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Research Article

Serum Albumin-to-Fibrinogen Ratio Predicts Contrast-Induced Nephropathy in Patients with Acute Coronary Syndrome after Percutaneous Coronary Intervention

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ABSTRACT

Objective: To explore the predictive value of Albumin-to-Fibrinogen Ratio（AFR) in Contrast-Induced Nephropathy (CIN) after Percutaneous Coronary Intervention（PCI) in patients with Acute Coronary Syndrome (ACS).

Methods: Selecting 620 ACS patients who underwent PCI from September 2018 to June 2020 were enrolled. According to the incidence of CIN after PCI, they were divided into CIN group (n=74) and non-CIN group (n=546) . Patients were divided into Q1 group (AFR ≤ 11.99, n=231) and Q2 group (AFR > 11.99, n=389) in the light of AFR level. The general data and laboratory examination indexes of patients in non-CIN group and CIN group were compared, together with the incidence of CIN in patients with different AFR levels. The influencing factors of CIN after PCI in ACS patients were analyzed by multivariate Logistic regression analysis, and ROC curve was drawn to evaluate the predictive value of Pre-PCI AFR level on CIN in ACS patients.

Results: i) There was no significant difference in age, male ratio, systolic blood pressure, diastolic blood pressure, smoking rate, hypertension, diabetes and the proportion of patients using β-blockers, ACEI/ ARB, CCB, statins and nitrates between non-CIN and CIN groups (P >0.05). The proportion of diuretics, low molecular weight heparin in CIN group were higher than those in non-CIN group, and the difference was statistically significant (P <0.05). ii) There was no significant difference in Pre-PCI triglyceride, high density lipoprotein, low density lipoprotein, fasting blood glucose, glycosylated hemoglobin, white blood cell count, monocyte count, neutrophil count, platelet count, red blood cell distribution width, platelet distribution width, total bilirubin, direct bilirubin, lipoprotein (a), serum creatinine, uric acid, blood urea, cystatin C and eGFR between non-CIN group and CIN group (P > 0.05). Pre-PCI serum albumin, AFR, total cholesterol, lymphocyte count, cystatin C and eGFR were lower in CIN group than those in non-CIN group, while Pre-PCI Fibrinogen , serum creatinine, uric acid and blood urea were higher than those in non-CIN group (P <0.05). iii) Multivariate Logistic regression analysis showed that AFR〔OR= 0.892, 95% CI(0.791, 1.006)〕, Pre-PCI serum albumin level〔OR= 0.893 ,95% CI(0.815, 0.978)〕,Fibrinogen〔(OR=1.412,[95%CI(1.127,1.894)〕, and lymphocyte count〔OR=0.493,95%CI(0.285,0.852)〕. iv) Conclusion Pre-PCI AFR level is an

independent risk factor of CIN after PCI in ACS patients, and has certain predictive value for CIN , which is helpful for early identification high-risk patients.

INTRODUCTION

Contrast-Induced Nephropathy (CIN) is an iatrogenic disorder resulted from exposure to contrast media. The term CIN indicates an impairment of renal function (the elevation of serum creatinine by ≥ 0.5 mg/dl or ≤ 25 %) occurring within 3 days following the intra-vascular administration of contrast media, not attributable to other causes [1]. CIN is associated with increased morbidity and mortality, particularly in high-risk patients who have undergone coronary angiography and/or Percutaneous Coronary Interventions (PCI) [2]. Therefore, finding a reliable biomarker has important clinical significance for early diagnosis and treatment of CIN disease. Serum albumin is an important inhibitor of platelet activation and aggregation, while fibrinogen is a well-known cardiovascular risk factor. It is speculated that the ratio of Albumin to Fibrinogen (AFR) may be valuable for predicting CIN in ACS patients after PCI. Therefore, this study retrospectively analyzed the clinical data of ACS patients who received PCI in our hospital, and discussed the relationship between the changes of serum AFR before PCI, in order to provide some reference evidence for early prediction of CIN.

OBJECTS AND METHODS

General information

Between September 1, 2018, and June 31, 2020, a total of 620 patients who had undergone coronary intervention procedure were enrolled. Among them 347 men and 273 women; median age was 64 (29–95 years).The patients were divided into CIN group (n=74) and non-CIN group (n=546) according to the incidence of CIN after PCI. The exclusion criteria were: i) PCI accepted previously or coronary artery bypass grafting; ii) End-stage renal disease, chronic renal failure, uremia or congenital renal insufficiency; iii) Severe infectious diseases, acute cerebrovascular diseases, malignant tumors and liver cirrhosis; iv) Recent use of radioactive contrast agents, glycoprotein IIb/IIIa antagonists, corticosteroids, diuretics or nephrotoxic drugs which affecting creatinine level; v) Incomplete clinical data; vi) Patients with severe chronic heart failure (NYHA grade ≥ 3), cardiogenic shock and autoimmune diseases. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Affiliated Hospital of Xuzhou Medical University. Written informed consent was obtained from all participants.

Collecting indicators and methods

Collecting general data of all patients, including age, sex, blood pressure at admission, smoking, hypertension, diabetes and drug use during hospitalization (including aspirin, Clopidogrel or Ticagrelor, beta blockers, ACEI/ARB, CCB, diuretics, statins, nitrates and low molecular heparin).Three milliliters venous blood was collected Pre-PCI and within 72h after PCI , and send it to the inspection center of our hospital for determination. Among them laboratory examination indexes include blood routine indexes (including hemoglobin, leukocyte count and monocyte count, neutrophil count, lymphocyte count, platelet count, red blood cell distribution width and platelet distribution width), blood lipid indexes (including triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein and lipoprotein A), direct bilirubin, indirect bilirubin, serum fibrinogen, serum albumin level, fasting blood glucose, Glycosylated hemoglobin, hypersensitive C reactive protein and renal function indexes (including serum creatinine, blood uric acid, blood urea, cystatin c, eGFR (Renal function was assessed by the estimated Glomerular Fifiltration Rate (eGFR) using the MDRD formula for Chinese patients [ml/min/1.73m2)] = 175× Scr (mg/dl) -1.154×age-0.203×(0.79 if female) [3]. Blood lipid index, serum albumin level, fasting blood glucose and renal function index were detected by Olympus AU2700 all-active immunity biochemical analyzer, and blood routine was detected by Beckman Coulter LH755 all-automated hematology analyzer.

Statistical analysis and processing

SPSS 26.0 software was used for statistical analysis. Continuous variables are expressed as mean ± Standard Deviation (SD), and categorical data were presented as absolute values and percentages. t test and one-way analysis of variance (ANOVA) with post-Sheffe-type comparison test were used for parametric comparison. Mann–Whitney U and Kruskal–Wallis test were used for nonparametric comparison. Chi-square or the Fisher's exact tests were used for comparison

of categorical variables as required. Multivariate predictors of CIN were identified by logistic regression using stepwise selection. A two-sided 95 % Confidence Interval (CI) was constructed around the point estimate of the odds ratio (OR). The variables chosen by the model included all the potential confounding variables. All hypothesis testing was two tailed. The Receiver Operating Characteristic (ROC) curve was used to evaluate the value of AFR in predicting CIN. P value＜0.05 was considered as statistically significant.

RESULT

Comparison of clinical baseline data between the two groups

There was no significant difference in age, male ratio, systolic blood pressure, diastolic blood pressure, smoking rate, incidence of hypertension, incidence of diabetes and use of β-blocker, angiotensin converting enzyme inhibitor (ACEI) / Angiotensin II Receptor Antagonist (ARB), Calcium Channel Blocker (CCB), statins and nitrates between non-CIN group and CIN group. The proportion of diuretics, low molecular weight heparin and contrast medium in CIN group were significantly higher than those in non-CIN group (P < 0.05) (Table 1).

Table 1: Comparison of basic clinical data between CIN group and non-CIN group.

Variables	Non-CIN（n=546）	CIN（n=49）	*P*-value
Age（years）a	63.9±11.2	66.6±12.1	0.051
Male gender,n(%)	301（55.1）	46(62.2)	0.449
Hypertension,n(%)	291（53.3）	43（58.1）	0.445
Diabetes mellitus,n(%)	139（25.5）	19（25.7）	0.975
Current smoking, n (%)	192（35.2）	28（37.8）	0.66
Systolicbloodpressure(mmHg)[a]	131.1±20.3	131.2±22.4	0.949
β-blocker, n (%)	438（80.2）	59（79.7）	0.897
ACE-I or ARB, n (%)	309（56.6）	40（54.1）	0.667
CCB，n (%)	131（24.0）	15（20.3）	0.474
Diuretic, n (%)	79（14.5）	41（55.4）	<0.01
Statin, n (%)	498（91.2）	72（97.3）	0.077
Nitrates,n (%)	369（67.6）	52（70.3）	0.657
LMWH，n (%)	301（55.1）	50（67.6）	0.044

Abbreviations: [a]Data are presented as the mean ± standard deviation or the median and interquartile range (25–75%); CIN: contrast–induced nephropathy; ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blockers; LMWH: low molecular weight heparin.

Table 2: Comparison of Pre-PCI laboratory examination results between CIN group and non-CIN group.

Variables	Non-CIN, n=546[a]	CIN, n=49[a]	*P*-value
Triglyceride, mmol/l	2.17±1.53	2.41±1.83	0.327
Total cholesterol, mmol/l	3.85±1.88	3.29±1.70	0.029
High-density lipoprotein, mmol/l	1.19±0.46	1.14±0.24	0.207
Low-density lipoprotein, mmol/l	2.64±1.07	2.71±0.82	0.608
Albumin, g/l	41.95±4.68	39.28±4.87	<0.001
Glucose, mmol/l	6.68±2.62	6.68±2.63	0.989
Fibrinogen, g/l	3.17±1.01	3.54±1.20	<0.001
AFR	14.07±5.82	12.09±4.19	<0.001
Urea nitrogen，mmol/L	5.77±1.99	5.75±2.09	0.938
Serum creatinine, μmol/l	69.19±18.47	66.55±22.47	0.262
Uric acid, μmol/l	317.42±95.25	305.97±102.24	0.371
Cystatin C, mg/l	0.86±0.22	0.88±0.31	0.647
eGFR, ml/min	104.75±26.83	114.01±38.79	0.05
Lipoprotein (a)，mg/l	268.17±212.13	346.31±280.67	0.049
Total bilirubin，μmol/l	14.44±8.65	14.27±6.27	0.877
Direct bilirubin，μmol/l	4.99±3.90	4.98±3.47	0.989
Glycosylated hemoglobin (%)	6.90±1.52	7.06±1.80	0.516
hs-CRP（mg/L，$\bar{x}\pm s$）	12.08±28.63	14.60±28.22	0.557
Monocyte count (* 10^9/L)	0.527±0.65	0.476±0.69	0.534
Neutrophil count (* 10^9/L)	5.77±2.67	5.95±2.72	0.598
Lymphocyte count (* 10^9/l)	1.59±1.22	1.29±0.53	0.034
Platelet count (* 10^9/L)	197.43±63.60	185.10±60.32	0.119
Red blood cell distribution width (%)	12.90±0.80	13.03±0.97	0.284
Platelet distribution width (%)	14.69±4.84	14.87±2.56	0.758
B, Post-operative			
Urea nitrogen，mmol/L	4.73±1.98	6.90±4.19	<0.001
Serum creatinine, μmol/l	69.81±18.50	91.86±39.19	<0.001
Uric acid, μmol/l	287.97±115.66	374.57±149.57	<0.001
Cystatin C, mg/l	16.86±79.11	1.03±0.41	<0.001
eGFR, ml/min	99.16±33.63	79.85±28.54	<0.001

Abbreviations: [a]Data are presented as the mean ± standard deviation or the median and interquartile range (25-75%). CIN: contrast-induced nephropathy; hs-CRP: hypersensitive C reactive protein; AFR: Serum albumin-to-fibrinogen ratio; eGFR: estimated glomerular filtration rate.

Comparison of laboratory inspection indexes

There was no significant difference in triglyceride, high density lipoprotein, low density lipoprotein, fasting blood glucose, glycosylated hemoglobin, white blood cell count, monocyte

count, neutrophil count, platelet count, red blood cell distribution width, platelet distribution width, total bilirubin, direct bilirubin, serum creatinine, serum uric acid, blood urea, cystatin C and eGFR between non-CIN group and CIN group before operation. Serum albumin, AFR, total cholesterol, lymphocyte count and postoperative cystatin C, eGFR in CIN group were lower than those in non-CIN group. Pre-PCI FIB, lipoprotein (a), serum creatinine, serum uric acid and blood urea in CIN group were significantly higher than those in non-CIN group (Table 2).

Comparison of the incidence of CIN after PCI in patients with different Pre-PCI AFR levels According to the Pre-PCI AFR level, 620 patients with ACS were divided into Q1 group (low AFR group, AFR ≤ 11.99) and Q2 group (high AFR group, AFR > 11.99). The incidence of CIN after PCI in patients with ACS was compared between the two groups. The results showed that there were 231 cases in Q1 group, including 43 cases of CIN, 188 cases of non-CIN, the incidence of CIN was 18.61%. In Q2 group, 389 cases developed CIN, 358 cases were non-CIN, and the incidence of CIN was 7.97%. There was significant difference in the incidence of CIN after PCI in patients with different Pre-PCI AFR levels (c2 = 15.627, P < 0.01).

Univariate and multivariate logistic regression analysis

The use of diuretics (assignment: no = 0, yes = 1), low molecular weight heparin (assignment: no = 0, yes = 1) and Pre-PCI fibrinogen, albumin, AFR, total cholesterol, lymphocyte count as independent variables, and CIN as dependent variables (assignment: no occurrence = 0, occurrence = 1) were analyzed by multivariate Logistic regression analysis. Multiple Logistic regression analysis showed that albumin, fibrinogen, AFR and lymphocyte count were independent risk factors for CIN (Table 2).

ROC Curve

The ROC curve shows that the Pre-PCI AFR level predicts that the area under the curve of CIN in ACS patients after PCI is 0.625 [95%CI (0.560 ~ 0.691)], the best cutoff value is 11.99, the sensitivity is 58.1%, and the specificity is 66.32%, as shown in (Figure 1).

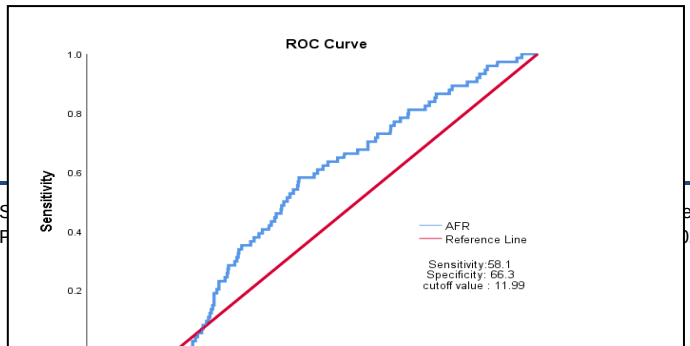

Figure 1: ROC curve of Pre-PCI AFR level predicting CIN after PCI in ACS patients.

Table 3: Multivariate Logistic regression analysis of influencing factors of CIN after PCI in ACS patients.

Variables	B	SE	Wald value	*P* value	Odds ratio	95% confidence interval
TC	-0.094	0.092	1.034	0.309	0.910	0.760-1.091
FIB	0.278	0.23	4.091	0.042	1.412	1.127-1.894
AFR	0.114	0.061	3.481	0.039	0.892	0.791-1.006
Albumin	-0.114	0.047	5.958	0.015	0.893	0.815-0.978
Lymphocyte count	-0.708	0.28	6.402	0.011	0.493	0.285-0.852
Diuretic	-0.292	0.308	0.902	0.342	0.747	0.409-1.364
LMWH	-0.182	0.323	0.318	0.573	0.833	0.443-1.570

Abbreviations: TC: Total cholesterol; FIB: Fibrinogen; AFR: Serum albumin to fibrinogen ratio; LMWH: low molecular weight heparin.

DISCUSSION

Percutaneous Coronary Intervention (PCI) is the preferred treatment for ACS patients. CIN in patients with ACS after PCI has become the focus of clinical attention, which not only increases the difficulty of clinical treatment, but also has a great impact on the prognosis of patients. Previous studies have shown that CIN is the third most common cause of in hospital-acquired acute renal injury (AKI) [4]. It not only prolongs the length of stay of patients, but also increases the mortality and the incidence of cardiovascular events during hospitalization, and affects the long-term prognosis of patients [5]. However, the specific pathogenesis of CIN is not completely clear. The main pathogenesis may be inflammatory reaction, oxidative stress, free radical damage and endothelial dysfunction.

Albumin is the most important protein in human plasma, which plays an important role in maintaining plasma colloid osmotic

pressure, metabolic transport and nutrition. Some studies have shown that albumin is significantly associated with the adverse consequences of cardiovascular disease. Recently, the predictive value of albumin in acute renal injury has been emphasized [6]. Although the exact mechanism of the relationship between low albumin level and CIN is not fully understood, the use of albumin to predict CIN in patients undergoing emergency PCI has its biological basis, and low serum albumin level is associated with increased cardiovascular mortality and morbidity. Our previous research found that Pre-PCI serum albumin level is an independent risk factor of CIN after PCI in patients with ACS, and has a certain predictive value for CIN after PCI, which is helpful to identify high risk patients with CIN. One possible mechanism is that albumin plays a vital role in maintaining cell swelling pressure and increasing renal blood flow and urine volume. Albumin can inhibit the release of a variety of cytokines and chemokines from endothelial cells and activated platelets, thus inhibiting the migration and proliferation of vascular smooth muscle cells [7]. Albumin is also an important antioxidant in the body. it has antioxidant properties and free radical scavenging effect. In addition, albumin is an important inhibitor of platelet aggregation, which can increase Prostaglandin D2 (PGD2), produced by ring peroxides. It is an effective antiaggregation agent [8].

Fibrinogen, also known as coagulation factor I, can be converted into fibrin after the action of thrombin and factor XIII a, and then participate in the coagulation reaction. The increase of fibrinogen indicates that the blood of patients is in a state of hypercoagulability, and the most important factors affecting fibrin clots are the concentration of fibrinogen and the process of fibrinogen conversion to fibrin. Fibrinogen and other important thrombotic factors are important risk factors for cardiovascular disease, can be used as indicators of thrombotic state, are markers of inflammation and play a key role in the inflammatory process, such as regulating macrophage adhesion and activating the production of cytokines/che-mokine [9]. At the same time, baseline plasma fibrinogen levels can predict cardiovascular events in the general population, predict ACS patients after PCI treatment, and independently correlated with the severity and complexity of coronary artery disease [10]. Sweetnam et al [11] showed that the long-term relationship between fibrinogen and viscosity is a strong independent predictor of ischemic coronary heart disease risk. Fibrinogen has also been studied as a marker of deep venous thrombosis [12]. In addition, fibrinogen is related to renal function, and fibrinogen promotes renal fibrosis by stimulating the proliferation of renal fibroblasts. Many studies have confirmed a strong correlation between serum fibrinogen levels and an increased risk of CIN, cardiovascular events and stroke [13-16]. It is related to the pathophysiology, existence, severity and prognosis of coronary heart disease. Fibrinogen was positively correlated with the severity of coronary artery disease in patients with ACS, and it was an independent factor affecting the severity of coronary artery disease in patients with ACS [17]. Similar to the decrease of albumin level, the increase of fibrinogen level may be associated with endothelial dysfunction. As a result of interaction, high fibrinogen / albumin ratio seems to indicate chronic inflammatory load. When patients have chronic inflammation, albumin decreases and fibrinogen increases. However, when patients are malnourished, both albumin and fibrinogen will decreases [18]. Studies have shown that AFR can better predict the prognosis of patients than fibrin and albumin alone, such as myocardial infarction and soft tissue sarcoma [19]. AFR is a new immune biomarker for predicting prognosis. Some studies have shown that AFR plays an important role in the prognosis of lung cancer, chronic lymphoblastic leukemia and cardiovascular disease [20,21]. The results of this study showed that the incidence of CIN after PCI in ACS patients with AFR $\leq$ 11.99 was significantly higher than that in patients with AFR $>$ 11.99. Multivariate Logistic regression analysis showed that Pre-PCI AFR level was one of the independent risk factors for the occurrence of CIN after PCI. It is suggested that the decrease of AFR level is related to the occurrence and development of CIN in patients after PCI, which is consistent with the literature.

Collectively, AFR level as a common and easily available clinical index, AFR level is an independent risk factor for CIN in patients with ACS after PCI. Pre-PCI intervention may reduce the risk of postoperative CIN. At the same time, our research still has some limitations. First of all, all the patients selected in this study were from a single center study, so there was a selection bias at the time of patient registration. Second, the

measurement of peak serum creatinine levels may be omitted due to changes in measurement time, which may underestimate the incidence of CIN. Finally, whether the relationship between AFR level and CIN level is the role of AFR level or only reflects the severity of clinical status of these patients, this study still needs multicenter, expand the sample size to further confirm the clinical value of AFR level in CIN after PCI in ACS patients.

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