Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 7, Oct. 2024
Manuscript ZUMJ-2404-3314 (R1) DOI . 10.21608/zumj.2024.281313.3314
ORIGINAL ARTICLE

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

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Submit Date: 03-04-2024
Revise Date : 06-04-2024
Accept Date: 14-04-2024

ABSTRACT

Background: Soluble urokinase-type plasminogen activator receptor (suPAR) is a circulating protein that has been found to be a promising biomarker for a variety of kidney injuries. The predictive utility of suPAR in contrast-induced acute kidney damage (CI-AKI) in percutaneous coronary intervention (PCI) is uncertain.

Aim: This study aimed to assess the prediction of CI-AKI using suPAR in patients undergoing PCI.

Methods: This case-control study was carried out on 80 subjects undergoing PCI. The subjects were divided into two groups. Forty patients developed CI-AKI, in addition to the control group, which included 40 subjects with non-CI-AKI.The radial or right femoral artery was punctured using the PCI Seldinger puncture technique. A specific laboratory investigation was the evaluation of suPAR in serum using the Luminex assay.

Results: The suPAR marker was a significant predictor of CI-AKI among PCI patients (AUC=0.982, P<0.001). The suPAR cutoff point (>2.55 ng/mL) showed a sensitivity of 92.5% and a specificity of 97.5% for the diagnosis of CI-AKI. Combined creatinine before contrast and suPAR cutoff points showed a sensitivity of 95% and a specificity of 100%. In CI-AKI patients, there was a significant positive correlation between suPAR marker levels and each creatinine level after contrast (r=0.375, P=0.017) and urinary albumin creatinine ratio (r=0.396, P=0.011). Increased levels of suPAR were associated with higher odds for having CI-AKI (OR 2334.63).

Conclusions: Higher suPAR levels were detected in cases in comparison to controls. SuPAR showed accepted performance criteria in CI-AKI prediction. The combined creatinine level before contrast and suPAR improves the sensitivity and specificity. The suPAR seems to be a predictor of CI-AKI in primary PCI.

Keywords: Soluble urokinase-type plasminogen activator receptor; Contrast media; Acute kidney injury; Percutaneous coronary intervention

INTRODUCTION

After reduced renal perfusion and nephrotoxic drugs, contrast-induced acute kidney injury (CI-AKI) is the third most frequent reason for kidney damage acquired in hospitals. insufficiency, ultimately resulting in acute renal failure. Scholars have documented that, contingent upon the intravenous contrast medium and CI-AKI criteria employed, the incidence of CI-AKI in primary percutaneous

coronary intervention (PCI) operations ranges from 4% to 28%. The injection of intravenous contrast media intermittently during coronary angiography and percutaneous coronary intervention (PCI) results in the highest prevalence of Contrast-induced neohropathy CIN **[1].**

The majority of CI-AKI literature bases diagnostic criteria on either the decrease of diuresis (clinical criterion) within a specified time frame or the elevation of a biomarker, or laboratory criterion, which is mainly the absolute or percentage value of serum creatinine (SCr). In the first 48 hours following contrast material exposure, the Acute Kidney Injury Network (AKIN) revised the RIFLE criteria (risk, injury, failure, loss of function, end-stage kidney disease) and defined AKI as an increase in SCr of 0.5 mg/dL, or a 50% increase over baseline. These variables' cut-off and reference values have been and continue to be debated, but they advise using these guidelines **[2].**

Due to the seriousness of CI-AKI prognosis ,it should be recognized as soon as possible ,effectively treated ,and preferably prevented. When evaluating contrast-associated AKI, it is not necessarily sufficient to monitor renal function based on creatinine and/or glomerular filtration rate. Because serum creatinine levels don't always accurately reflect injury and don't catch subclinical disease, they have long been viewed as an imprecise gold standard in the field of renal diseases. This increased the need to identify novel acute kidney injury biomarkers that could aid in the prediction and subsequent prevention of CI-AKI **[3].** A glycophosphatidylinositol-anchored protein known as certain bone marrow cells, immune cells, endothelial cells, fibroblasts, and podocytes have cell membranes that include the urokinase-type plasminogen activator receptor (uPAR) **[4].**Phospholipase C breaks the glycosyl phosphatidylinositol anchor of uPAR in response to inflammation and immune activation. Following the release of uPAR from the membranes of activated immune cells and endothelial cells, circulating soluble uPAR (suPAR) is created and released **[5]**.

Increased suPAR levels have been linked to worsening renal function and a poor prognosis in individuals with chronic kidney disease (CKD). Numerous kidney disorders, among them focal segmental glomerulosclerosis and diabetic nephropathy, have the suPAR implicated in their pathophysiology **[6]**.Furthermore, in addition to AKI, suPAR has become a promising biomarker for a number of chronic renal disorders. Moreover, an experimental investigation showed that the overexpression of suPAR led to severe AKI, which was characterized by an increased production of superoxide in the mitochondria and energy requirements **[7]**.

Given the function of suPAR in inflammation and oxidative damage, we postulated that a high level of suPAR corresponds to a higher frequency of CI-AKI. The purpose of this study was to use suPAR to predict CI-AKI in patients receiving primary PCI.

METHODS

This case-control study was performed on 80 patients undergoing primary PCI, 40 of whom developed CI-AKI (case group), and 40 control patients undergoing PCI without CI-AKI at the Clinical Pathology Department and Cardiology Department in Zagazig University Hospitals, during the period of January 2022 to November 2023. The study was approved by the Zagazig University local ethics commission (ZU-IRB # 10256). From all patients participating in this study, informed consent was obtained. The study follows the Helsinki Declaration,

which is the World Medical Association's guideline of ethics for research involving human subjects.

Inclusion criteria included patients undergoing primary PCI and patients above 18 years old or below 80 years old. Exclusion criteria included patient refusal to share in the study, patients below 18 years old or above 80 years old. Known chronic kidney disease patients and patients received amount of contrast >350 mL was also excluded. Patients with congestive heart failure, cancer, and active inflammatory disease were excluded.

All study subjects were subjected to complete history-taking as well as clinical examination. The samples were taken before undergoing PCI. Venous blood samples were aseptically withdrawn from each subject by venipuncture and were divided. Two mL of the blood sample were delivered into a sterile tube containing ethylene diamine Tetra acetic acid (EDTA) for a complete blood count (CBC) examination. Three mL were delivered into a sterile plain vacutainer tube, left to clot at 37°C for 10 minutes, and centrifuged at 1200 xg for 10 minutes. Then, the serum was used for kidney functions. Serum aliquots were stored at -20℃ until analysis of suPAR. Random urine samples of 3-5 ml were collected from each subject. Another venous sample was collected 48 hours after the contrast to reevaluate the creatinine.

CBC was done on an automated cell counter, model XN-330 (Sysmex, Japan). Kidney function tests were done on the Roche Cobas 8000 autoanalyzer, C702 molecule, using kits supplied by manufacture (Roche, Germany). Urinary albumin and creatinine were Urinary albumin creatinine ratio (uACR) was determined by dividing albumin concentration (mg) by creatinine concentration (gm) using a Roche Cobas 6000 autoanalyzer, C501 (Roche, Germany).

A specific laboratory investigation involved the evaluation of suPAR in serum using a Luminex assay. The Luminex 100/200 (**Luminex Corporation, Austin, Texas, USA**) analyzer was intended to be used with assay multiplex kits. For every distinct microparticle region, predetermined ratios of fluorophores were incorporated in magnetic microparticles onto which analyte-specific antibodies were percoated. When standards, samples, and microparticles were pipetted into wells, the immobilized antibodies bind the target analytes. Once any unbound materials had been removed, a biotinylated antibody cocktail specific to the analytes of interest was added to each well. Next, streptavidin-phycoerythrin conjugate (streptavidin-PE), which binds to the biotinylated antibody, was added to each well, after a wash to remove any unbound biotinylated antibody. The last rinses get rid of unbound streptavidin-PE. The superparamagnetic microparticles were captured and held in a monolayer by the analyzer's magnet, which was used to read the microparticles once they have been resuspended in diluent RD2-1. The microparticles were illuminated by two light-emitting diodes (LEDS) with different spectra. To determine the area, one LED activates the dyes within each microparticle, and a second LED stimulates the PE to determine the quantity of analyte attached to the microparticle. A camera with a set of filters was used to image a sample from each well in order to distinguish between different excitation levels. The Luminex 100/200 analyzer uses two lasers: one to assess the amount of analyte that was excited and attached to the microparticle of the PE, and the other to identify the microparticle region

by excitation of the dyes within each microparticle. Using an Avalanche photodiode and a photomultiplier tube (PMT), every excitation generated during the passage of every microparticle through the flow cell was examined.

***Reagent Preparation*:**Before use, all reagents were brought to room temperature. To make 500 mL of wash buffer, 480 mL of distilled water and 20 mL of wash buffer concentrate were combined.The standards included in the kit vary based on the chosen analytes. Every Standard Cocktail is a 10X concentrate after reconstitution. Standard was prepared using polypropylene tubes by mixing 100 µL of each standard cocktail with calibrator diluent RD6-52. The standard tube held a final volume of 1000 µL. Before making dilutions, the standard was left to sit with mild agitation for at least fifteen minutes. Calibrator diluent RD6-52 was used as the blank, while standard was used as the high standard. Five test tubes with the labels 2–6 was serial pipetted with 100 µL of calibrator diluent RD6–52.

Diluted microparticle cocktail preparation:Before the cap was removed, the vial containing the microparticle cocktail was centrifuged at 1000 x g for 30 seconds. To resuspend the microparticles, the vial was gently vortexed, being careful not to invert it. Diluent RD2-1 was used in the supplied mixing bottle to dilute the microparticle cocktail.

***Diluted biotin-antibody cocktail preparation*:**Before taking off the cap, the vial containing the biotin-antibody cocktail was centrifuged at 1000 x g for 30 seconds. The vial was carefully swirled, being careful not to turn it inside out. In Diluent RD2-1, the biotin-antibody cocktail was diluted.

***Streptavidin-PE preparation*:**During handling and storage, the streptavidin-PE was shielded from light using an aluminum foil-wrapped polypropylene test tube. Before taking off the cap, the streptavidin-PE vial was centrifuged for 30 seconds at 1000 x g. The vial was carefully swirled, being careful not to turn it inside out. In wash buffer, the streptavidin-PE concentrate was diluted. Streptavidin-PE and microparticles were constantly shielded from light.

Steps: Every reagent was ready per the directions. Each well received 50 µl of either the standard or the sample. Each well received 50 µl of a diluted microparticle cocktail. After that, the mixture was shaken at 800 rpm for two hours at room temperature (RT). Washing was done three times: once with the liquid removed from each well, once with 100 µl of Wash Buffer, and once again with the liquid removed. Each well received 50 µl of diluted Biotin-Antibody Cocktail, which was placed on a shaker set to 800 rpm, covered, and allowed to incubate for one hour at room temperature. The steps of wash procedure were repeated. Each well received 50 µl of diluted streptavidin-PE, which was added, and the wells were shaken at 800 rpm for 30 minutes at room temperature. The steps of wash procedure were repeated. Each well received 100 µl of wash buffer, and the wells were shaken at 800 rpm for two minutes at room temperature. Using a Luminex, it finished reading in ninety minutes. Using standard the calibration curve was made and used for calculating the level of suPAR. The suPAR concentrations were given in ng/mL.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical program for social sciences (SPSS) version 28 (IBM Co., Armonk, NY, USA). The Kolmogorov-Smirnov tests were used to validate assumptions for parametric tests. The

quantitative data were given as mean and standard deviation (SD) and evaluated using the unpaired student t-test. Categorical data were given as frequency and percentage, then evaluated using the Chi-square test or Fisher's exact test as applicable. Pearson's correlation coefficient was used to determine the level of correlation between two quantitative variables. The diagnostic performance was evaluated using ROC curve analysis with area under the curve (AUC), and a cutoff point was chosen based on the Youden index. Linear stepwise regression analysis was used to determine the associated independent factors for the dependent factor and to predict the value of one variable based on the value of another. A two-tailed P value of <0.05 was judged statistically significant.

RESULTS

As shown in **Table1**, CI-AKI cases were significantly older than the controls (P<0.001). Regarding risk factors, the prevalence of DM and HTN was significantly higher among cases than controls (P<0.001, 0.005, respectively). On the other hand, the CI-AKI group included a significantly lower percentage of smokers than the control group (P=0.007). Moreover, both groups were comparable in terms of sex distribution and the prevalence of hyperlipidemia.

In terms of routine laboratory investigations (**Table 1**), hemoglobin and platelet count were significantly lower in CI-AKI cases than the controls (P<0.001, 0.015, respectively). We also found that creatinine levels (either before or after contrast) were significantly higher in cases than controls (P<0.001). As for uACR, it was significantly increased in cases compared to controls (P<0.001). Noteworthy, no statistically significant difference was detected between both groups regarding total leukocytic count level.

CI-AKI cases elicited significantly higher levels of suPAR marker in comparison to the controls (with a mean of 3.91 ± 0.77 vs. 2.13 ± 0.31 ng/mL, respectively, P<0.001) (Figure 1).

Based on the results of ROC curve analysis, creatinine was a significant predictor of CI-AKI among PCI patients (AUC=0.892, P<0.001). The creatinine cutoff point (>0.89 mg/dL) showed a sensitivity of 85%, a specificity of 75%, positive predictive value (PPV) of 77.3% and negative predictive value (NPV) of 83.3% for the diagnosis of CI-AKI (**Table 2, Figure 2A).** Based on the results of ROC curve analysis, the suPAR marker was a significant predictor of CI-AKI among PCI patients (AUC=0.982, P<0.001). The suPAR cutoff point (>2.55 ng/mL) showed a sensitivity of 92.5%, a specificity of 97.5%, PPV of 97.4% and NPV of 92.9% for the diagnosis of CI-AKI (**Table 2, Figure 2B)**. Based on the results of ROC curve analysis, combined creatinine marker before contrast and suPAR were significant predictors of CI-AKI among PCI patients (AUC=0.999, P<0.001). Combined creatinine before contrast and suPAR showed a sensitivity of 95%, a specificity of 100%, PPV of 100% and NPV of 95.2% for the diagnosis of CI-AKI (**Table 2, Figure 2C).**

In CI-AKI patients, there was a significant positive correlation between suPAR marker levels and each creatinine level after contrast (r=0.375, P=0.017) and uACR (r=0.396, P=0.011). On the other hand, a significant negative correlation was detected between suPAR marker levels and TLC (r=-0.523, P=0.001), hemoglobin (r=-0.364, P=0.021) and platelet (r=-0.331, P=0.037). Moreover, there was no statistically significant correlation between suPAR levels and age, creatinine level before contrast, or the amount of contrast **(Table 3)**.

In simple regression analysis (**Table 4**), we found that increased levels of creatinine before contrast, uACR, and suPAR were significantly associated with higher odds of having CI-AKI, with coefficients (95% CI) of 21884.22 , 1.57 and 2334.63 and P values of <0.001, 0.018, and 0.005, respectively.
1.

Table 1: Baseline characteristics and laboratory results of the studied groups

Parameters		**Case group (n=40)**	**Control group (n=40)**	**P value**
Age (years)	Mean ± SD	58.55 ± 8.18	50.23 ± 8.39	<0.001*
	Range	40 - 78	34 – 66	
Sex	Male	32 (80%)	35 (87.5%)	0.363
	Female	8 (20%)	5 (12.5%)	
Risk factor	DM	29 (72.5%)	9 (22.5%)	<0.001*
	HTN	20 (50%)	8 (20%)	0.005*
	Hyperlipidaemia	1 (2.5%)	6 (15%)	0.108
	Smoking	15 (37.5%)	27 (67.5%)	0.007*
Amount of contrast (mL)	Mean ± SD	286.25 ± 30.02	273.75 ± 42.23	0.131
	Range	220 - 340	200 – 340	
TLC (x10^{3}cells/µl)	Mean ± SD	9.16 ± 3.16	10.15 ± 3.28	0.176
	Range	4.5 - 18	5.2 - 18	
Hb (g/dL)	Mean ± SD	11.88 ± 1.57	14.06 ± 2.3	<0.001*
	Range	9 - 15	9.5 - 18	
PLT (x10^{3}cells/µl)	Mean ± SD	213.3 ± 51.55	244.2 ± 59.57	0.015*
	Range	98 - 322	150 - 401	
Creatinine before contrast (mg/dL)	Mean ± SD	1.14 ± 0.23	0.79 ± 0.17	<0.001*
	Range	0.77 - 1.65	0.3 - 1.12	
Creatinine after contrast (mg/dL)	Mean ± SD	2.26 ± 0.47	0.99 ± 0.19	<0.001*
	Range	1.69 - 3.78	0.4 - 1.3	
uACR	Mean ± SD	79.58 ± 23.72	27 ± 7.13	<0.001*
	Range	40 - 140	15 – 45	

Data are presented as frequency (%) unless otherwise mentioned.
DM: Diabetes Mellitus, HTN: Hypertension, TLC: Total Leucocyte Count, Hb: Hemoglobin, PLT: Platelet, uACR: Urine albumin - to - creatinine ratio
*: Statistically significant.

Table 2: Diagnostic performance before contrast for the prediction of CI-AKI in PCI patients

Parameter	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	P value
Creatinine before contrast (mg/dL)	>0.89	85	75	77.3	83.3	0.892	**<0.001***
suPAR (ng/mL)	>2.55	92.5	97.5	97.4	92.9	0.982	**<0.001***
Combined creatinine before contrast (mg/dL) and suPAR (ng/ml)	>0.89 and >2.55 respectively	95	100	100	95.2	0.999	**<0.001***

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve
**: Statistically significant*

Table 3: Correlation between suPAR marker levels and different characteristics of CI-AKI patients (n=40)

Parameters	U-PAR (ng/mL)	
	r	P value
Age (years)	0.022	0.892
TLC (x10^{3}cells/µl)	-0.523	**0.001***
Hb (g/dL)	-0.364	**0.021***
PLT (x10^{3}cells/µl)	-0.331	**0.037***
Creatinine before contrast (mg/dL)	0.143	0.379
Amount of contrast (ml)	0.030	0.852
Creatinine after contrast (mg/dL)	0.375	**0.017***
uACR	0.396	**0.011***

r: Pearson's correlation coefficient, TLC: Total Leucocyte Count, Hb: Hemoglobin, PLT: Platelet, uACR: Urine albumin - to - creatinine ratio
*: Statistically significant.

Table 4: Simple logistic regression analysis for factors associated with CI-AKI in PCI patients.

	OR	95%CI	P value
Age (years)	1.13	1.06 to 1.21	<0.001*
Sex			
Male	Ref		
Female	1.75	0.52 to 5.9	0.367
Risk factor			
DM	9.08	3.29 to 25.08	<0.001*
HTN	4	1.48 to 10.79	0.006*
Hyperlipidaemia	0.15	0.02 to 1.27	0.081
Smoking	0.29	0.12 to 0.73	0.008*
Laboratory			
TLC (x10^{3}cells/µl)	0.91	0.79 to 1.04	0.176
Hb (g/dL)	0.59	0.46 to 0.77	<0.001*
PLT (x10^{3}cells/µl)	0.99	0.98 to 1	0.02*
Creatinine before contrast (mg/dL)	21884.22	211.04 to 2269280	<0.001*
Amount of contrast (ml)	1.01	0.997 to 1.02	0.132
uACR	1.57	1.08 to 2.27	0.018*
suPAR (ng/mL)	2334.63	10.45 to 521750.7	0.005*

OR: Odds ratio, CI: Confidence interval,DM: Diabetes, HTN: Hypertension, TLC: Total Leucocyte Count, Hb: Hemoglobin, PLT: Platelet, uACR: Urine albumin - to - creatinine ratio

*: Statistically significant

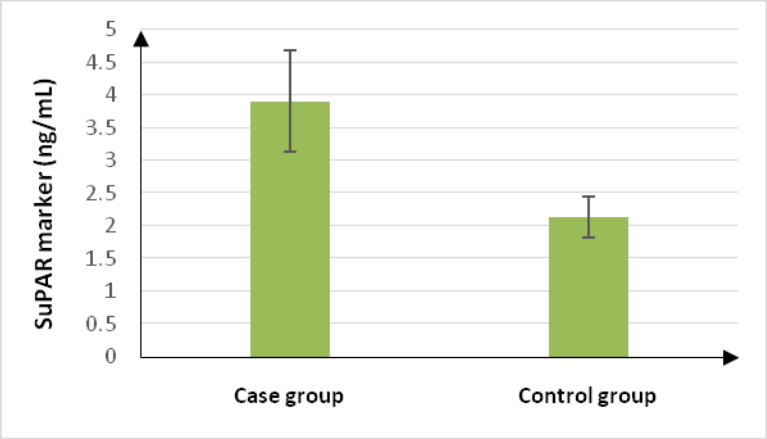

Figure 1: ThesuPAR marker levels of the studied groups

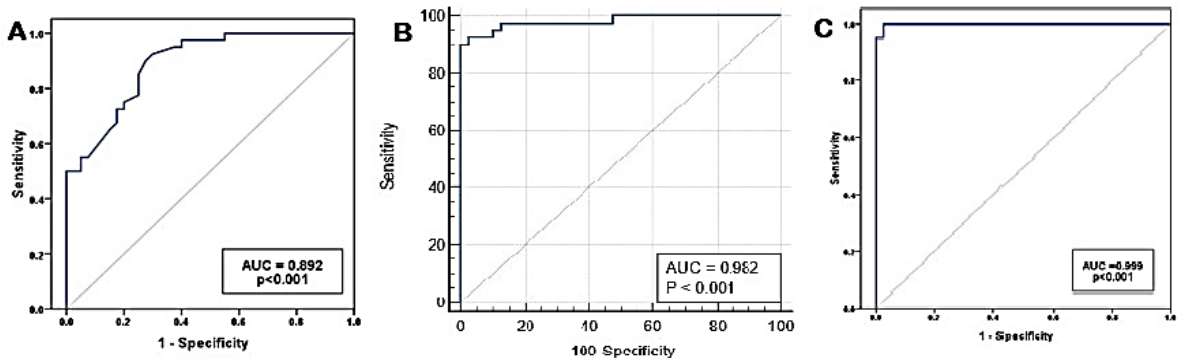

Figure 2: ROC curve of (A): creatinine marker before contrast, (B): suPAR, and (C): combined creatinine before contrast and suPAR markers for the prediction of CI-AKI in PCI patients

DISCUSSION

Regarding risk factors, the prevalence of DM and HTN was significantly higher among cases than controls. On the other hand, the case group included a significantly lower percentage of smokers than the control group. Also, **Wang et al. [8]**revealed a high prevalence of DM and HTN in the cases.In a recent study, DM and HTN were documented as risk factors for CI-AKI **[9].**

Concerning the amount of contrast applied to the studied groups, according to the current study, there was no difference between the instances that were statistically significant and controls regarding the amount of contrast. This result is in similarity with **Marenzi et al. [10],**who estimated that the amount of contrast applied to all the study participants was the same amount of contrast and the amount of administered ranged from 30 to 1316 mL (mean, 265 mL).

In routine laboratory investigations of the studied groups, the current study reveals that hemoglobin and platelet count were significantly lower in CI-AKI cases than the controls. In this context, **Liang et al. [11]**mentioned that anemia (OR, 1.82; 95% CI, 1.27–2.61) was a significant risk factor for CI-AKI. Furthermore, the overall pooled result and the outcomes of the sensitivity and subgroup analyses were essentially consistent. An increased risk of CI-AKI in individuals undergoing coronary angiography may be associated with anemia. In this study, there was no significant difference between cases and controls regarding white blood cells. This

result is mismatched with **Mossanen et al. [12],** who found that patients developing AKI had a higher white blood cell counts at baseline than the control group.

We also found that creatinine level (either before or after contrast) was significantly higher in cases than controls, and for urine albumin /creatinine ratio (uACR), comparing cases to controls, there was a notable increase in it. According to **Wang et al. [13],** creatinine and uACR had predictive values for CI-AKI.

This study was conducted to identify the significance of suPAR prediction in CI-AKI in patients receiving initial PCI. RegardingthesuPAR levels of the studied groups**,** the current study mentions that CI-AKI cases elicited significantly higher levels of suPAR in comparison to the controls (with a mean of 3.91 ± 0.77 vs. 2.13 ± 0.31 ng/mL, respectively). This result is in agreement with **Reisinger et al. [14],** who mentioned that individuals with COVID-19, CKD, moderate-to-severe liver disease, sepsis, including septic shock, and SuPAR levels were noticeably lower in patients who had experienced an acute myocardial infarction. while patients with toxication and acute myocardial infarction exhibited noticeably higher levels. Additionally, patients with AKI upon admission had greater levels of suPAR (11.2 vs. 6.6 ng/mL) than patients without AKI **[14]**.

In relation to the correlation between suPAR marker levels and different characteristics of CI-AKI patients, the present study illustrates that in CI-AKI patients, there was a significant positive correlation between suPAR marker levels and each creatinine level after contrast and uACR. However, a noteworthy negative association was found between suPAR marker levels and total leukocytic count, hemoglobin, and platelet. Moreover, age and suPAR levels did not significantly correlate statistically with creatinine level before contrast or the amount of contrast. Also, **Afangbedji et al. [15]**reported that suPAR was strongly correlated with estimated glomerular filtration rate, kidney functions, and kidney disease progression.

Concerning thediagnostic performance of creatinine before contrast, this study performed ROC curve analysis, creatinine marker was a significant predictor of CI-AKI among PCI patients. creatinine cutoff point (>0.89 mg/dL) showed a sensitivity of 85%, a specificity of 75% for the diagnosis of CI-AKI. This result is in line with **Ribichini et al. [16],**who reported 75% sensitivity and 72% specificity. The suPAR was a highly reliable indicator of CI-AKI in PCI patients. The suPAR cutoff point (>2.55 ng/mL) showed a sensitivity of 92.5%, a specificity of 97.5% for the diagnosis of CI-AKI. This result is matched with **Qin et al. [17],**who illustrated that suPAR could predict CI-AKI with 63.1% sensitivity and 82.3% specificity. The combination of creatinine before contrast and suPAR markers showed higher sensitivity and specificity.

There are some limitations on the current study to begin with; it is a single center study. Also, the sample size was quite small. Thus, to verify the findings of this study, a more extensive one is needed.

CONCLUSIONS

Higher suPAR levels were detected in CI-AKI cases in comparison to those undergoing PCI without developing CI-AKI. SuPAR showed accepted performance criteria in CI-AKI prediction. The combined creatinine level before contrast and suPAR improves the sensitivity and specificity. The suPAR is a predictor of CI-AKI in primary PCI.

Conflict of interest: None

Funding source: None.

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Citation:
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