10.48047/jocaaa.2024.33.06.114

Emerging Biomarkers in Nephrocritical Care: The Predictive Value of suPAR for Acute Kidney Injury

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ABSTRACT

Background: Acute kidney injury (AKI) is a frequent and severe complication in critically ill patients, associated with high morbidity, mortality, and healthcare costs. Early detection of AKI is challenging, as traditional biomarkers such as serum creatinine and urine output often lack sensitivity and specificity in the initial stages of kidney injury. Soluble urokinase plasminogen activator receptor (suPAR), a circulating form of the membrane-bound uPAR, has emerged as a novel biomarker reflecting immune activation and systemic inflammation. Recent studies indicate that suPAR levels are elevated before the onset of AKI, offering the potential for early risk stratification in intensive care unit (ICU) settings. This review explores the pathophysiology of AKI in critically ill patients, highlights the limitations of current diagnostic approaches, and evaluates the mechanistic links between suPAR and renal injury. We discuss suPAR's predictive accuracy compared with established biomarkers, its prognostic implications, and its role in different ICU-related etiologies of AKI, including sepsis, major surgery, and COVID-19. The article also addresses potential confounders in suPAR interpretation, such as chronic kidney disease and systemic inflammation, and considers the implications of suPAR-guided decision-making in nephrocritical care. By synthesizing current evidence, we aim to clarify suPAR's role as an early, sensitive, and clinically relevant biomarker for AKI, while outlining future research priorities. Ultimately, integrating suPAR into ICU risk assessment protocols may facilitate timely interventions, improve patient outcomes, and reduce the burden of AKI-related complications.

Keywords*: Biomarkers, Acute Kidney Injury, suPAR*

INTRODUCTION

Acute kidney injury (AKI) is a prevalent and serious complication among critically ill patients, affecting between 30% and 50% of individuals admitted to intensive care units (ICUs) worldwide [1]. It is characterized by an abrupt decline in renal function, leading to the accumulation of metabolic waste products, electrolyte imbalances, and fluid overload. Despite improvements in supportive care, mortality rates in severe AKI remain unacceptably high, ranging from 40% to 60% in ICU populations [2]. A key challenge in AKI management lies in its delayed diagnosis, as traditional markers such as serum creatinine and urine output often reflect injury only after significant nephron loss has occurred [3]. This time lag severely limits the window for early therapeutic intervention.

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In the last decade, there has been a paradigm shift toward identifying novel biomarkers capable of detecting AKI before irreversible damage ensues [4]. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7) have improved early diagnostic capabilities in some clinical contexts [5]. However, their sensitivity and specificity vary across AKI etiologies and patient populations, and they may not fully capture the complex interplay of inflammation, hemodynamic instability, and cellular injury seen in critically ill patients [6]. This has prompted interest in molecules like soluble urokinase plasminogen activator receptor (suPAR), which may serve as a more universal indicator of AKI risk.

suPAR is a stable, circulating form of the membrane-bound uPAR, expressed predominantly on immune cells and endothelial surfaces [7]. It is a marker of systemic immune activation and has been implicated in various inflammatory and infectious conditions, including sepsis, cardiovascular disease, and chronic kidney disease [8]. Its role in AKI appears to be linked to its ability to promote leukocyte recruitment, endothelial dysfunction, and microvascular injury—mechanisms central to kidney damage in critically ill patients [9]. Unlike many injury markers, suPAR levels can rise well before overt functional decline, making it particularly promising for early AKI prediction.

The aim of this review is to evaluate the predictive value of suPAR for AKI in the nephrocritical care setting, with emphasis on its pathophysiological relevance, diagnostic performance, and potential integration into clinical practice [10]. We will explore current evidence, compare suPAR with established biomarkers, and discuss limitations, confounders, and future research directions. By consolidating the available literature, we aim to inform clinicians and researchers about the emerging role of suPAR as an early warning tool in AKI among critically ill patients.

A. Pathophysiology of AKI in Critically Ill Patients

The pathophysiology of AKI in critically ill patients is multifactorial, involving hemodynamic disturbances, inflammatory cascades, oxidative stress, and microvascular dysfunction [11]. A central feature is the interplay between systemic illness and renal susceptibility. In conditions such as sepsis, hypovolemia, and major surgery, decreased renal perfusion initiates ischemia-reperfusion injury, which disrupts tubular epithelial cell polarity and leads to cytoskeletal damage [12]. These events trigger apoptosis, necrosis, and shedding of tubular cells into the urine, compromising nephron function even before overt creatinine elevation occurs [13].

Systemic inflammation is a major driver of AKI in the ICU. Circulating pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), activate endothelial cells and recruit leukocytes to the renal microvasculature [14]. Endothelial activation increases vascular permeability, promotes microthrombi formation, and disrupts nitric oxide homeostasis, leading to regional hypoxia and tissue ischemia [15]. This “endotheliopathy” is now recognized as a key link between critical illness and kidney injury, and biomarkers such as suPAR may provide a quantifiable reflection of this process [16].

Another important component is oxidative stress, which occurs when reactive oxygen species (ROS) production exceeds the cell’s antioxidant capacity [17]. During critical illness, excessive ROS damage DNA, proteins, and lipids in renal tubular cells. The resultant mitochondrial dysfunction impairs ATP production, further compromising the kidney’s ability to maintain ion gradients and filtration [18]. Additionally, activation of the

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complement cascade can amplify injury by promoting leukocyte infiltration and releasing pro-inflammatory mediators directly toxic to renal tissue [19].

Microvascular dysfunction contributes significantly to AKI pathogenesis in the ICU. Loss of autoregulatory control, endothelial swelling, and intrarenal shunting lead to heterogeneous blood flow distribution within the kidney [20]. Even when systemic blood pressure appears normal, areas of the renal cortex and medulla may experience profound ischemia. This explains why AKI can develop despite seemingly adequate macrocirculatory parameters. suPAR, by reflecting systemic immune activation and endothelial injury, may act as a surrogate marker for these microvascular insults [21].

Finally, maladaptive repair responses can perpetuate injury and promote fibrosis. Persistent activation of fibroblasts and myofibroblasts leads to extracellular matrix deposition and tubular atrophy [22]. In critically ill patients, prolonged inflammation and repeated ischemic hits increase the risk that AKI will transition to chronic kidney disease (CKD). Early identification of patients at risk through biomarkers like suPAR could allow for targeted therapies aimed at interrupting this maladaptive cycle [23].

B. AKI in Critically Ill Cases

AKI is one of the most common organ dysfunctions encountered in intensive care settings, with reported incidence rates ranging from 20% to 50%, depending on the diagnostic criteria applied [24]. The heterogeneity of ICU populations—ranging from trauma victims to septic shock patients—means that AKI etiologies are diverse and often multifactorial [25]. Many cases occur in the context of systemic illness, where kidney injury is both a manifestation and a driver of disease severity. This bidirectional relationship complicates management and underscores the need for early identification of at-risk patients to guide interventions [26].

Sepsis-associated AKI represents nearly half of all ICU AKI cases and is characterized by profound inflammatory activation, endothelial injury, and microvascular collapse [27]. The kidney in sepsis is particularly vulnerable due to its high metabolic demands and complex microvascular architecture. Unlike purely hemodynamic forms of AKI, septic AKI often occurs despite preserved or even elevated renal blood flow, highlighting the dominant role of microcirculatory derangements and cellular metabolic dysfunction [28]. suPAR, as a marker of immune activation, may be particularly suited to identifying patients in whom inflammation is the primary driver of kidney injury [29].

Cardiac surgery–associated AKI is another frequent scenario in critically ill patients, with incidences of 20–30% following procedures requiring cardiopulmonary bypass [30]. Mechanisms include ischemia-reperfusion injury, oxidative stress, hemolysis, and systemic inflammatory responses triggered by extracorporeal circulation [31]. Post-operative suPAR elevation could reflect both the pre-existing inflammatory state and acute perioperative insults, providing a window for early post-surgical risk stratification [32].

Trauma, burns, and multi-organ failure syndromes also predispose ICU patients to AKI through combined effects of shock, rhabdomyolysis, systemic inflammation, and nephrotoxin exposure [33]. In these settings, kidney injury is often compounded by the complexity of supportive therapies, including high-dose vasopressors, mechanical ventilation, and broad-spectrum antibiotics [34]. A biomarker capable of capturing the cumulative inflammatory and endothelial burden—such as suPAR—could help distinguish patients who will develop AKI from those whose renal function will remain stable despite severe systemic illness [35].

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C. Common Causes of AKI in the ICU

Sepsis is the leading cause of AKI in critically ill patients, accounting for approximately 40–50% of ICU cases [36]. The pathophysiology of sepsis-induced AKI involves a complex interplay between systemic inflammation, microvascular dysfunction, and metabolic reprogramming of tubular epithelial cells [37]. While global renal blood flow may remain preserved or even elevated in some cases, profound heterogeneity in microcirculatory perfusion leads to tissue hypoxia and cellular injury [38]. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 amplify endothelial damage and leukocyte infiltration, perpetuating renal injury. suPAR, being a sensitive marker of immune activation, may rise early in septic patients and thus serve as a warning signal before AKI becomes clinically evident [39].

Cardiac surgery–associated AKI is another common cause, occurring in 20–30% of patients undergoing cardiopulmonary bypass [40]. Mechanisms include ischemia-reperfusion injury during aortic cross-clamping, systemic inflammation induced by extracorporeal circulation, oxidative stress from hemolysis, and nephrotoxin exposure in the perioperative period [41]. Pre-existing comorbidities such as chronic kidney disease, diabetes, and hypertension further increase susceptibility [42]. Monitoring perioperative suPAR levels could help identify patients at high risk and tailor preventive measures accordingly [43].

Nephrotoxin-induced AKI is also prevalent in ICU settings. Common agents include aminoglycoside antibiotics, amphotericin B, calcineurin inhibitors, and iodinated contrast media [44]. Critically ill patients are particularly vulnerable because these drugs are often used in high doses and in combination with other nephrotoxic insults such as hypotension or sepsis [45]. Biomarkers that reflect early cellular stress or systemic inflammation—like suPAR—may provide additional predictive value beyond drug dosing and exposure histories [46].

Hypovolemia and shock, whether due to hemorrhage, gastrointestinal losses, or distributive states such as anaphylaxis, remain classic precipitants of AKI in the ICU [47]. Prolonged hypotension reduces renal perfusion pressure, triggering ischemia-reperfusion injury and activating maladaptive inflammatory cascades [48]. While prompt fluid resuscitation can reverse early changes, many patients progress to overt AKI despite hemodynamic correction, reflecting the importance of early risk stratification [49]. In this context, suPAR could help identify patients in whom systemic inflammatory activation—rather than pure hemodynamic failure—is the primary driver of kidney injury.

Finally, multi-organ dysfunction syndromes (MODS) significantly contribute to AKI incidence in the ICU [50]. AKI may develop secondary to respiratory failure, hepatic dysfunction, or systemic coagulopathy, as these conditions promote generalized inflammation, endothelial injury, and metabolic derangements [51]. In MODS, kidney injury often represents the culmination of multiple simultaneous insults. A biomarker like suPAR, which integrates information on immune activation and endothelial status, may thus have broad predictive relevance across diverse ICU populations [52].

D. Prognosis and Outcome of Patients with AKI

The development of AKI in critically ill patients is strongly associated with increased short- and long-term mortality [53]. Mortality rates vary depending on AKI severity, with stage 3 AKI in the ICU carrying an in-hospital mortality risk as high as 60% [54]. Even relatively mild AKI episodes are linked to worse outcomes compared to patients without kidney injury, suggesting that AKI is not merely a marker of illness severity but

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also a direct contributor to mortality [55]. This relationship persists after adjusting for comorbidities, indicating that AKI has an independent prognostic impact [56].

Beyond immediate survival, AKI significantly affects long-term renal health. Survivors of critical illness who experience AKI are at elevated risk of developing chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [57]. The likelihood of CKD progression correlates with both the severity and duration of the AKI episode [58]. This underscores the importance of early detection and intervention, as timely measures to limit injury or promote recovery could mitigate irreversible nephron loss [59]. Predictive biomarkers like suPAR could help identify patients most in need of close post-discharge renal follow-up.

Functional recovery from AKI is highly variable. Some patients regain baseline kidney function, while others experience incomplete recovery, resulting in reduced renal reserve [60]. These patients are more susceptible to recurrent AKI episodes during subsequent illnesses, leading to a vicious cycle of progressive renal decline [61]. This vulnerability highlights the need for risk stratification tools not only during the ICU stay but also in the outpatient setting [62]. suPAR, due to its stability in circulation and association with chronic inflammation, may serve as a prognostic tool for identifying patients at risk of incomplete recovery.

AKI also has broader systemic consequences in critically ill patients. It is associated with prolonged mechanical ventilation, increased susceptibility to infections, and worsened cardiovascular outcomes [63]. Fluid overload secondary to oliguria can exacerbate pulmonary edema and impair oxygenation, while electrolyte disturbances may trigger life-threatening arrhythmias [64]. The cumulative effect of these complications contributes to longer ICU and hospital stays, increased healthcare costs, and diminished quality of life for survivors [65]. Incorporating biomarkers like suPAR into prognostic models could improve individualized care planning and resource allocation.

E. Biomarkers of AKI

The search for accurate biomarkers of AKI stems from the limitations of traditional indicators such as serum creatinine and urine output, which often change only after significant nephron injury has occurred [66]. Creatinine levels are influenced by muscle mass, hydration status, and catabolic state, making them unreliable in the acute phase of critical illness [67]. Urine output can be affected by non-renal factors such as diuretic use or hemodynamic changes, further reducing its specificity [68]. Consequently, there is a growing interest in biomarkers that can detect subclinical AKI before irreversible damage occurs.

Several injury and stress biomarkers have been studied for their potential to improve early detection. Neutrophil gelatinase-associated lipocalin (NGAL) rises within hours of tubular injury and is one of the most extensively validated AKI biomarkers [69]. Kidney injury molecule-1 (KIM-1) reflects proximal tubular cell injury and is particularly relevant in ischemic and nephrotoxic AKI [70]. The combination of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), commercialized as the NephroCheck® test, has been shown to predict AKI risk in ICU patients by detecting cell cycle arrest [71]. Despite promising performance, variability across patient populations and AKI etiologies limits their universal applicability [72].

Cystatin C, a marker of glomerular filtration independent of muscle mass, has been investigated as an earlier alternative to creatinine for detecting functional decline [73]. However, its levels can be affected by

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corticosteroid use, thyroid function, and systemic inflammation, reducing specificity in the critically ill [74]. Interleukin-18 (IL-18) and liver-type fatty acid-binding protein (L-FABP) are other candidates reflecting inflammatory and oxidative stress pathways, but their diagnostic value in heterogeneous ICU cohorts remains uncertain [75].

A key limitation of many existing biomarkers is that they primarily reflect tubular injury or functional impairment, rather than the upstream inflammatory and endothelial processes that often precede overt renal damage in critically ill patients [76]. suPAR offers a complementary approach by serving as a stable circulating marker of systemic immune activation and microvascular pathology [77]. Its kinetics suggest that elevated levels can be detected well before traditional injury markers rise, potentially extending the window for preventive strategies [78]. The combination of suPAR with established biomarkers may yield a multi-dimensional diagnostic profile that improves sensitivity and specificity for AKI detection across diverse ICU scenarios [79].

F. Soluble Urokinase Plasminogen Activator Receptor

Soluble urokinase plasminogen activator receptor (suPAR) is the circulating form of the membrane-bound uPAR, a glycosylphosphatidylinositol-anchored protein expressed on immune cells, endothelial cells, and various epithelial tissues [80]. uPAR plays a pivotal role in cell adhesion, migration, and tissue remodeling by binding to urokinase plasminogen activator (uPA) and interacting with integrins and vitronectin [81]. suPAR is generated through proteolytic cleavage of membrane-bound uPAR and is detectable in plasma, serum, and other body fluids [82]. Because it is highly stable in circulation and resistant to degradation, suPAR offers an advantage over many other biomarkers that fluctuate rapidly in response to acute physiological changes [83].

The biological significance of suPAR lies in its function as a marker of immune activation and systemic inflammation [84]. Elevated levels have been observed in a wide range of conditions, including sepsis, chronic kidney disease, cardiovascular disease, HIV infection, and certain malignancies [85]. In the context of kidney disease, suPAR has been implicated in podocyte injury through activation of β3 integrins, leading to cytoskeletal rearrangements and disruption of the glomerular filtration barrier [86]. This pathogenic role has been most extensively studied in focal segmental glomerulosclerosis (FSGS), but evidence suggests similar mechanisms may contribute to AKI in critically ill patients [87].

Mechanistically, suPAR is thought to contribute to renal injury by promoting leukocyte recruitment, amplifying inflammatory signaling, and impairing endothelial function [88]. Endothelial activation, a hallmark of critical illness, increases vascular permeability and promotes microthrombosis, processes that are reflected in elevated suPAR levels [89]. Furthermore, high suPAR concentrations have been associated with microvascular rarefaction and reduced renal perfusion in experimental models, suggesting that it is more than a passive marker and may play an active role in AKI pathogenesis [90].

Clinically, suPAR levels correlate with disease severity and prognosis across multiple acute care settings [91]. In the ICU, high baseline suPAR concentrations have been shown to predict the development of AKI, the need for renal replacement therapy, and increased mortality [92]. Unlike transiently elevated cytokines, suPAR remains elevated for prolonged periods, which may allow for a broader diagnostic window in identifying at-risk patients [93]. This stability also facilitates single-timepoint measurement, which is advantageous in resource-limited settings or when repeated sampling is impractical [94].

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Importantly, suPAR is not a disease-specific marker, and its interpretation requires consideration of comorbidities and concurrent inflammatory states [95]. Chronic kidney disease, autoimmune disorders, and malignancies can all raise baseline suPAR levels, potentially confounding its specificity for AKI [96]. Nevertheless, its unique ability to integrate information about systemic inflammation and endothelial health positions it as a promising tool in nephrocritical care, especially when combined with other functional and injury biomarkers [97].

G. suPAR and AKI

Emerging evidence suggests that suPAR is not merely a bystander biomarker but may actively participate in the pathogenesis of AKI in critically ill patients [98]. Elevated suPAR levels have been detected hours to days before AKI diagnosis based on creatinine criteria, indicating its potential as an early warning marker [99]. This temporal advantage is clinically relevant in ICU practice, where early identification of high-risk patients can trigger preventive measures such as nephrotoxin avoidance, hemodynamic optimization, and close renal function monitoring [100].

In a large multicenter prospective cohort study, baseline suPAR concentrations were independently associated with the development of AKI, even after adjusting for age, comorbidities, and illness severity scores [101]. Importantly, patients in the highest quartile of suPAR had a several-fold higher risk of requiring renal replacement therapy compared to those with lower levels [102]. This predictive capacity was observed across diverse ICU populations, including those admitted for sepsis, cardiac surgery, and trauma [103].

Mechanistically, suPAR appears to promote renal injury by activating β3 integrins on podocytes, leading to cytoskeletal rearrangement and disruption of the glomerular filtration barrier [104]. Additionally, suPAR-induced endothelial dysfunction may impair renal microcirculation, exacerbating ischemia and contributing to tubular injury [105]. In sepsis models, elevated suPAR has been linked to increased leukocyte-endothelial interactions and microvascular rarefaction, both of which are implicated in septic AKI [106]. These mechanistic insights support the biological plausibility of suPAR as a causal factor rather than a mere epiphenomenon.

From a diagnostic standpoint, combining suPAR with existing injury biomarkers such as NGAL or [TIMP-2]·[IGFBP7] may significantly improve predictive accuracy [107]. This multi-marker approach integrates functional, injury, and inflammatory dimensions of AKI risk, providing a more comprehensive risk assessment [108]. Furthermore, suPAR's stability in plasma allows for single-sample testing without the need for precise timing relative to injury onset, making it a practical option for ICU workflows [109].

However, suPAR interpretation in AKI is not without challenges. Elevated baseline levels are common in patients with chronic kidney disease, cardiovascular disease, or chronic inflammatory disorders, potentially reducing specificity [110]. In such cases, relative changes from baseline, rather than absolute levels, may provide more clinically meaningful information [111]. Despite these limitations, accumulating evidence supports the integration of suPAR into AKI risk prediction algorithms, particularly for high-acuity ICU populations [112]. Future research should focus on refining cutoff values, validating predictive models in diverse settings, and exploring whether suPAR-guided interventions can improve renal and overall patient outcomes [113].

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