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ORIGINAL RESEARCH

The Predictive Value of Soluble Urokinase-Type Plasminogen Activator Receptor in Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Intervention

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Objective: Soluble urokinase-type plasminogen activator receptor (SuPAR) is a circulating protein and a novel identified promising biomarker for various renal diseases and kidney injury. However, it remains unknown on the predictive value of suPAR in contrast induced acute kidney injury (CI-AKI) in patients undergoing percutaneous coronary intervention (PCI).

Methods: A total of 399 patients undergoing PCI were enrolled in the research from June 2020 to June 2021 in Zhongda Hospital. Patients were divided into CI-AKI and non-CI-AKI groups according to the preoperative and postoperative serum creatinine levels. Plasma suPAR level was detected through enzyme-linked immunosorbent assay on admission. Demographic data, hematological parameters, coronary angiography data and medications were recorded and compared between CI-AKI and non-CI-AKI groups. Logistic regression analysis and receiver operator characteristic (ROC) curve analysis were performed for identifying the independent risk factors of CI-AKI and assessment of the predictive value of suPAR for CI-AKI.

Results: CI-AKI occurred in 65 (16.3%) patients undergoing PCI. The level of suPAR in CI-AKI group was significantly higher than that in the non-CI-AKI group. Multivariate logistic regression indicated diabetes, lower LVEF, lower hydration rate, lower baseline eGFR, higher plasma suPAR (OR = 2.875, 95% CI = 2.038–3.672, P < 0.001) and volume of contrast media were all independent risk factors for CI-AKI after adjustment of the confounding factors. ROC analysis illustrated that the optimal area under the curve was 0.765, indicating plasma suPAR was a splendid predictor for CI-AKI. The corresponding cut-off value was 3.305 ng/mL, and the sensitivity and specificity were 63.1% and 82.3%, respectively.

Conclusion: Increased suPAR level is independently associated with elevated risk of suffering CI-AKI, and suPAR is a strong predictor for CI-AKI in patients undergoing PCI. SuPAR might act as a novel biomarker for CI-AKI in clinical practice.

Keywords: soluble urokinase-type plasminogen activator receptor, contrast media, acute kidney injury, percutaneous coronary intervention

Introduction

Iatrogenic renal impairment caused by contrast agents administration is the third leading cause of hospital-acquired acute renal injury after hypoperfusion- and drug-associated renal injury.[1] The term "contrast induced acute kidney injury" (CI-AKI) is proposed by the Kidney Disease Improving Global Outcomes (KDIGO) working

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group.[2] Multiple researches have demonstrated the relationship between CI-AKI, increased mortality rate,[3] and accelerated progression of underlying renal disease. Long-term deterioration of kidney function was also reported correlated with CI-AKI.[4]

CI-AKI induced by percutaneous coronary intervention (PCI) remains a concern despite the raised awareness and improvements of prevention and risk stratification of CI-AKI.[5] Emerging predictors for CI-AKI in patients subjected to PCI have been discovered recently, which might help the diagnosis and risk assessment of CI-AKI.[6,7]

Urokinase-type plasminogen activator receptor (uPAR) is a glycosylphosphatidylinositol-anchored protein, it is distributed on the cell membrane of a variety of bone marrow cells, immune cells, endothelial cells, fibroblasts and podocytes.[8] Under inflammation and immune activation, the glycosyl phosphatidylinositol anchor of uPAR is cleaved by phospholipase C. uPAR Sheds from the activated immune and endothelial cell membrane, then circulating soluble uPAR (suPAR) is formed and released.[9] It has been acknowledged that suPAR is correlated with immune activation and inflammation in patients with cardiovascular diseases[10] and critically ill patients.[11] Recent investigation has suggested Increased suPAR level contribute to deteriorated renal function and poor prognosis in patients with CKD.[12] suPAR is involved in the pathogenesis of various kidney diseases, including diabetic nephropathy and focal segmental glomerulosclerosis.[13] Elevated suPAR level contributes to endothelial dysfunction in inflammatory diseases, leading to subclinical organ damage and vascular complication in patients with CKD.[14] In addition, suPAR has emerged as a promising biomarker in multiple chronic renal diseases as well as AKI.[15,16] Furthermore, experimental study demonstrated suPAR overexpression resulted in severe AKI characterized by enhanced generation of mitochondrial superoxide and energetic demand.[17]

Considering the role of suPAR in oxidative damage and inflammation, we hypothesized whether high suPAR level is associated with high incidence of CI-AKI. The present research aims to evaluate the relationship between suPAR and CI-AKI in patients undergoing PCI and assess the predictive value of suPAR for CI-AKI induced by PCI.

Materials and Methods

Study Design and Protocol

The present study is a prospective study performed in Zhongda Hospital affiliated to Southeast University. Three hundred and ninety-nine patients underwent PCI were admitted from June 2020 to June 2021. The study was approved by the Ethics Committee of Zhongda Hospital and all participants provided written informed consent. Patients aged over 18 and underwent PCI procedure were enrolled in the research. The exclusion criteria were as follows: 1) patients with cardiogenic shock or hemodynamic instability; 2) allergy history of iodine contrast agent; 3) chronic renal insufficiency with eGFR < 15 mL/min/1.73 m^2 or patients receiving maintenance hemodialysis; 4) received enhanced computed tomography, magnetic resonance imaging, or vascular angiography procedures within previous 2 weeks before admission; 5) suffered acute kidney insufficiency or history of taking nephrotoxic drugs during the past 2 weeks; 6) patients with autoimmune diseases, severe liver/kidney dysfunction, severe infectious disease; and malignant tumor. Patients with incomplete clinical data were also excluded. The clinical registration number is ChiCTR2100050487.

Coronary Angiography and Percutaneous Coronary Intervention

Seldinger puncture method was utilized to puncture the radial or right femoral artery. All included patients in the research were subjected to PCI by at least 2 experienced interventional operators. Use of standard hydration protocols and the type of stents were determined by the interventional physician, and a minimum required amount of nonionic, low-osmolality contrast agents were used during the procedure. The standard hydration protocol is as followed: 0.9% NaCl was administered intravenously in patients with according to guidelines (1.0 mL/kg/h during 12 h before and 12 h after contrast administration).[18]

Definition of CI-AKI

Serum creatinine (Scr) increased by 1.5 times or more over the baseline value within 7 days after contrast medium exposure; or serum creatinine level increased by at least 0.3 mg/dl (26.5 μmol/l) over the baseline value within 48 hours after contrast medium exposure; or a urinary volume of less than 0.5 mL/kg/h and persists for at least 6 hours after exposure.[2]

Measurement of suPAR and Serum Creatinine

Fasting venous blood samples for suPAR were collected on admission before the angiology procedure and stored at −80°C. Serum concentrations of suPAR were measured

through a commercially enzyme-linked immunosorbent assay (ELISA) kit (suPARnostic® Elisa kit; ViroGates, Copenhagen, Denmark) according to the manufacturer's protocol. Preoperative and postoperative Scr levels were measured within one week after exposure of contrast agent.

Statistical Analysis

Data were analyzed through SPSS 19.0 statistical software, normally and non-normally distributed numerical data were presented as mean±standard deviation and median [25–75% interquartile range], respectively. In addition, independent sample *t*-test or Mann–Whitney *U*-test was performed for comparison of normally and non-normally distributed data. Classification data were expressed as frequencies and percentages, and compared using the $\chi 2$ and Fisher exact tests. Univariate and multivariate logistic regression analysis were utilized for identification of independent risk factor of CI-AKI.

The predictive value of suPAR for CI-AKI and the optimal cut-off value were evaluated by receiver operator characteristic (ROC) curve. $P < 0.05$ was considered a statistically significant difference.

Results

Baseline Characteristics of CI-AKI and Non-CI-AKI Groups

Three hundred and ninety-nine patients who underwent PCI were enrolled consecutively. The research population included 258 male and 141 female patients with an average age of 65±13. CI-AKI was observed in 65 patients (16.3%). The baseline characteristics of included population are summarized in Table 1. Patients who developed CI-AKI are older, had higher incidence of diabetes, higher CKD, higher triple-vessel disease, higher volume of contrast media, higher baseline serum creatinine, lower hydration rates, lower eGFR level, lower left ventricular ejection fraction (LVEF) compared with those who do not developed CI-AKI ($p < 0.05$). Interestingly, suPAR level was significantly higher in subjects suffered CI-AKI compared with non-CI-AKI population ($p < 0.001$). No significantly statistical differences were found in other demographic data, hematological parameters, coronary angiography data and medications in patients with/without CI-AKI ($p \geq 0.05$).

SuPAR is an Independent Risk Factor for CI-AKI

Univariate logistic regression analysis identified the following factors independently associated with CI-AKI (Table 2): age, diabetes history, CKD history, LVEF, hydration, baseline serum creatinine, baseline eGFR, suPAR, triple vessel disease, volume of contrast media. Multivariate logistic analysis displayed the following independent risk factors for the development CI-AKI: diabetes (OR = 2.141, 95% CI = 1.491–2.679, p = 0.045), LVEF (OR = 0.866, 95% CI = 0.764–0.924 p = 0.039), hydration (OR = 0.703, 95% CI = 0.528–0.817, p = 0.035), baseline eGFR (OR = 0.692, 95% CI = 0.507–0.789, p = 0.014), suPAR (OR = 2.694, 95% CI = 2.379–2.928, p = 0.009), volume of contrast media (OR = 2.245, 95% CI = 1.683–2.294, p = 0.028) (Table 2). In addition, Figure 1 presents a forest plot of multivariate predictors for CI-AKI more intuitively.

ROC Curve Analysis of suPAR for CI-AKI

ROC curve analysis was utilized for evaluating the predictive value of suPAR in CI-AKI. Figure 2 shows the AUC (area under the curve) of suPAR is 0.765 (95% CI = 0.696–0.834, p = 0.035). The optimal cut-off value is 3.305 ng/mL, the corresponding sensitivity and specificity are 63.1% and 82.3%, respectively (Figure 2, Table 3). We explored the predictive value of the model incorporating all the independent risk factors selected through multivariate regression analysis (model 1), the results presented in Figure 2 and Table 3 indicate that model 1 significantly improved the predictive value for CI-AKI, the AUC reached 0.905 (95% CI = 0.848–0.952, p = 0.006). Interestingly, the model incorporating all the independent risk factors except for suPAR (model 2) had relatively lower predictive value for CI-AKI compared with model 1.

Discussion

The current prospective study for the first time to our knowledge demonstrated that higher suPAR level was associated with increased risk for developing CI-AKI and identified suPAR as an independent risk factor for CI-AKI in patients undergoing PCI. The ROC curve shows a fine predictive capacity of suPAR, and the prediction model included suPAR exerts as an outstanding predictor for CI-AKI in patients undergoing PCI.

Despite the advancements in the field of interventional cardiology and increased awareness of CI-AKI, iodinated

Table 1 Baseline Characteristics Between CI-AKI Group and Non-CI-AKI Group

Variables	CI-AKI (65)	Non-CI-AKI (334)	P value
Age (years)	67±12	63±13	0.029
Male (n,%)	46 (70.8%)	212 (63.5%)	0.260
Systolic BP (mmHg)	133±21	130±19	0.649
Diastolic BP (mmHg)	78±15	75±14	0.304
BMI (kg/m^2)	24.4±2.4	24.8±2.8	0.498
Hypertension (n,%)	45 (69.2%)	221 (66.2%)	0.632
Diabetes (n,%)	27 (41.5%)	95 (28.4%)	0.036
CKD (n,%)	4 (6.2%)	5 (1.5%)	0.043
Previous MI (n,%)	10 (15.4%)	55 (16.5%)	0.829
Previous PCI (n,%)	10 (15.4%)	53 (15.9%)	0.922
ACS (n,%)	23 (35.4%)	125 (37.4%)	0.755
Hydration (n,%)	38 (58.5%)	245 (73.4%)	0.016
LVEF (%)	0.49±0.12	0.54±0.14	0.045
Hematological parameters			
WBC (×10^9/L)	8.9 (7.5–9.7)	9.1 (8.6–10.4)	0.678
Hemoglobin (g/L)	130±16	135±18	0.597
Baseline serum creatinine (μmol/l)	99.2 (93.5–104.8)	90.4 (84.1–98.3)	<0.001
Baseline eGFR (mL/min/1.73m^2)	66.3 (63.4–74.9)	76.7 (70.1–81.6)	<0.001
TG (mmol/l)	1.8 (1.3–2.4)	1.6 (1.1–2.4)	0.360
TC (mmol/l)	4.3±1.8	4.1±2.0	0.784
LDL-c (mmol/l)	2.5±1.0	2.3±0.8	0.562
SuPAR (ng/mL)	3.5 (2.8–4.0)	2.8 (2.3–3.4)	<0.001
Coronary angiography			
Triple vessel disease (n,%)	24 (36.9%)	75 (22.5%)	0.013
Number of stents	1.8±0.8	1.5±0.6	0.302
Dose of contrast media (mL)	138 (115–157)	113 (98–130)	0.031
Medications			
ACEI/ARB (n,%)	32 (49.2%)	163 (48.8%)	0.95
β-blockers (n,%)	50 (76.9%)	238 (71.3%)	0.351
CCB (n,%)	13 (20.0%)	60 (18.0%)	0.698
Statin (n,%)	58 (89.2%)	301 (90.1%)	0.827
Aspirin (n,%)	60 (92.3%)	310 (92.8%)	0.798
Clopidogrel/ticagrelor (n,%)	62 (95.4%)	322 (96.4%)	0.720
Diuretic (n,%)	10 (15.4%)	40 (12.0%)	0.448

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI; myocardial infarction; PCI, percutaneous coronary intervention; SuPAR, soluble urokinase-type plasminogen activator receptor; TC, total cholesterol; TG, triglyceride; WBC, white blood count.

contrast remains to pose a risk of CI-AKI, especially for patients at high risk. It was reported CI-AKI occurs in 7–18% of percutaneous cardiac procedures and it is closely related to poor prognosis.[19] Multiple blood biomarkers and risk-stratification models have been proposed for evaluation of the risk of develop CI-AKI, and they might help evaluate the diagnosis of CI-AKI before the change of serum creatinine and eGFR. Incorporation of these new biomarkers could increase its prognostic capacity and lower the cost of trials.[20] However, there is still a long way to go before clinical application due to limited research population and unknown crucial variables before the procedure, such as the volume of contrast media.[21] The current investigation indicated increased suPAR level is closely associated with higher incidence of developing CI-AKI, and it might become a promising noninvasive biomarker for CI-AKI in the perioperative setting.

The exact pathophysiological mechanisms underlying CI-AKI have not been completely elucidated. Enhanced metabolic demand causes renal medulla susceptible to the

Table 2 Univariate and Multivariate Logistic Regression for the Independent Risk Factors of CI-AKI in Patients Undergoing PCI

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.028	1.012–1.049	0.031	1.005	0.94–1.037	0.893
Diabetes	2.397	1.983–2.891	0.036	2.141	1.491–2.679	0.045
CKD	1.018	1.009–1.025	0.043	1.025	0.644–2.078	0.453
LVEF	0.910	0.839–0.972	0.026	0.866	0.764–0.924	0.039
Hydration	0.732	0.594–0.893	0.016	0.703	0.528–0.817	0.035
Baseline serum creatinine	2.193	1.793–2.831	<0.001	1.393	0.793–1.942	0.190
Baseline eGFR	0.582	0.532–0.741	<0.001	0.692	0.507–0.789	0.014
SuPAR	3.015	2.692–3.792	<0.001	2.694	2.379–2.928	0.009
Triple vessel disease	2.595	2.176–3.177	0.013	1.373	0.929–1.624	0.688
Volume of contrast media	2.789	2.183–3.698	0.025	2.245	1.683–2.940	0.028

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SuPAR, soluble urokinase-type plasminogen activator receptor.

vasoconstrictor effects of contrast media due to the low partial oxygen pressure. Contrast agents directly contribute to apoptosis and necrosis of tubular epithelial cells, leading to function loss. The release of vasoactive agents including endothelin, nitric oxide, and prostaglandins result in ischemic injury.[22,23] More importantly, new findings have established the requisite role of epithelial inflammatory caspases[24] and immune sensor NLRP3[25] in CI-AKI model, which might be related to the increased level of suPAR.

Previous reports have indicated suPAR levels are correlated with disease severity, readmission and mortality rate in patients admitted to acute care.[26] Significant association has been found between increased plasma suPAR and various kinds of cardiovascular diseases, renal diseases and other pathologies.[27] Salim reported elevated suPAR was independently associated with the incidence of chronic kidney disease.[13] Emerging evidence has indicated suPAR is involved in the underlying mechanisms of diabetic nephropathy,[28] lupus nephritis,[29] and focal segmental glomerulosclerosis[30] through a variety of molecular mechanisms, such as activation of $\alpha_V\beta_3$ integrin, modification of CD40 autoantibodies and acid sphingomyelinase-like phosphodiesterase 3b.[31–33] In terms of AKI, our findings are largely consistent with the results from a clinical study enrolled 107 patients underwent cardiac surgery, indicating that preoperative suPAR level might become a predictive biomarker for AKI.[15] Mechanistically, previous experimental evidence has shown suPAR exposure contributed to higher cellular energetic demand and oxidative stress, leading to injury of proximal tubules. SuPAR inhibitors remarkably alleviated the deterioration of kidney function caused by iohexol and reversed the bioenergetic changes in HK-2 cells.[17]

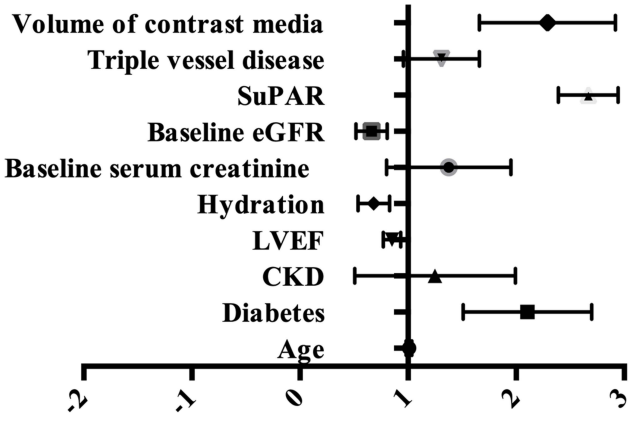

Figure 1 Forest plot of multivariate predictors for CI-AKI.

It was suggested that suPAR could be freely filtered by kidney and it is a biomarker beyond sensitive filtration marker. The association of suPAR with CI-AKI remained significant after adjustment for eGFR, indicating suPAR reflects more than reduced filtration but a characteristic of renal disease.[34] In addition, increased suPAR concentration might be related to the potential tissue damage caused by systemic chronic inflammation. However, whether suPAR is involved in the pathogenesis of CI-AKI and the underlying mechanism remains unexplored.[35] There are several crucial advantages for suPAR acting as a biomarker of CI-AKI. SuPAR is a highly stable biomarker and the serum concentration of suPAR is independent of diets, drugs, inflammation and the collection time throughout the day.[36] Secondly, suPAR has a fine prognostic value for CI-AKI. Early monitoring of SuPAR could help risk stratification for patients undergoing PCI and guide clinical evaluations and treatment.

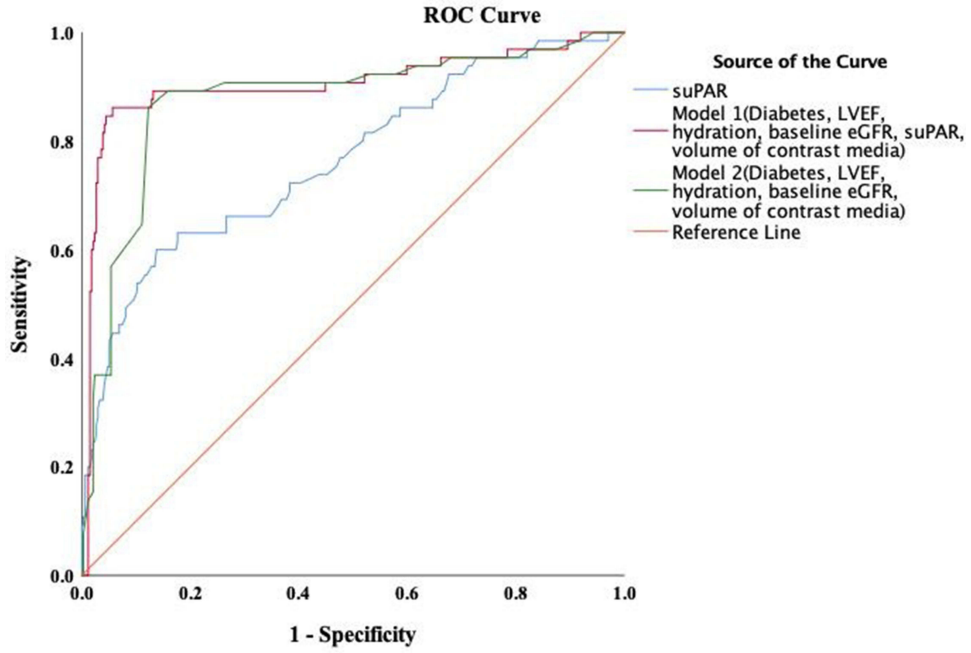

Figure 2 The ROC curve of suPAR and models for predicting CI-AKI in patients undergoing PCI.

There are several limitations of the current research. Firstly, this is a single-center prospective study and the sample size is relatively small. Furthermore, the findings of the present study need to be validated through more large-scale prospective clinical research to ensure its consistency of observed associations. In addition, suPAR is not a commonly used detection indicator in clinical practice, and its clinical applicability is limited to some extent.

Conclusion

In conclusion, elevated suPAR in patients undergoing PCI was independently associated with higher risk for developing CI-AKI. suPAR might become a candidate plasma biomarker and included in the risk stratification model for CI-AKI in clinical application. Further experimental studies need to be carried out to investigate the underlying role of suPAR in CI-AKI and even explore potential novel therapeutic approaches for CI-AKI.

Table 3 Risk Discrimination Metrics for CI-AKI

Variables	AUC	95% CI	p value
SuPAR	0.765	0.696–0.834	0.035
Model: Diabetes, LVEF, hydration, baseline eGFR, suPAR, volume of contrast media.	0.905	0.848–0.952	0.006

Abbreviations: eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SuPAR, soluble urokinase-type plasminogen activator receptor.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participant

This study was approved by the Ethics Committee of Zhongda Hospital, Medical School of Southeast University. All participants provided informed consent to participate in this research and that it was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests concerning the paper.

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