate (eGFR) was calculated with CKD-EPI Equation [21]. Diabetes mellitus was defined as either a new diagnosis according to the latest guidelines [22] or previous diagnosis with antidiabetic medications. Hypertension was defined as a systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg, or a history of taking antihypertensive medications.

Statistical analysis

Continuous data are expressed as mean±SD or median (25th–75th percentiles), and were compared using the Student t test or the Mann-Whitney U test, as appropriate. Categorical data are expressed as number (percentage) and were compared by chi-square or Fisher exact test. To make comparison for PC-AKI prediction, the area under the receiver-operating characteristic (ROC) curve (AUC) was calculated and analyzed with DeLong's test [23] using MedCalc, version 19.0.4. The optimal cutoff value was determined by maximal Youden's index. Forward stepwise multivariable logistic regression, which included the variables that were statistically significant in the univariable analysis (P<0.05),

Table 1. Patients characteristics.

	PC-AKI (+) (n=43)	PC-AKI (–) (n=248)	P-value
Age	67±9	62±10	0.002
BMI	25.4±3.7	24.6±3.5	0.136
Male gender	31 (72%)	202 (81%)	0.156
Smoking	16 (37%)	114 (46%)	0.286
Hypertension	41 (95%)	190 (77%)	0.005
Diabetes	27 (63%)	81 (33%)	<0.001
Chronic heart failure	26 (60%)	77 (31%)	<0.001
Hemoglobin (g/L)	119±18	132±17	<0.001
NLR	2.8 (1.9–3.8)	2.2 (1.7–2.8)	0.003
Albumin (g/L)	39.9±4.5	41.7±4.3	0.012
Fibrinogen (g/L)	4.2 (3.2–5.1)	3.4 (2.9–4.1)	0.001
FAR	10.2 (8.0–13.3)	8.1 (7.0–9.8)	<0.001
HbA1c (%)	6.5 (5.8–7.4)	6.3 (5.9–6.5)	0.062
Total cholesterol (mmol/L)	4.64±1.06	4.45±1.06	0.268
Triglycerides (mmol/L)	1.70 (1.03–2.47)	1.32 (0.97–2.16)	0.103
LDL-C (mmol/L)	2.61±0.94	2.50±0.92	0.478
Creatinine (umol/L)	107 (84–119)	88 (73–109)	0.001
eGFR (ml/min/1.73 m^2)	60±20	76±20	<0.001
CK-MB (U/L)	14 (10–19)	13 (10–17)	0.380
LVEF (%)	59 (41–69)	66 (60–71)	<0.001
Contrast volume	150 (130–200)	150 (130–200)	0.976

Data are expressed as mean±SD, or median (25th–75th percentiles), or number (percentage). BMI – body mass index; CK-MB – creatine kinase MB form; eGFR – estimated glomerular filtration rate; FAR – fibrinogen to albumin ratio; HbA1c – hemoglobin A1c; LDL-C – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; NLR – neutrophil to lymphocyte ratio; PC-AKI – post-contrast acute kidney injury.

was performed to assess the independent predictors for PC-AKI. To investigate the interaction effects of FAR levels and conventional risk factors on the PC-AKI prediction, we introduced interaction terms "FAR×relevant variables" into the multivariable logistic model. To investigate the incremental value of fibrinogen, albumin, and FAR for PC-AKI prediction over Mehran risk score, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated using R software, version 3.6.0. A two-tailed *P* value <0.05 was regarded as statistically significant. Statistical analysis was performed using SPSS, version 22, unless otherwise stated.

Results

Patients' characteristics

From total 291 patients, PC-AKI occurred in 43 patients (14.8%). The clinical characteristics and baseline laboratory data are summarized in Table 1. Patients with PC-AKI were older and had a higher frequency of hypertension, diabetes, and history of chronic heart failure compared to non-PC-AKI patients. In addition, patients with PC-AKI had higher baseline levels of neutrophil to lymphocyte ratio, fibrinogen, and FAR, but lower levels of hemoglobin, albumin, eGFR, and left ventricular ejection fraction (LVEF) compared to non-PC-AKI patients. There was a trend toward higher hemoglobin A1c levels in patients with PC-AKI compared to those without, although that did not reach statistical difference (P=0.062). Notably, there was no difference in the contrast volume between PC-AKI and non-PC-AKI patients.

Comparison of FAR, fibrinogen, and albumin for predicting PC-AKI

As shown in Figure 1, ROC analysis indicated that FAR can predict the occurrence of PC-AKI (optimal cutoff value: 9.83 with 58% sensitivity and 75% specificity, AUC, 0.691, 95% confidence
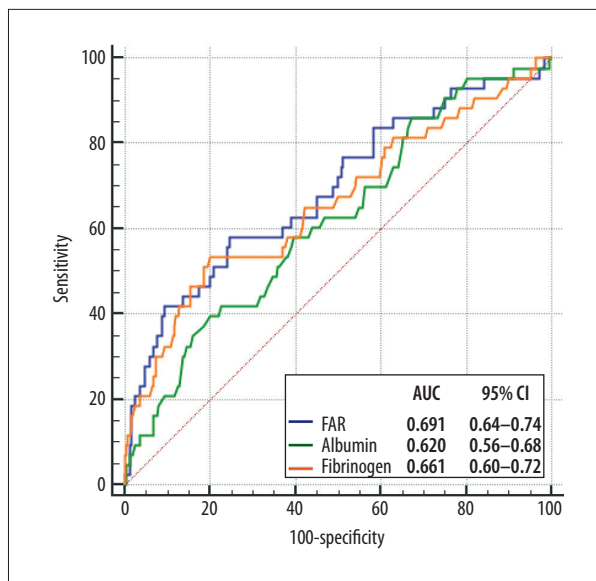
Figure 1. ROC curve analysis of albumin, fibrinogen, and FAR for predicting PC-AKI.

interval [CI], 0.64–0.74; P<0.001). FAR displayed higher AUC value in comparison to fibrinogen (P=0.032), but not albumin (P=0.206), as a predictor of PC-AKI (Figure 1).

Logistic regression analysis of predictive factors for PC-AKI

In univariable logistic regression analysis (Table 2), fibrinogen (per 1 g/L, OR: 2.00, 95% CI: 1.45–2.76; P<0.001), albumin (per 1 g/L, OR: 0.91, 95% CI: 0.85–0.98; P=0.015), and FAR (per

1 unit, OR: 1.27, 95% CI: 1.13–1.42; P<0.001) were significantly associated with the occurrence of PC-AKI. Stepwise multivariable logistic regression suggested that FAR (per 1 unit, OR: 1.15, 95% CI: 1.02–1.30; P=0.026) was an independent predictor of PC-AKI. In addition, hypertension (OR: 4.75, 95% CI: 1.04–21.59; P=0.044), diabetes (OR: 3.04, 95% CI: 1.41–6.57; P=0.005), hemoglobin (per 10 g/L, OR: 0.79, 95% CI: 0.63–0.99; P=0.039), eGFR (per 10 ml/min/1.73m^2, OR: 0.79, 95% CI: 0.66–0.95; P=0.011), and LVEF (per 10%, OR: 0.62, 95% CI: 0.47–0.84; P=0.002) were also independently associated with the occurrence of PC-AKI (Table 2). In the subgroup analysis, no predictive interaction was observed between FAR and the conventional PC-AKI risk factors, including age (>75, ≤75), sex (male, female), diabetes, chronic heart failure, anemia, eGFR (eGFR <60, eGFR ≥60), and LVEF (LVEF ≤40, LVEF >40) (Data was not shown).

Improvement of PC-AKI prediction by fibrinogen, albumin, and FAR to Mehran risk score

We calculated Mehran risk scores for all patients. As shown in Table 3, addition of fibrinogen, albumin, and FAR to Mehran risk score was not associated with a significant improvement in the AUC for PC-AKI prediction. However, FAR significantly improved PC-AKI prediction in the continuous NRI (NRI: 0.400, 95%CI: 0.080–0.721, P=0.014) and IDI (IDI: 0.050, 95%CI: 0.009–0.091, P=0.017) over Mehran risk score, whereas fibrinogen had less predictive improvement, and albumin had no added value (Table 3).

Table 2. Logistic regression analysis of the factors in predicting PC-AKI.

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, per 10 years	1.83 (1.24–2.70)	0.002	–	–
Hypertension	6.26 (1.47–26.66)	0.013	4.75 (1.04–21.59)	0.044
Diabetes	3.48 (1.78–6.82)	<0.001	3.04 (1.41–6.57)	0.005
Chronic heart failure	3.40 (1.74–6.62)	<0.001	–	–
Hemoglobin, per 10 g/L	0.68 (0.56–0.82)	<0.001	0.79 (0.63–0.99)	0.039
NLR, per 1 unit	1.29 (1.09–1.53)	0.004	–	–
Fibrinogen, per 1 g/L	2.00 (1.45–2.76)	<0.001	–	–
Albumin, per 1 g/L	0.91 (0.85–0.98)	0.015	–	–
FAR, per 1 unit	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.026
eGFR, per 10 ml/min/1.73 m^2	0.68 (0.58–0.81)	<0.001	0.79 (0.66–0.95)	0.011
LVEF, per 10%	0.61 (0.48–0.78)	<0.001	0.62 (0.47–0.84)	0.002

CI – confidence interval; eGFR – estimated glomerular filtration rate; FAR – fibrinogen to albumin ratio; LVEF – left ventricular ejection fraction; NLR – neutrophil to lymphocyte ratio; OR – odds ratio.

Table 3. Improvement of PC-AKI prediction by albumin, fibrinogen, and FAR over Mehran risk score.

	AUC (95% CI)	P value	Continuous NRI (95% CI)	P value	IDI (95% CI)	P value
Mehran score	0.780 (0.728–0.826)	Reference	Reference	Reference	Reference	Reference
Mehran score+albumin	0.794 (0.743–0.839)	0.271	0.268 (−0.052–0.588)	0.101	0.011 (−0.006–0.028)	0.210
Mehran score+fibrinogen	0.797 (0.746–0.842)	0.382	0.368 (0.047–0.689)	0.025	0.049 (0.009–0.089)	0.016
Mehran score+FAR	0.806 (0.755–0.849)	0.158	0.400 (0.080–0.721)	0.014	0.050 (0.009–0.091)	0.017

AUC – area under curve; CI – confidence interval; FAR – fibrinogen to albumin ratio; IDI – integrated discrimination improvement; NRI – net reclassification improvement.

Discussion

This study for the first time revealed that FAR was independently associated with PC-AKI occurrence in the setting of elective PCI, and significantly improved PC-AKI prediction over Mehran score.

Although not fully understood, the pathophysiological mechanisms of PC-AKI mainly include direct cytotoxic effects, renal vasoconstriction, endothelial dysfunction, renal tubular injury, and medullary hypoxia [4,7,8]. Fibrinogen and albumin are 2 proteins with inflammatory, thrombotic, and hemorheological properties [24–26], which are involved in the biological pathways predisposing to PC-AKI. Fibrinogen, an important coagulation factor, functions beyond blood clotting and regulates inflammation through facilitating leukocyte transmigration and enhancing the functions of leukocyte effector within damaged tissue [27–29]. Fibrinogen is significantly up-regulated in the kidney tissues after AKI [30], and urinary fibrinogen levels were increased significantly as early as 2 hours after coronary angiography [31]. Also, fibrinogen is increased in circulation during inflammatory state [28], and can promote platelet aggregation [32]. Elevated fibrinogen has an influence on blood viscosity, which can lead to endothelial shear-stress damage, tissue hypoperfusion, and medullary hypoxia [33,34]. It has been recently found that elevated serum fibrinogen level is independently associated with a higher risk of PC-AKI in patients undergoing emergency PCI [35].

Albumin is a major blood protein that regulates colloid osmotic pressure. Inflammation can reduce albumin level by decreasing its synthesis and enhancing its catabolism [36]. In addition, albumin possesses anti-inflammatory and antioxidant properties [37,38], and its serum levels are inversely correlated with systemic inflammatory status [36]. Albumin is a potent inhibitor of platelet activation and aggregation [39], and decreased albumin level can affect the blood viscosity and

impair endothelial function [40,41]. Epidemiological evidence has linked low serum albumin levels with many cardiovascular diseases, such as coronary artery disease, heart failure, and stroke [42]. Furthermore, hypoalbuminemia is a well-established risk factor for PC-AKI [43].

FAR, a risk index integrating fibrinogen and albumin, allows for more sensitive reflection of the inflammatory status, blood viscosity, and thrombogenicity. FAR has been found to improve the clinical implication in multiple settings, including cardiovascular diseases. For example, FAR has been reported to be significantly correlated with the severity of coronary stenosis in patients with stable angina [44] and ST-elevation myocardial infarction [45], and can predict the occurrence of adverse cardiovascular events after PCI [14–16]. Furthermore, FAR is a useful biomarker for predicting the coronary slow-flow and no-reflow phenomenon [46,47]. Of note, studies have recently found that elevated FAR level is associated with the occurrence of PC-AKI. You et al. [18] found that elevated FAR can predict PC-AKI in acute myocardial infarction with an AUC of 0.721 (95% CI: 0.68–0.76). Ertas et al. [17] reported that FAR is an independent predictor of PC-AKI in patients undergoing carotid angiography, and they found that FAR can significantly improve risk reclassification for PC-AKI over fibrinogen and albumin alone. However, these studies did not conduct comprehensive discrimination analysis (AUC, continuous NRI, and IDI) to assess whether FAR provides incremental predictive information over the multivariable models, such as Mehran risk score.

Our study used the definition of PC-AKI according to the new guidelines of the ESUR, and we demonstrated that FAR was also an independent predictor of PC-AKI in the setting of elective PCI. In addition, FAR could significantly improve PC-AKI prediction in the continuous NRI and IDI over Mehran risk score. These findings indicated that FAR, a readily available laboratory index, is a useful biomarker in conjunction with the conventional risk factors for predicting PC-AKI. Prophylaxis strategies

are needed to reduce PC-AKI for patients at high risk. Further large studies are required to explore the optimal risk threshold of FAR for PC-AKI prediction.

Several limitations of this study should be considered: First, it was limited by the retrospective design with small sample size, and thus there was a certain degree of bias. Second, as we had no information regarding the unmeasured hematological and biochemical parameters, such as blood viscosity status, C-reactive protein, and cystatin C, the independent value of fibrinogen in our multivariable logistic regression analysis might be misleading. Third, the prognostic information, including the long-term renal functions and overall mortality, was not considered in our study. More studies are needed in the future.

Conclusions

FAR is independently associated with the occurrence of PC-AKI, and can significantly improve PC-AKI prediction over Mehran risk score in patients undergoing elective PCI.

Conflicts of interest

None

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