KARBALA JOURNAL OF MEDICINE

Research Article

Soluble Urokinase Plasminogen Activator Receptor (suPAR) as a Predictive Biomarker for Renal Failure Stratification and Urinary Tract Infections in Hemodialysis Patients

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Article information:
Received: 18-05-2025
Accepted: 25-06-2025
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https://doi.org/10.70863/karbalajm.v18i1.3853

Abstract

Background: Hemodialysis (HD) is a vital therapeutic intervention for patients with renal failure; however, it is also associated with various health complications, including urinary tract infections (UTIs), which significantly increase the risk of adverse outcomes, This study assessed the role of soluble urokinase plasminogen activator receptor (suPAR) in predicting disease progression, infection severity, and kidney dysfunction in renal failure patients (with/without UTIs) versus controls, determining its potential for early diagnosis and clinical management in hemodialysis populations.

Methods: A case-control study was conducted on 90 subjects and compared with 30 healthy controls at Al-Hussein Teaching Medical City Hospital between October 2024 and January 2025. Participants were divided into three groups: Group I included 30 patients with UTI not on hemodialysis; Group II included 30 patients with renal failure and UTI; and Group III included 30 patients with renal failure without UTI. Bacterial pathogens were identified using the VITEK 2 Compact System, and concentrations of suPAR were measured using the sandwich ELISA technique.

Results: The prevalence of UTI was significantly higher in females, with *E. coli* being the most common pathogen. Overall, suPAR levels were markedly elevated in patients with renal failure, both with and without UTI, compared to those in the UTI and control groups.

Conclusions: suPAR demonstrated high sensitivity, specificity, and predictive values, suggesting its reliability as a biomarker for early diagnosis and clinical monitoring of renal dysfunction and associated infections. It may serve as a dependable biomarker for renal failure patients and holds promise for diagnostic and prognostic use in clinical settings.

Key words: Soluble urokinase plasminogen activator receptor (suPAR), Hemodialysis. Renal failure, UTI

Introduction

Renal failure, often referred to as end-stage kidney disease, is a condition marked by severely reduced kidney function, typically less than 15% of normal capacity [1]. Various factors can contribute to the development of acute renal failure, such as low blood pressure (hypotension), urinary tract obstruction, hemolytic uremic syndrome, and certain medications. In contrast, chronic renal failure is primarily caused by diabetes, hypertension, polycystic kidney disease, and nephrotic syndrome [2]. The prevalence of chronic kidney disease (CKD) patients will continue to rise, reflecting the growing elderly population and the increasing rates of diabetes and hypertension among individuals [3].

Renal failure can result from a variety of causes. Some conditions lead to a sudden decline in kidney function, known as acute kidney injury (AKI) or acute renal failure, while others cause a gradual loss of function, referred to as chronic kidney disease (CKD) or chronic renal failure [4]. In both cases, the kidneys cannot effectively filter metabolic waste products, such as creatinine and urea nitrogen, from the blood. Their ability to regulate fluid balance, electrolyte levels (including sodium, potassium, calcium, and phosphate), and

acid-base homeostasis is also significantly impaired [5]. Dialysis is a common form of renal replacement therapy used to support patients with kidney failure [6].

Hemodialysis improves the quality of life and reduces morbidity and mortality in individuals with end-stage renal disease. At the same time, modern healthcare has increasingly emphasized the daily experiences and needs of patients throughout the course of treatment [7]. Morbidity and mortality rates among patients receiving conventional hemodialysis remain unacceptably high. Over the past two decades, research has provided significant insights into the advantages and limitations of more frequent hemodialysis therapy, whether administered in clinical settings or at home [8]. This estimate aligns with a previous report indicating that over 3 million people worldwide die each year due to a lack of access to kidney replacement therapy (KRT) [9].

The immune system and the kidneys are closely interconnected. Immune components contribute to the development of acute kidney injury and play a critical role in the progression of chronic kidney disease [10]. Beyond their pathogenic functions, the immune system also helps maintain immunological homeostasis in healthy kidneys. In turn, the kidneys support immune balance by filtering metabolic waste and toxins, thereby reducing both local and systemic inflammation [11].

Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker produced by macrophages, monocytes, neutrophils, activated T cells, endothelial cells, and circulating tumor cells [12]. It represents a soluble form of the urokinase-type plasminogen activator receptor. suPAR is considered a novel biomarker that reflects altered inflammatory activity in various inflammatory disorders and the severity of systemic inflammation [13]. Thus, the suPAR serves as a biomarker of innate immunity and inflammation, and has been shown to predict both cardiovascular and non-cardiovascular events in various settings, including in patients with type 2 diabetes undergoing dialysis [14]. However, the relationship between suPAR levels and clinical outcomes in the general hemodialysis population remains largely unexplored [15]. The aims of this study are to evaluate the clinical significance of suPAR levels in patients with renal failure, both with and without UTIs, to determine its potential as a predictive biomarker for disease progression and severity. By comparing suPAR concentrations across different patient groups and healthy controls, the research seeks to assess suPAR's utility in early diagnosis, risk stratification, and monitoring of renal dysfunction and associated infections.

Material and Method

Patient

This case-control study was conducted from October 2024 to January 2025 at Al-Hussein Teaching Medical City Hospital. A total of 90 participants (43 males, 47 females; aged 15–70 years) were enrolled and divided into three groups: Group I included 30 patients with urinary tract infections (UTIs) not undergoing hemodialysis, selected from the Nephrology Department in the hospital; Group II comprised 30 patients with renal failure and UTIs; and Group III consisted of 30 patients with renal failure without UTIs, selected from the Habib Ibn Mudhaher Dialysis Center in the hospital. These groups were compared with 30 healthy controls.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients with chronic renal failure diagnosed based on clinical symptoms and other investigations, including both males and females across different age groups.

Exclusion Criteria: Patients with cancer, those taking immunosuppressive drugs, or those with autoimmune diseases, allergies, asthma, or a Foley catheter were excluded.

Isolation of the organisms

Four milliliters of clean midstream urine were collected from each patient in a sterile tube and promptly transferred to the laboratory for analysis before hemodialysis. Pure bacterial cultures were isolated and maintained using various differential and selective media, including MacConkey agar, blood agar, and chocolate agar (Oxoid, England). The streaking technique was used to isolate pathogens on various differential and selective media, and the plates were incubated at 37°C for 24 hours. Microscopic analysis of the isolates was performed based on bacterial size, shape, and staining characteristics. Initial identification of the selected isolates was carried out using the Gram staining technique, and all bacterial isolates were subsequently identified using the VITEK 2 compact system (BioMerieux, France).

Determination of soluble urokinase plasminogen activator receptor (suPAR) levels

Serum concentrations of suPAR were quantified using the suPAR ELISA Kit (BT Lab Biological Technology, China), following the manufacturer's instructions. The detection range of the kit is between 7.81 and 500 pg/mL. The assay

employed a biotin double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) technique for suPAR quantification.

Ethical approval

The study protocol was sent to the relevant ethical committee in the health directorate in Karbala and approved by the Institutional Review Board (IRB) of Al-Hussein Teaching Medical City Hospital (Ethical No. 3772). Also, verbal approval is taken from each participant before taking the sample. During sample collection, health measures and safety were taken.

Statistical Analysis

Data was introduced into specific software, Statistical Package for the Social Sciences (SPSS), for statistical analysis. Chi-square, ANOVA, and Kruskal-Wallis tests have been utilized in this study.

Results

Age distribution across patient groups (UTI, RF without UTI, RF with UTI) showed no significant differences (p = 0.2646). The UTI group had the highest proportion of individuals aged <40 years (43.3%, n=13), followed by those ≥60 years (36.7%, n=11). In contrast, RF with UTI patients were also predominantly aged <40 years (40.0%, n=12). Sex distribution differed significantly (p = <0.001), with females comprising 70.0% (n=21) of UTI cases and 63.3% (n=19) of RF with UTI cases, while males dominated the RF without UTI group (76.7%, n=23). Overall, the cohort exhibited near-equal sex representation (males: 47.8%, females: 52.2%) (Table 1).

Culture investigations, based on morphological, biochemical, and VITEK 2 Compact system results, showed a statistically significant difference in the overall distribution of pathogens (p = < 0.001). *Escherichia coli* was the most commonly isolated organism, accounting for 30 isolates (50.00%), followed by *Klebsiella pneumoniae* with 10 isolates (16.67%), and *Staphylococcus aureus* with 7 isolates (11.67%). Other identified pathogens included *Enterococcus faecalis* (3 isolates; 5%), *Pseudomonas aeruginosa* (3 isolates; 5%), and *Proteus mirabilis* (3 isolates; 5%). Additionally, single isolates (1 each; 1.67%) were identified for *Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus,* and *Acinetobacter baumannii* (Figure 1).

The suPAR parameter showed a statistically significant (P-value of < 0.001) when comparisons were made across different study groups. The mean and Standard deviation of suPAR levels exhibited the highest value (441.802+347.014) in renal failure without UTI group, followed by renal failure with UTI (275.167+258.077), and less in the UTI group (116.465+58.729), but still elevated than the control group (75.529 +34.792). Overall, suPAR levels in this data are elevated in renal failure, with or without UTI, compared to the control and UTI groups (Table 2).

The diagnostic performance of immunological markers (suPAR) in patients with renal failure (RF) demonstrated a high level of accuracy, with an area under the curve (AUC) of 93.56% at a cutoff point of 104.373. The sensitivity and specificity were 88.33% and 83.33%, respectively, resulting in an overall accuracy of 91.67%. The positive predictive value (PPV) was 85.71%, while the negative predictive value (NPV) reached 100%. The test showed a statistically significant result with a p-value of 0.002, and the 95% confidence interval ranged from 0.889 to 0.982 (Table 3).

Discussion

This study demonstrated that females are far more susceptible to urinary tract infections than males. The youngest age group exhibited the highest susceptibility to UTIs, closely followed by older participants. Notably, while middle-aged adults had a somewhat lower prevalence of UTIs, they demonstrated a higher proportion of risk factors linked with UTIs. When compared with previous studies, these findings presented here closely align with established research, emphasizing that women have greater susceptibility to UTIs, primarily due to anatomical differences, notably their shorter urethra, and facilitating bacterial access to the bladder [16-17].

Table 1: Distribution of patient sex and age groups, detailing the levels, and percentage representation

Parameters	Group	UTI	RF withoutUTI	RF with UTI	Total	P-value
Age (years)	< 40	13(43.33%)	12(40.00%)	8 (26.67%)	33(36.67%)	0.264
	40 - 59	6 (20.00%)	12 (40.00%)	12 (40.00%)	30(33.33%)	
	>= 60	11(36.67%)	6(20.00%)	10(33.33%)	27(30.00%)	
Sex	Male	9(30.00%)	23(76.67%)	11(36.67%)	43(47.78%	<0.001
	Female	21(70.00%)	7 (23.33%)	19(63.33%)	47(52.22%	

The Chi-square test has been utilized to analyze the categorical variables

*. Association is significant at the 0.05 level.

UTI = Urinary Tract Infection; RF = Renal Failure.

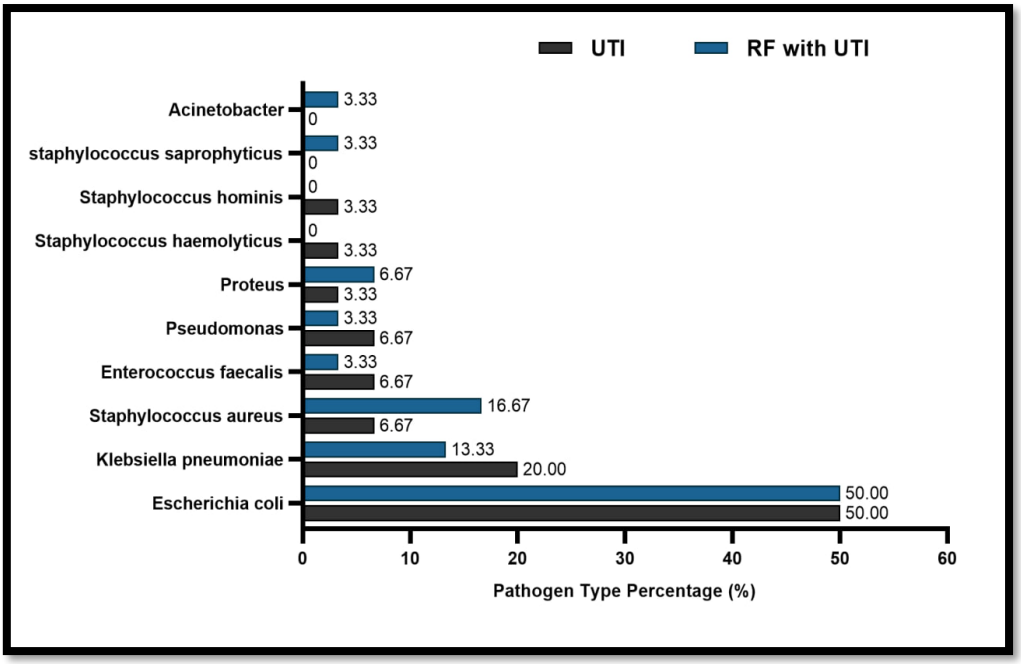

Figure 1: Distribution of pathogens with the levels and percentage representation

Table 2: The Comparisons between research groups according to the suPAR parameter.

Groups	Mean	Standard deviation	P-value
Control	75.529	34.792	< 0.001
UTI	116.465	58.729	
RF without UTI	441.802	147.014	
RF with UTI	275.167	78.077	

UTI = Urinary Tract Infection; RF = Renal Failure.

Table 3: Model prediction of subject working characteristic curves according to the immunological markers.

Metrics		Renal failure patient
		suPAR levels (pg/mL)
Standard error		0.024
Asymptotic significance		0.002
Asymptotic 95% Confidence Interval	Lower Bound	0.889
	Upper Bound	0.982
Cutoff Point		104.373
Area Under Curve (AUC)		93.556%
Sensitivity		88.333%
Specificity		83.333%
Accuracy		91.667%
Positive Predictive Value		85.714%
Negative Predictive Value		100.000%

In the present study, it was observed that males predominate in RF without UTI cases, whereas females predominate in RF with UTI cases. This agrees with Yamashita *et al.* (2022), indicating that men are more susceptible to renal failure from systemic illnesses such as hypertension or diabetes. In contrast, women are more vulnerable to UTIs due to anatomical features [18]. Our study disagrees with Majeed *et al*. (2019), a study in Al-Najaf City in Iraq, revealed that among 120 patients with UTIs, the predominant age group was 51–60 years, accounting for 40% of the total cases. This cohort comprised 22 patients without kidney disease (WKD) and 26 patients with chronic kidney disease (CKD) out of 48 participants [19].

In this study, younger patients were more commonly observed in the RF without UTI group, whereas older patients were more prevalent in the RF with UTI group. The same results are found in other studies that showed increased risk of UTIs among elderly individuals, which is attributable to their weakened immune systems and comorbidities

[20,21]. A thorough comprehension of gender and age characteristics is essential for formulating targeted prevention and treatment strategies for renal failure.

Escherichia coli is the predominant pathogen in UTIs, representing 50% of cases in the supplied data. When compared with previous studies, *E. coli* was the predominant pathogen in UTI in renal failure patients [22]. Other study consistently identifies *E. coli* as the predominant cause of UTI, with incidence rates between 41% and 83% across different contexts [23]. The analysis identifies *E. coli* as the primary causative agent of UTIs, underscoring its substantial impact on disease prevalence and the drug susceptibility patterns that influence human health and society [24]. Following *E. coli*, other significant pathogens include *K. pneumonia*, which was the second most commonly isolated pathogen in UTI, in both community and hospital environments. In patients with chronic kidney disease, *K. pneumoniae* was responsible for 32.60% of UTI cases, indicating its substantial role in this population [25]. Additional infections, including *Proteus mirabilis, Enterococcus faecalis*, and *Pseudomonas aeruginosa*, contribute to the situation, with prevalence rates differing according to patient demographics and underlying health conditions [26].

suPAR levels exhibited substantial variation among groups and showed significant differences, in line with previous studies that agree with Valaperta *et al.* (2024). Their study found a significant correlation between elevated plasma suPAR levels and a decline in estimated glomerular filtration rate (eGFR) (P=0.0001), indicating that higher suPAR levels may be associated with worsening kidney function [27]. The study of Skalec *et al*. (2022) demonstrates that suPAR levels are markedly increased in septic patients with acute kidney injury (AKI) relative to a control group devoid of sepsis and renal failure (13.01 ng/mL vs. 4.05 ng/mL, $p < 0.001$)[28]. A study of acute medical patients found that elevated suPAR levels at hospital admission correlated with a heightened risk of developing both chronic and acute kidney diseases. Increased suPAR levels have been associated with the advancement of CKD, underscoring its potential as a biomarker for renal pathology [29].

The study indicated that suPAR levels were markedly elevated in patients with glomerulonephritis relative to healthy subjects, with mean levels of 166.06 ± 127.66 pg/ml in patients compared to 119.67 ± 70.53 pg/ml in the control group (p= 0.001)[30]. However, Ni *et al*. (2016) showed that suPAR is identified as a biomarker of immunological activation and inflammation, with increased levels found in numerous bacterial infections. A meta-analysis demonstrated suPAR's effectiveness in diagnosing and prognosticating bacterial infections, revealing a pooled sensitivity of 0.73 and specificity of 0.79 for infection diagnosis [31].

In this study, suPAR had a high value of AUC, which agree with Huang *et al.* (2023)**,** The meta-analysis revealed that the overall sensitivity of suPAR for predicting AKI was 0.77 (95% CI: 0.67-0.84), while the specificity was 0.64 (95% CI: 0.53-0.75). The diagnostic odds ratio was 6 (95% CI 3-10), the pooled positive likelihood ratio was 2.2 (95% CI: 1.6-2.9), and the pooled negative likelihood ratio was 0.36 (95% CI: 0.26-0.52). Additionally, the area under the summary receiver-operating characteristic (SROC) curve was 0.77 (95% CI: 0.12-0.99) [32]. The sensitivity (88.333%) and specificity (83.333%) results align with the findings of Hayek *et al.* (2017), who reported that suPAR strongly predicts outcomes and incident CKD in patients with cardiovascular disease with comparable diagnostic metrics [33].

The standard errors of suPAR indicated high precision, as noted in the study of Roumeliotis *et al.* (2024), which found that ROC curve analysis can be used to evaluate if a novel biomarker might be useful in the diagnosis of a certain condition [34].

Conclusions

Gram-negative bacteria, particularly *E. coli* were identified as the most predominant causative agents of urinary tract infections in this study, with a higher prevalence observed among females. This study was conducted to evaluate the prognostic value of the immunological marker suPAR in patients undergoing hemodialysis. The findings suggest that suPAR could serve as a strong prognostic marker, offering valuable evidence for the early diagnosis of kidney failure. Additionally, it may help monitor the severity of urinary tract infections in dialysis patients and assess kidney function more effectively.

Funding: There is no funding for this research.

Conflict of interest: The authors state that there is no conflict of interest

Authors contribution: Conceptualization: A.G.A., Methodology: A.G.A., Formal analysis and investigation: A.H.K., Writing: A.H.K, Resource: M.R.A, Supervision: A.G.A., and M.R.A.

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