Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://doi.org/10.21608/zumj.2025.414693.4116 Volume 31, Issue 11 November. 2025

Manuscript ID:ZUMJ-2508-4116
DOI:10.21608/zumj.2025.414693.4116

ORIGINAL ARTICLE

Soluble Urokinase Plasminogen Activator Receptor as an Early Detector of Acute Kidney Injury in Critically Ill Patients

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Submit Date: 16-08-2025
Revise Date: 27-08-2025
Accept Date: 15-09-2025

ABSTRACT:

Background: Acute kidney injury (AKI) remains a prevalent complication among critically ill patients and is linked with higher rates of morbidity in addition to mortality. Soluble urokinase plasminogen activator receptor (suPAR) has emerged as a potential early biomarker, but its predictive value remains uncertain. We aimed to evaluate the role of suPAR for early detection of AKI among critically ill patients with also exploring its potential in improving clinical outcomes.

Methods: We did this prospective observational cohort research on 32 ICU patients categorized into AKI (n = 19) and non-AKI (n = 13) groups based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Serum suPAR was measured at admission (0 h), 24 h, and 48 h. Clinical scores (SOFA, APACHE II), laboratory parameters, and outcomes were compared. ROC curve and logistic regression analyses assessed the predictive performance of suPAR.

Results: Neurological deficits were more prevalent among AKI patients (72.7% vs. 27.3%, p = 0.023). Potassium, serum creatinine, as well as BUN at 24,48 hours were significantly higher in AKI patients (all p < 0.005). APACHE II scores were also elevated (17.53 vs. 12.31, p = 0.036). suPAR levels were slightly higher at 24 h and 48 h but not significant, though they correlated with creatinine at 24 h (r = 0.379, p = 0.032), WBCs (r = –0.409, p = 0.02), and albumin (r = –0.353, p = 0.047). ROC curves showed poor AKI discrimination (AUC 0.425–0.551; all p > 0.05). In multivariable analysis, only creatinine at 24 h independently predicted AKI (OR = 1904, p = 0.015).

Conclusion: suPAR levels were not independently predictive of AKI among critically ill ICU patients, whereas conventional clinical scores and renal function tests remained more reliable predictors. Combining suPAR with other biomarkers may enhance early AKI risk stratification.

Keywords: Acute Kidney Injury, suPAR, biomarker, ICU, Critically Ill.

INTRODUCTION

Acute kidney injury is a serious disorder that is characterized by an abrupt decline in renal function, resulting in increased rates of morbidity, mortality, and healthcare utilization [1]. It is frequently triggered by sepsis, ischemic injury, or exposure to

nephrotoxic substances, particularly among critically ill patients [2]. Early recognition of AKI is essential to prevent its progression to chronic kidney disease (CKD) or end-stage renal disease (ESRD) [3].

Conventional diagnostic tools, like serum creatinine measurement and urine output monitoring, remain the mainstay in AKI detection. However, both are delayed indicators that often rise only after significant kidney injury has occurred [4]. This lag limits the window for early therapeutic intervention and highlights the need for novel biomarkers capable of detecting renal injury at an earlier stage [5].

Soluble urokinase plasminogen activator receptor (suPAR) has emerged as a promising biomarker for the early identification of AKI. suPAR is a stable circulating glycoprotein linked to immune activation and systemic inflammation [6]. Elevated levels have been correlated with an increased risk of kidney dysfunction, adverse outcomes, and disease progression [7]. Importantly, unlike creatinine, which reflects past renal injury, suPAR levels may indicate ongoing pathophysiological processes that precede measurable functional decline [8]. Recent studies have demonstrated its potential in risk stratification and early detection of AKI in critically ill and perioperative patients, showing an association with improved clinical decision-making when incorporated into assessment protocols [9,10].

Despite the growing body of evidence supporting suPAR as a predictive biomarker for AKI, its clinical role in intensive care settings remains insufficiently validated. There is a need for further studies to confirm its diagnostic accuracy, determine optimal cut-off values, and establish how it could be integrated with current clinical and laboratory parameters to improve patient outcomes. So, this research aimed to evaluate the role of suPAR for early detection of AKI among critically ill patients with exploring its potential in improving clinical outcomes.

METHODS

We conducted this prospective observational cohort research in the Intensive Care Unit (ICU) of Zagazig University Hospitals. The study spanned a three-day observation period, during which eligible patients were monitored for the development of AKI.

A total of 32 adult patients (≥18 years) admitted to the ICU were enrolled. Blood and urine samples were collected on admission, at 24 hours, and at 48 hours. Patients were categorized into two groups: those who developed AKI (n=19) and others who did not (non-AKI group, n=13) through the study duration. The study protocol was reviewed and approved by the Institutional Review Board of Zagazig University (ZU-IRB#395-26-May-2024). Written informed consent was obtained from all participants or their legal representatives prior to enrollment. The research was performed following the World Medical Association's Code of Ethics (Helsinki Declaration) for studies involving human subjects.

Sample size calculation: The minimum required sample size was calculated using G*Power 3.1 software, assuming an effect size of 0.8 (large effect) for differences in biomarker levels between AKI and non-AKI groups, with a significance level (α) of 0.05 and power ($1-\beta$) of 0.80. This yielded a target sample of 26 patients. To account for potential dropouts and missing data, we enrolled 32 patients in total.

Inclusion criteria encompassed adult patients with ages of 18 years or older who were admitted to ICU. Eligibility required the availability of both baseline and follow-up measurements for suPAR levels and serum creatinine to enable comprehensive assessment of biomarker dynamics and renal function over the course of ICU stay.

Exclusion criteria included established ESRD or dialysis dependency, known acute kidney injury at enrollment, chronic kidney disease, anticipated ICU stay of less than 48 hours, missing or incomplete laboratory data, and refusal of consent by the patient or legal representative.

AKI was defined per KDIGO criteria as serum creatinine rise ≥0.3 mg/dL within 48 hours, ≥1.5× baseline within 7 days, or urine output <0.5 mL/kg/h for ≥6 hours [11].

Demographic data included age, sex, residence, occupation, and smoking history. Medical history covered comorbidities like diabetes, hypertension, cardiovascular, neurological, and hepatic disease. Clinical parameters included blood pressure, heart rate, respiratory rate, temperature, urine output (monitored via urinary catheterization), and medication history, including use of nephrotoxic agents or diuretics.

A complete general examination was performed for all patients. Neurological manifestations were assessed through detailed neurological examination and review of clinical history. Manifestations included examinations level of consciousness, seizures, focal neurological deficits, and peripheral neuropathy. The presence or absence of these findings was recorded and compared between AKI and non-AKI groups.

The Sequential Organ Failure Assessment (SOFA) score was utilized to quantify organ dysfunction, with a total score ranging from 0 to 24; a change of ≥2 points from baseline indicated significant dysfunction [12]. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated within 1st 24 hours of ICU admission to estimate illness severity and mortality risk [13].

Imaging studies, performed as clinically indicated, included pelvi-abdominal ultrasound, echocardiography, and computed tomography (CT) scans.

Laboratory investigations included routine testing of kidney function parameters—serum creatinine (SCr) as well as blood urea nitrogen (BUN) measured by spectrophotometry on the Roche Cobas 8000 (c702 module) at admission, 24 hours, and 48 hours. Electrolytes (sodium and potassium) were assessed by indirect potentiometry on the Cobas ISE module (Roche Diagnostics, Mannheim, Germany). Inflammatory and hematological markers, including complete blood count (CBC) via Sysmex XN-2000 (Sysmex, Kobe, Japan), C-reactive protein (CRP), and procalcitonin (PCT) via the Cobas autoanalyzer (Roche Diagnostics), were also obtained. Liver function tests serum albumin, total bilirubin, and direct bilirubin were performed using the Cobas autoanalyzer. Arterial blood gas analysis was conducted with the Cobas b 221 system (Roche Diagnostics).

suPAR Measurement

Plasma suPAR concentrations were measured using a commercially available ELISA kit (Sunred, Shanghai, China) in line with the supplier's instructions. Blood specimens were obtained in EDTA-containing tubes and centrifuged at 1500–2000 g for 10

minutes to separate plasma. Each sample was assayed in duplicate. Absorbance values were recorded at 450 nm with a microplate reader, and the corresponding concentrations were calculated from a standard calibration curve.

STATISTICAL ANALYSIS

Data were analyzed using SPSS v26. Continuous variables were tested for normality and summarized as mean ± SD or median (IQR); categorical variables as frequencies and percentages. Group comparisons used t-test, Mann–Whitney U, or Chi-square tests. Spearman's correlation assessed relationships between suPAR and clinical/lab parameters. ROC curves evaluated suPAR's predictive performance, and logistic regression identified independent AKI predictors. Significance was set at $p < 0.05$. Visualizations (boxplots, ROC curves, bar charts, scatter plots) were created in SPSS Chart Editor.

RESULTS

Out of 32 critically ill patients enrolled, 19 (59.4%) developed AKI during the study period. The mean age of the cohort was 58.9 ± 16.2 years, with AKI patients being older on average than non-AKI patients (62.8 ± 15.9 vs. 53.2 ± 15.5 years, $p = 0.101$). Neurological deficits were significantly more prevalent among the AKI group (72.7% vs. 27.3%, $p = 0.023$). No other demographic or comorbidity differences have reached statistical significance **(Table 1).**

Baseline laboratory data were comparable between groups except for serum potassium, which was significantly higher in AKI patients (4.18 ± 0.72 vs. 3.37 ± 0.71 mmol/L, $p = 0.003$). Median serum creatinine and BUN at 24 and 48 hours were markedly higher in the AKI group (all $p < 0.005$). No other hematological or biochemical parameters showed significant differences **(Table 2).**

APACHE II scores were significantly higher among AKI patients than non-AKI patients (17.53 ± 7.49 vs. 12.31 ± 4.96, $p = 0.036$). GCS and SOFA scores were also higher among the AKI group, with non-statistically significant difference ($p = 0.051$ and $p = 0.054$, respectively) **(Table 3).**

Median suPAR concentrations were higher in AKI patients than non-AKI patients at admission (162 vs. 199 pg/mL), 24 h (183 vs. 180 pg/mL), and 48 h (181 vs. 177 pg/mL), with non-statistically significant difference (all $p > 0.05$). Baseline suPAR levels were also slightly higher in females than males ($p = 0.273$), though without statistical significance **(Table 4).**

At admission, suPAR showed significant negative correlations with WBC count ($r = –0.409$, $p = 0.020$) and serum albumin ($r = –0.353$, $p = 0.047$). At 24 hours, plasma suPAR levels demonstrated a significant positive correlation with serum creatinine ($r = 0.379$, $p = 0.032$). However, no associations were detected between suPAR and SOFA score, C-reactive protein, procalcitonin, total bilirubin, blood urea nitrogen, or creatinine measured at other time intervals **(Table 5).**

ROC analysis showed poor diagnostic ability of suPAR at admission, 24 h, and 48 h for predicting AKI (AUCs 0.425, 0.551, and 0.540; all $p > 0.47$). At admission, a cutoff of 117.5 pg/mL achieved high sensitivity (94.7%) but very low specificity (23.1%). At 24 h, the optimal cutoff (242.5 pg/mL) yielded low sensitivity (26.3%) but high specificity (92.3%). At 48 h, a cutoff of 212 pg/mL offered moderate sensitivity (47.4%) and high specificity (84.6%) **(Table 6, Fig. S1).**

On univariate analysis, higher SOFA score (OR 1.228, p = 0.045), higher APACHE II score (OR 1.136, p = 0.047), elevated potassium (OR 5.531, p = 0.013), and increased serum creatinine and BUN at both 24 h and 48 h were significantly associated with AKI (all p < 0.05). suPAR levels at any time point were not significantly associated with AKI. In multivariable analysis including SOFA score, serum creatinine at 24 h, and baseline suPAR, only serum creatinine at 24 h remained an independent predictor (OR 1904, p = 0.015). Baseline suPAR showed no independent predictive value (OR 0.19, p = 0.986) **(Table 7).**

Table 1: Baseline demographic and clinical characteristics of the study groups

Variable	AKI group N = 19	Non AKI group N = 13	p-value	
	Mean ±SD			T
Age	62.79 ±15.856	53.23 ±15.450	0.101	1.692
	Frequency (%)			X^2
Sex				
Male Female	11 (73.3%) 8 (47.1%)	4 (26.7%) 9 (52.9%)	0.131	2.281
DM	9 (81.8%)	2 (18.2%)	0.061	3.500
HTN	8 (57.1%)	6 (42.9%)	0.821	0.051
Cardiac	5 (50%)	5 (50%)	0.467	0.530
Hepatic	7 (58.3%)	5 (41.7%)	0.926	0.009
Respiratory	7 (50%)	7 (50%)	0.341	0.907
Nephrotoxic	11 (61.1%)	7 (38.9%)	0.821	0.051
Neurological	16 (72.7%)	6 (27.3%)	0.023	5.203
Vasopressor	10 (76.9%)	3 (23.15)	0.095	2.795
Ventilated	12 (63.2%)	7 (36.8%)	0.598	0.277

AKI: Acute Kidney Injury, DM: Diabetes Mellitus, HTN: Hypertension, T: independent sample T-test, X^2: Chi-square test, SD: Standard Deviation.

Table 2: Comparison of hematological and biochemistry data between AKI and non AKI groups

Variable	AKI group N=19	Non AKI group N=13	p-value	T
	Mean ±SD			
Hemoglobin	9.811±1.419	9.723±1.76	0.878	0.155
WBCs	15.458±9.657	13.008±7.349	0.446	0.773
Platelets	170.84±92.66	180.46±98.163	0.78	0.282
S.Cr (at 0h)	0.653±0.165	0.592±0.175	0.329	0.992
S. albumin	2.779±0.565	2.923±0.662	0.514	0.661
K^+	4.184±0.715	3.369±0.708	0.003	3.18
Ph	7.264±0.097	7.273±0.083	0.777	0.286
	Median (IQR)			U
BUN (at 0h)	27.26(18-33)	18.23(11.5-25)	0.05	72.5
S.Cr (at 24h)	1.032(0.6-1.2)	0.585(0.5-0.7)	0.001	34

Variable	AKI group N=19	Non AKI group N=13	p-value	T
BUN (at 24h)	39.79(21-48)	18.54(11-25)	0.002	44
S.Cr (at 48h)	1.4(0.8-1.8)	0.6(0.45-0.75)	<0.001	18
BUN (at 48h)	54.05(26-76)	21.31(14.5-27)	<0.001	29.5
CRP	116(54-224)	158(12-220)	0.759	115.5
Procalcitonin	1.1(0.2-1.7)	0.6(0.2-1.75)	0.817	117.5
T.bilirubin	0.9(0.7-1.4)	0.6(0.4-1.15)	0.143	85.5
HCO_3^-	17(14-19)	18(15-24)	0.347	99

AKI: Acute Kidney Injury, WBCs: White Blood Cells, S.Cr: Serum Creatinine, S. albumin: Serum Albumin, K^+: Potassium, BUN: Blood Urea Nitrogen, CRP: C-Reactive Protein, T. bilirubin: Total Bilirubin, HCO_3^-: Bicarbonate, SD: Standard Deviation, IQR: Interquartile Range, U: Mann Whitney U statistics

Table 3: Comparison between AKI and non AKI groups regarding clinical scores

Score	AKI (N=19)	Non AKI (N=13)	p-value	T
	Mean ±SD			
APACHE	17.53+7.493	12.31+4.956	0.036	-2.198
	Median (IQR)			U
GCS	6(4-10)	8(6.5-13.5)	0.051	73
SOFA	10(7-16)	7(5-9.5)	0.054	73.5

AKI: Acute Kidney Injury, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, SOFA: Sequential Organ Failure Assessment, SD: Standard Deviation, IQR: Interquartile Range, T: Student's t-test, U: Mann–Whitney U test.

Table 4. Comparison of Serum suPAR Levels by AKI Status at Different Time Points and by Sex at Baseline

Time Point / Group	AKI (N = 19) Median (IQR)	Non-AKI (N = 13) Median (IQR)	U	p-value
suPAR at admission	162 (139–201)	199 (135–233.5)	105	0.478
suPAR after 24 h	183 (156–248)	180 (157–214)	111	0.631
suPAR after 48 h	181 (139–279)	177 (158.5–207)	113.5	0.701
Baseline suPAR by sex				
suPAR at 0 h: Male (N = 15) vs. Female (N = 17)			98.5	0.273

AKI: Acute kidney injury; suPAR: soluble urokinase-type plasminogen activator receptor; IQR: Interquartile range; U: Mann–Whitney U statistic; N: Number of patients. Statistical test used: Mann–Whitney U test for group comparisons.

Table 5: Correlation between suPAR and different clinical parameters

Variable pair	Spearman's r	p-value
suPAR 0 h and age	-0.146	0.426
suPAR 0 h and SOFA	-0.035	0.848
suPAR 0 h and CRP	-0.057	0.758
suPAR 0 h and procalcitonin	-0.237	0.191
suPAR 0 h and T.bilirubin	-0.093	0.614
suPAR 0 h and WBCs	-0.409	0.02

Variable pair	Spearman's r	p-value
suPAR 0 h and s.albumin	-0.353	0.047
suPAR 0 h and SCr 0 h	0.184	0.314
suPAR 0 h and BUN 0 h	-0.125	0.496
suPAR 24 h and SCr 24 h	0.379	0.032
suPAR 24 h and BUN 24 h	0.042	0.818
suPAR 48 h and SCr 48 h	0.238	0.116
suPAR 48 h and BUN 48 h	-0.015	0.935

suPAR: Soluble Urokinase Plasminogen Activator Receptor, SOFA: Sequential Organ Failure Assessment, CRP: C-Reactive Protein, T. bilirubin: Total Bilirubin, WBCs: White Blood Cells, s. albumin: Serum Albumin, SCr: Serum Creatinine, BUN: Blood Urea Nitrogen., r = spearman rank correlation coefficient

Table 6: Validity of suPAR in prediction of AKI occurrence in ICU patients

	AUC	95% CI	Cutoff (pg/ml)	sensitivity	specificity	p-value
suPAR 0 h	0.425	0.208 - 0.642	117.5	94.7%	23.1%	0.478
suPAR 24 h	0.551	0.345 – 0.756	242.5	26.3%	92.3%	0.631
suPAR 48 h	0.540	0.363 – 0.745	212.0	47.4%	84.6%	0.701

suPAR: Soluble Urokinase Plasminogen

Table 7: Univariate and multivariable regression analysis of suPAR and other variables ability in AKI prediction in patients admitted at ICU

	Univariate			Multivariable		
	OR	95%CI	P value	OR	95%CI	P
Age	1.041	0.991-1.094	0.113			
Hgb	1.039	0.652-1.654	0.873			
WBCs	1.035	0.949-1.129	0.434			
s.albumin	0.66	0.196-2.215	0.501			
T.bilirubin	2.314	0.663-8.074	0.188			
SOFA	1.228	1.004-1.501	0.045	1.25	0.958-1.628	0.1
APACHE	1.136	1.002-1.288	0.047			
CRP	0.999	0.992-1.006	0.754			
procalcitonin	1.142	0.489-2.668	0.758			
HCO_3^-	0.911	0.785-1.058	0.221			
K^+	5.531	1.437-21.289	0.013			
S.Cr (at 0h)	9.298	0.116-744.898	0.319			
BUN (at 0h)	1.094	0.999-1.199	0.052			
S.Cr (at 24h)	1454.17	4.31-490428.7	0.014	1904	4.329-837437	0.015
BUN (at 24h)	1.132	1.022-1.254	0.017			
S.Cr (at 48h)	103589.3	7.31-14673	0.018			
BUN (at 48h)	1.143	1.02-1.281	0.022			

	Univariate			Multivariable		
	OR	**95%CI**	**P value**	**OR**	**95%CI**	**P**
suPAR 0 h	**0.998**	**0.987-1.009**	**0.673**	**0.19**	**0.964-1.007**	**0.986**
suPAR 24 h	**1.005**	**0.996-1.014**	**0.27**			
suPAR 48 h	**1.005**	**0.996-1.013**	**0.279**			

OR: Odds Ratio, CI: Confidence Interval, Hgb: Hemoglobin, WBCs: White Blood Cells, s. albumin: Serum Albumin, T. bilirubin: Total Bilirubin, SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, CRP: C-Reactive Protein, HCO_3^-: Bicarbonate, K^+: Potassium, S.Cr: Serum Creatinine, BUN: Blood Urea Nitrogen, suPAR: Soluble Urokinase Plasminogen Activator Receptor.

DISCUSSION

The role of suPAR as an early biomarker for AKI has been evaluated in numerous studies, yet reported diagnostic and predictive performances vary widely. Such variability may partly arise from ethnic and geographic differences influencing baseline suPAR levels. Meijers et al. [14] found that healthy European cohorts had lower baseline suPAR values compared with African or Middle Eastern populations, emphasizing the need for context-specific reference ranges. Given that our cohort consisted exclusively of Egyptian patients, it is plausible that genetic, dietary, or environmental factors could alter baseline concentrations, potentially masking an association with AKI unless comparisons are adjusted for ethnicity or conducted against matched controls.

Age is another factor known to affect circulating suPAR levels independent of acute illness. In the current study, AKI patients were older than non-AKI patients (62.8 ± 15.9 vs. 53.2 ± 15.5 years), although this difference was not statistically significant. Wlazeł et al. [15] reported a similar age-related rise in suPAR, with correlations persisting after adjustment for age. Likewise, Jhee et al. [16] showed that in a large cohort without chronic kidney disease, higher suPAR predicted accelerated eGFR decline even after controlling for age and sex. These observations suggest that in ICU populations, elevated baseline suPAR in older individuals may attenuate its apparent predictive value for AKI unless age adjustment is performed.

Sex-related differences in baseline suPAR were also observed in our study, with higher median values in females despite a greater incidence of AKI among males. Large general population analyses have shown that asymptomatic women have approximately 10% higher suPAR levels than men after adjusting for cardiovascular risk factors, but predictive accuracy for adverse outcomes remains similar when sex-specific cutoffs are applied. Gaudino et al. [17] proposed that such thresholds may improve interpretation in mixed-sex ICU cohorts, a consideration that could enhance the clinical utility of suPAR in AKI prediction.

Disease severity scoring systems remain essential in ICU practice. Several studies have reported correlations between suPAR and established scores such as SOFA and APACHE II. Schmidt et al. [18] found a strong association between elevated suPAR and higher SOFA scores, suggesting that suPAR may reflect the overall burden of disease rather than specific organ dysfunction. In our cohort, SOFA scores were significantly higher in AKI patients and were independently associated with AKI, whereas suPAR showed no such

independent relationship. This aligns with Schulz et al. [19], who recommended using suPAR alongside severity scores, as it likely represents systemic illness rather than serving as an isolated AKI predictor.

Mechanical ventilation is often a surrogate for critical illness severity. Hayek et al. [7] observed significantly higher suPAR levels among ventilated patients, likely reflecting systemic stress and multiorgan involvement. In contrast, our cohort demonstrated no significant difference in suPAR levels between ventilated and non-ventilated patients. This discrepancy may stem from our smaller sample size or differences in ventilation duration and underlying pathology.

In the current study, although mechanical ventilation was more frequent among AKI patients, suPAR levels did not significantly differ between ventilated and non-ventilated patients. This may reflect that suPAR is more indicative of systemic immune activation rather than a direct marker of respiratory failure. Importantly, when evaluating other clinical outcomes such as vasopressor requirement, mortality, and ICU length of stay, no independent associations with suPAR were observed. These findings suggest that while suPAR may capture the overall burden of systemic illness, it does not appear to independently predict specific clinical outcomes in critically ill patients beyond established severity scores. Nevertheless, larger studies are needed to clarify whether integrating suPAR into composite prognostic models could improve outcome prediction in this high-risk population.

Vasopressor requirement is another marker of hemodynamic instability. Reiser and Gupta [20] demonstrated that suPAR may contribute to endothelial dysfunction and vasoplegia via β3-integrin activation. In our study, however, vasopressor use was not significantly linked to elevated suPAR levels or AKI occurrence, suggesting a potentially different inflammatory phenotype or patient distribution.

Chronic inflammation in diabetic patients has been associated with higher baseline suPAR levels. Huang et al. [21] reported elevated suPAR in diabetics, possibly reflecting persistent endothelial injury. In our results, diabetes mellitus was not significantly associated with either AKI or higher suPAR concentrations, likely influenced by the small diabetic subgroup or heterogeneity in glycemic control and disease duration.

In our analysis, hypertension showed no significant association with either suPAR levels or AKI incidence, suggesting that in heterogeneous ICU settings, suPAR's predictive utility may be diluted by multiple coexisting pathologies.

Routine laboratory markers have been evaluated in relation to suPAR to better contextualize its clinical relevance. Azam et al. [22] found moderate correlations between suPAR and both serum creatinine and BUN in critically ill COVID-19 patients. In our cohort, a significant positive correlation was observed only between suPAR at 24 h and serum creatinine at the same time point, with no association noted for potassium or arterial blood gas parameters. Similarly, Gong et al. [10] reported no significant correlation between suPAR and electrolyte or pH disturbances, indicating that while suPAR may reflect systemic stress, it does not necessarily track acid–base or electrolyte changes.

We also found no significant relationship between suPAR and traditional inflammatory markers such as CRP, PCT, or WBC count, despite modestly higher median suPAR values in AKI patients at 24 h and 48 h. This supports the concept proposed by Rasmussen et al. [23] that suPAR reflects chronic immune activation rather than acute inflammation measured by acute-phase reactants. In contrast, Azam et al. [22] observed a weak correlation between suPAR and PCT in septic patients, highlighting that disease context may influence these associations.

Diagnostic studies in systemic inflammation have further explored suPAR's value. Raggam et al. [24] found that in patients with systemic inflammatory response syndrome, suPAR achieved an AUC of 0.726 for bacteremia detection, comparable to PCT and IL-6, and superior to CRP, with improved discrimination when combined with PCT and IL-6 (AUC 0.804). Similarly, Donadello et al. [25] noted that while suPAR levels rise in infection, its diagnostic value is often comparable to PCT and slightly better than CRP in prognostic applications.

In our cohort, baseline, 24 and 48 hours suPAR levels were modestly higher in AKI patients compared to non-AKI patients, with a significant correlation between suPAR and serum creatinine at 24 h. In a multicenter study of 925 cardiac surgery patients, Rasmussen et al. [23] reported that preoperative suPAR independently predicted postoperative AKI, particularly moderate-to-severe cases (KDIGO stage 2–3), with no added value from postoperative measurements, underscoring the importance of baseline assessment. Schmidt et al. [26] found that in septic ICU patients, suPAR remained persistently elevated during the first 48–72 h, especially in non-survivors, in contrast to the dynamic changes seen in CRP and PCT. This pattern reinforces the concept of suPAR as a marker of ongoing immune activation and endothelial injury rather than a transient inflammatory signal.

Finally, in a large cohort from the Emory Cardiovascular Biobank, Hayek et al. [7] demonstrated that higher baseline suPAR predicted future CKD development and progressive eGFR decline, suggesting long-term prognostic value even from a single early measurement.

In the present study, AKI was classified as present or absent based on KDIGO criteria without further subdivision into stages. Therefore, we could not evaluate whether suPAR levels varied across AKI severity stages. Previous studies, however, suggest that higher baseline suPAR may be associated with more advanced AKI. Rasmussen et al. [23] reported that suPAR predicted moderate-to-severe AKI (KDIGO stage 2–3) after cardiac surgery, while Schmidt et al. [26] demonstrated persistently elevated suPAR in ICU patients with severe AKI who later experienced poor outcomes. This implies that suPAR might better capture risk in advanced AKI rather than in early or mild cases. Moreover, outcomes such as mortality and renal recovery have been linked with suPAR in prior studies [18,26], but in our cohort, no independent association between suPAR and clinical outcomes was observed. Larger, adequately powered studies that incorporate AKI staging are needed to clarify whether suPAR can stratify risk across different AKI severities and predict outcomes more reliably.

In our study, although suPAR was not an independent predictor of AKI, its elevation may indicate concurrent cardiovascular stress that predisposes certain patients—particularly those with underlying heart failure or ischemic disease—to renal injury. Reiner et al. [27] demonstrated that suPAR independently predicted incident heart failure and cardiovascular mortality in more than 5,000 patients from the Emory Cardiovascular Biobank, even after adjustment for high-sensitivity troponin I, CRP, and renal function markers (HR for death ≈ 2.37; $p < 0.001$). Similarly, in a cohort of 1,635 patients undergoing coronary angiography, Hodges et al. [28] found that higher suPAR predicted death and myocardial infarction independently of traditional risk factors (HR ≈ 1.88 per doubling; $p \leq 0.037$).

Respiratory failure and acute respiratory distress syndrome (ARDS) may trigger systemic inflammatory cascades, fluid shifts, and hypoxia, all of which can contribute to AKI risk. In critically ill patients with pulmonary infections or requiring mechanical ventilation, elevated suPAR could reflect both the severity of lung injury and a heightened risk for renal complications. Nusshag et al. [8] reported that in sepsis patients, those who developed ARDS had significantly higher baseline suPAR levels than those without ARDS. In their study, suPAR was an independent predictor of ARDS (cutoff ≈ 14 ng/mL) and correlated with APACHE II, SOFA, CRP, TNF-α, IL-6, and mortality (AUC for ARDS ≈ 0.64).

Liver dysfunction in critical illness can influence detoxification, coagulation, and circulatory dynamics, all of which may contribute to AKI risk. Elevated suPAR in hepatic disease is thought to reflect both disease severity and vascular dysregulation affecting renal perfusion. In a cohort of 193 cirrhotic patients, Garnæs et al. [29] reported that suPAR levels rose with advancing Child–Pugh class and correlated positively with portal hypertension ($r \approx 0.34$) and negatively with systemic vascular resistance ($r \approx -0.33$; both $p < 0.001$). Similarly, Rasmussen et al. [23] found that in ICU patients, elevated suPAR was common in moderate-to-severe liver disease and independently predicted ICU mortality and AKI stage 3 (OR for AKI stage 3 ≈ 1.89 per quartile; $p = 0.006$).

Multiple explanations may account for the absence of statistically significant relationships between suPAR concentrations and AKI in our cohort. Foremost, the relatively limited sample size ($n = 32$) may have reduced the power of the analysis, making it difficult to capture modest associations. This limitation is further compounded by the heterogeneity of the ICU population, characterized by diverse comorbid conditions and varying clinical profiles. The broad spectrum of systemic inflammatory syndromes, sepsis, and multi-organ failure in critically ill patients may obscure kidney-specific signals, as suPAR reflects generalized immune activation that can be driven by non-renal processes.

The study is limited by its relatively small sample size and single-center setting, which may restrict the generalizability of the results. Future large-scale, multicenter collaborative studies across ICUs are warranted to validate these findings and better define the role of suPAR in AKI risk stratification.

Additionally, the dynamic nature of AKI progression along with variability in onset and severity among patients

complicates the timing and interpretation of biomarker measurements. It is possible that even serial suPAR assessments may not fully capture the evolving balance between injury and recovery in the kidney when systemic illness exerts a dominant influence. Finally, methodological differences between studies, including assay type, patient selection criteria, and timing of biomarker sampling, could contribute to the observed inconsistencies in suPAR's predictive performance.

Conclusion

In the current study, suPAR levels were modestly higher in some AKI patients but did not independently predict AKI in critically ill ICU populations. Conventional clinical scores remained more reliable. Combining suPAR with other biomarkers may improve early risk prediction and guide timely intervention in high-risk patients.

Conflict of Interest & Funding Statement: This work was carried out without external funding, and no conflicts of interest have been declared by the authors.

Data Availability: Upon reasonable request, the data that support these findings will be supplied by the corresponding author.

Author contribution: R.Y.E.A. took the lead in coordinating the study and served as the corresponding author. A.A.G. and S.M.E. contributed to the study design, clinical supervision, and critical manuscript revision. A.M.A.H. provided expertise in laboratory analysis and interpretation of data. M.A.A.M. participated in patient follow-up and data acquisition. All authors reviewed and approved the final manuscript.

Conflict of Interest: The authors declare no conflict of interest.

Funding: No Funding.

Data Availability: Information is available for a reasonable reason with the corresponding author.

Supplementary Files: Figure S1.

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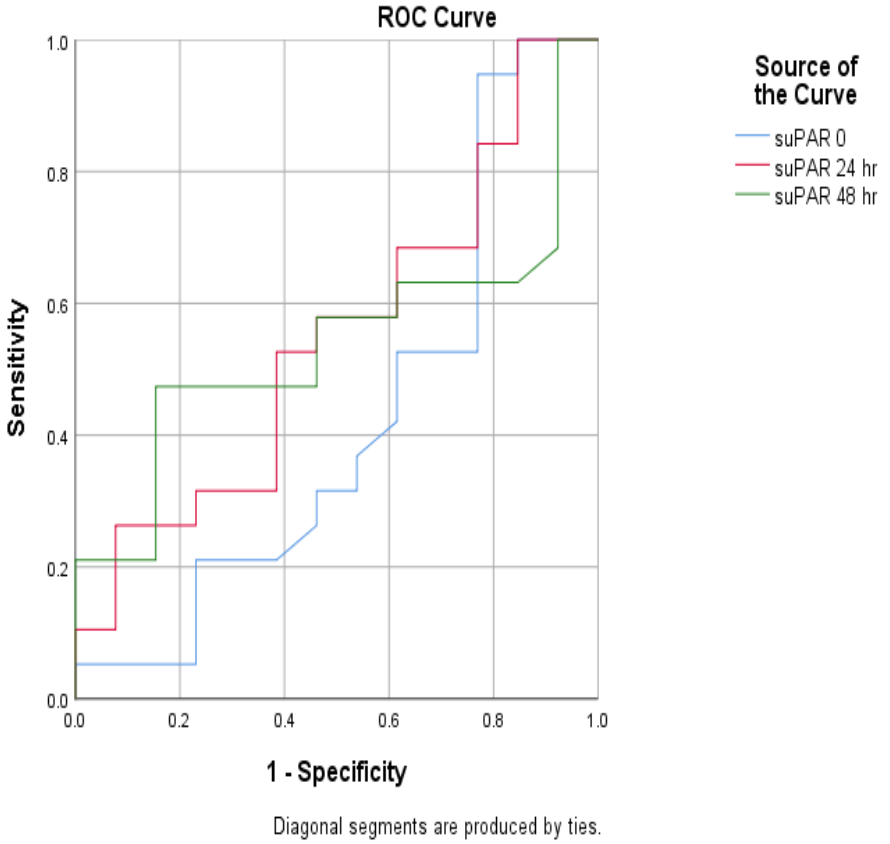

Fig. S1: ROC curve showing performance of suPAR in early prediction of AKI occurrence among studied patients.

Citation

Abdel Moniem, M., Ghorab, A., Al- Barshomy, S., Abd El hameed, A., Elsayed, R., Abdelrahim, M. Soluble Urokinase Plasminogen Activator Receptor as an Early Detector of Acute Kidney Injury in Critically Ill Patients. *Zagazig University Medical Journal*, 2025; (5348-5361): -. doi: 10.21608/zumj.2025.414693.4116